COMPARISON BETWEEN ALFUZOSIN MONOTHERAPY AND COMBINATION OF ALFUZOSIN WITH FINASTERIDE IN SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA

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Abstract

Background: Lower Urinary Tract Symptoms (LUTS) due to Benign Prostatic Hyperplasia (BPH) are common in elder men and a number of drugs alone or combined are clinically used for this disorder. This study was aimed to evaluate the efficacy and safety of Alfuzosin monotherapy versus combination of Alfuzosin and Finasteride in treatment of LUTS due to BPH. **Materials and methods:** This clinical trial was conducted in the outpatient Department of Urology Chittagong Medical College Hospital from May 2007 to October 2008. After assessing for the eligibility, consecutive consenting 60 patients with LUTS related to BPH were randomly assigned to either 10mg Alfuzosin (Group A) or combination of 10mg Alfuzosin and 5mg Finasteride (Group B) for 12 months. The response was assessed by measurements of International Prostate Symptoms Score (IPSS) Maximum urine flow rate (Qmax), Post Voidal Residual Volume (PVR) and prostate volume at baseline and 3 monthly thereafter. Safety was assessed by Adverse Drug Events (ADE) rate. **Results:** Both Groups showed comparable significant improvements in all parameters in terms of decreasing IPSS, PVR and increasing Qmax. Both treatments were well tolerated with respect to ADE and distribution of ADE was similar in two groups. **Conclusion:** In men with benign prostatic hyperplasia, Alfuzosin was effective therapy and the combination of Alfuzosin and Finasteride was no more effective than Alfuzosin alone.

Key words
BPH; Alfuzosin; Finasteride; IPSS; Qmax; PVR.

Introduction

Benign Prostatic Hyperplasia (BPH) is characterized by Lower Urinary Tract Symptoms (LUTS: Urinary frequency, urgency, a weak and intermittent stream needing to strain, a sense of incomplete emptying, and nocturia) and can lead to complications, including acute urinary retention[1,2]. BPH is common among older men, with approximately 25% of men over 40[3].

The treatment approach for BPH has changed since the recent introduction of medical therapies with evidence-based efficacy. The preferred medical treatment for symptomatic BPH is either with a α-Blocker (AB) which reduces smooth muscle-tone in the prostate or bladder neck or a 5α –Reductase Inhibitor (5ARI) that reduces prostate volume by inducing epithelial atrophy and apoptosis[4]. Treatment with an AB or a 5ARI can ameliorate symptoms and improve urinary flow rate[5]. Finasteride, a 5 ARI is more effective on large prostate (>40 cc) than small prostate (<40 cc)[6]. Finasteride also substantially reduces the risk of acute urinary retention and the need for surgery[7].

By virtue of their differential action on stromal and epithelial components respectively the combined effect of AB and a 5ARI should be at least additive. Hence, many trials across the world have evaluated combination therapy with a α-blocker and Finasteride for BPH.

Alfuzosin is a new AB which offers some potentially important safety advantages over other α-blocker owing to its unique α1A sub-selectivity especially in older patients. In a long term study, Alfuzosin once –daily at 10 or 20 mg was shown to be effective, safe and well tolerated in the target BPH population[8].

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In the background of the trend of employing combination, the clinicians recently opt to use Alfuzosin instead of adding Finasteride in order to find out a more effective monotherapy. Because, Finasteride is disrepute for its tardy action, at least 6 months required to clinical effect and notorious for sexual dysfunction[9]. In a long-term study, single Alfuzosin 10mg monotherapy offers distinct additional benefit.

However, there are no studies in Bangladesh comparing Alfuzosin monotherapy versus combined Alfuzosin and Finasteride as medical treatment of BPH. We therefore studied these two regimens to evaluate their safety and efficacy in such patients.

Material and methods

This was a hospital-based, open label, randomized trial, performed in 60 patients undergone medical management of BPH in the outpatient Department of Urology, in Chittagong Medical College Hospital, a tertiary care institute, in Bangladesh. After obtaining approval from the Institute Research Council and Ethics Committee, the study was conducted from May 2007 to October 2008.

All consecutive consenting male patients with BPH aged between 50 to 85 years, LUTS with moderate, 8 to 19 International Prostate Symptom Score (IPSS) Maximum flow rate (Qmax)>10ml to <15 ml/sec on Uroflowmetry (UFR) prostate volume measuring >40cc on transabdominal Ultrasound (US) and Post Void Residue (PVR) <100 ml on US were eligible for the study after obtaining a written informed consent. The exclusion criteria were the following: use of AB within 2 weeks/ 5ARI within 6 months or phytotherapy, active Urinary Tract Infection (UTI) bladder outlet obstruction due to any other cause like urethral stricture, bladder neck stenosis or diagnosed to have vesical calculus, urethral or bladder diverticulum, neurogenic bladder, prostatic or bladder cancer, significant Orthostatic Hypotension (OH) post-prostatectomy and renal impairment (Serum creatinine >2 mg/dl).

Patients were randomized to receive oral Alfuzosin 10 mg or Alfuzosin 10 mg plus Finasteride 5mg for 12 months by lottery method. Randomization was done by a person independent of the investigators. As it was an open label trial, the patient and the investigators who assessed the outcomes were not blinded about the treatment.

A standard protocol was used for all our patients. Patients were evaluated with detailed history regarding LUTS. Clinical and digital rectal examination was done. LUTS was assessed using the IPSS questionnaire (English and native language Bangale). Uroflowmetry (UFR) Ultrasound of the Kidney, Ureters, Bladder (KUB) and Prostate, with PVR, Serum Prostate Specific Antigen (PSA) Blood urea, Serum Creatinine, Blood Pressure (BP) in supine and standing position and Electrocardiogram were done in all patients at the beginning of the study. Follow-up was done at 3, 6, 9 and 12 months with LUTS assessment using IPSS, Qmax using UFR and US for PVR and side effects of each drug and BP in supine and standing positions.

The primary end points were improvement in IPSS LUTS scores, Qmax and PVR from baseline at 3, 6, 9 and 12 months. The secondary endpoints were ADE to the drugs.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) version 12 for Windows. The variables were summarized using mean, standard error, median, and percentages based on the characteristics of the variable. Student t test was used for the analysis of continuous variables. Chi-Square test was used for categorical variables. The p value of <0.05 was considered statistically significant.

Results

Table I : Baseline characteristics

Parameters	Group A (n=30)	Group B (n=30)	p value
Age, years			
Mean ±SD	63.3±12.99	65.0±10.02	0.122 NS
IPSS			
Mean ±SD	16.8±2.85	16.5±2.39	0.660 NS
QoL			
Mean ±SD	2.40 ±0.86	2.37 ±0.89	0.460 NS
Qmax, ml/sec			
Mean ±SD	11.6±2.09	11.0±1.82	0.226 NS
PVR, cc			
Mean ±SD	72.2±20.87	73.3±21.62	0.842 NS
Prostate weight, cc			
Mean ±SD	59.55±8.83	66.2±9.47	0.008 S
Serum creatinine, mg/dl			
Mean ±SD	1.01±0.89	1.03±0.78	0.580 NS

NS: Not significant in student t test, S: Significant in student t test
Group A: Alfuzosin (10mg) Group B: Alfuzosin (10mg) with Finasteride (5mg)

Table II : IPSS in Alfuzosin and Alfuzosin plus Finasteride at 3, 6, 9 and 12 months

IPSS (Points)	Group A (n=30) Mean ±SD	Group B (n=30) Mean±SD	p value
3 months	8.2±2.68	7.6±1.38	0.276 NS
6 months	7.7±1.64	7.0±1.20	0.071 NS
9 months	7.0±1.02	7.1±0.96	0.687 NS
12 months	6.8±1.10	6.5±0.82	0.232 NS

NS: Not significant in student t test

Table III : Qmax in Alfuzosin and Alfuzosin plus Finasteride at 3, 6, 9 and 12 months

Qmax (ml/s)	Group A (n=30) Mean±SD	Group B (n=30) Mean±SD	p value
3 months	14.1±1.24	13.9±0.84	0.472 NS
6 months	15.2±0.61	15.1±0.96	0.635 NS
9 months	15.3±0.47	15.6±1.06	0.162 NS
12 months	15.3±0.79	15.8±1.42	0.114 NS

NS: Not significant in student t test

Table IV : PVR in Alfuzosin and Alfuzosin plus Finasteride at 3, 6, 9 and 12 months

PVR (ml)	Group A (n=30) Mean±SD	Group B (n=30) Mean±SD	p value
3 months	50.3±10.31	51.3±11.87	0.740 NS
6 months	50.2±9.24	49.1±8.90	0.644 NS
9 months	50.1±8.19	50.5±7.33	0.812 NS
12 months	49.8±7.61	49.7±7.05	0.955 NS

NS: Not significant in student t test

Table V : Prostate volume in Alfuzosin and Alfuzosin plus Finasteride at 3, 6, 9 and 12 months

Prostate volume (cc)	Group A (n=30) Mean±SD	Group B (n=30) Mean±SD	p value
3 months	58.95±8.12	52.90±9.01	0.006 S
6 months	58.90±7.97	51.81±8.93	0.002 S
9 months	58.95±7.83	51.78±8.89	0.002 S
12 months	58.90±7.91	51.07±8.94	0.001 S

S= significant in student t-test

Table VI : Effect of Alfuzosin (10mg) on IPSS, Qmax, PVR and prostate volume over time

	Percentage (%) of change from baseline (Mean ± SD)				p value
	3 months	6 months	9 months	12 months	
IPSS	51.2±5.13	54.2±4.72	58.3±5.56	59.5±5.26	0.001*
Qmax	21.6±3.53	31.0±7.43	31.9±5.37	31.9±6.29	0.001*
PVR	30.3±26.50	30.5±29.07	30.6±26.53	31.0±29.59	0.001*
Prostate volume	1.00±1.51	1.10±1.43	1.00±1.39	1.10±1.63	>0.05†

* Significant in Paired t test † Non significant in Paired t test

Table VII : Effect of Alfuzosin (10mg) and Finasteride on IPSS, Qmax, PVR and prostate volume over time

	Percentage (%) of change from baseline (Mean ± SD)				p value
	3 months	6 months	9 months	12 months	
IPSS	53.9±5.47	57.6±6.41	57.0±4.76	60.6±5.53	0.001*
Qmax	26.4±3.65	37.3±4.72	46.4±5.51	43.6±6.17	0.001*
PVR	30.0±23.51	33.0±28.47	31.1±26.59	32.2±23.48	0.001*
Prostate volume	20.1±13.50	21.7±14.45	21.8±16.59	22.9±18.39	0.001*

* Significant in Paired t test

Table VIII : Adverse effects to Alfuzosin and Alfuzosin plus Finasteride at 3, 6, 9 and 12 months

Adverse effect	Time	Group A n (%)	Group B n (%)	p value
Hypotension	3 month	3(10%)	2(6.7%)	>0.05*
	6 month	2(6.7%)	3(10%)	>0.05*
	9 month	1(3.3%)	1(3.3%)	>0.05*
	12 month	2(6.7%)	2(6.7%)	>0.05*
Dizziness	3 month	14(46.7%)	15(50%)	>0.05*
	6 month	15(50%)	14(46.7%)	>0.05*
	9 month	16(53.3%)	17(56.7%)	>0.05*
	12 month	14(46.7%)	15(50%)	>0.05*
Headache	3 month	5(16.7%)	6(20%)	>0.05*
	6 month	3(10%)	4(13.3%)	>0.05*
	9 month	4(13.3%)	4(13.3%)	>0.05*
	12 month	5(16.7%)	4(13.3%)	>0.05*
Abnormal ejaculation	3 month	3(10%)	3(10%)	>0.05*
	6 month	1(3.3%)	4(13.3%)	>0.05*
	9 month	1(3.3%)	4(13.3%)	>0.05*
	12 month	1(3.3%)	2(6.7%)	>0.05*

* Not significant in Chi square test

For the purpose of tabulation and analysis, the groups were denoted as, Group A receiving 10 mg of Alfuzosin and Group B receiving 10 mg of Alfuzosin plus 5 mg of finasteride. The baseline patient characteristics like Age, Prostate volume, Qmax, and PVR were comparable (Table I).

The mean IPSS scores at baseline were comparable between the two groups (Table I; p = 0.66). At follow-up at 3 months, 6 months and 12 months the maximum improvement was observed in Group B and at end of the 9 month, the maximum improvement was seen in Group A, however, these did not reach statistical significance (p > 0.05) (Table II).

The mean Qmax at baseline was comparable between the three groups (Table I, p = 0.276). At follow-up, there were significant changes from base line in both groups, but the differences between groups were not statistically significant at all four intervals. (Table III)

The PVR was similar in the two groups at baseline. Though the PVR was reduced in both groups significantly from baseline, the inter group differences were not statistically significant at any follow up (Table IV).

The mean prostate volume was significantly higher in Group B at baseline (59.55±8.83 cc vs. 66.20±9.47 cc) (p=0.008) (Table I). After 12 months of treatment there was no significant change in volume in Group A, but it decreased significantly in Group B at 3 months and it persists till end of the trial (Table V).

The mean IPPS (Points) Qmax, and PVR were statistically significant (p<0.05) between baseline and each follow-up in Group A patients. The prostate volume did not show any significant change (Table VI).

The mean IPPS (points), Qmax, PVR and prostate volume were statistically significant (p<0.05) between baseline and each follow-up in group B patients (TableVII).

Adverse Drug Events (ADEs) were observed in 34 out of 60 patients (61.4%). Dizziness was the most common side effects in both groups. Other common ADEs were headache, hypotension and abnormal ejaculation. The incidence of ADE reduced with progression of time. However, there was no statistically significant difference at any point of time between the two groups (Table VIII).

Discussion

There is scarcity of studies in literature comparing the two regimens: Alfuzosin and Alfuzosin plus Finasteride in the medical management of LUTS due to BPH. We administered these regimens in symptomatic LUTS due to BPH in 60 patients for 12 months and observed for improvements in IPSS, Qmax, PVR, prostate volume and also for ADE. Robert et al recommended newer drugs and combination therapies like AB with 5ARI. They however suggested that selection of therapy is to be individualized[10]. Wang et al assessed the effect of alpha adrenoceptor antagonists, 5-alpha reductase inhibitors, and muscarinic receptor antagonists in a meta-analysis on 29,384 patients[11]. Yuan et al assessed the effect of AB, 5ARI, Muscarinic Receptor Antagonists (MRA) in a large number of patients. They found that AB and 5ARI were the most effective agents[12]. They also concluded that medical therapy in BPH is safe and drugs have a comparable ADE profile[3].

We observed that Alfuzosin alone or Alfuzosin plus Finasteride combination had significant improvement in IPSS scores at 3 months of treatment. Zhang et al observed Alfuzosin 10 mg to be effective and well tolerated in LUTS due to BPH with or without antihypertensive medications[13]. National PBM Drug monograph (2004) reported that the mean IPPS was 17.3±3.5 points during baseline and after three months treated by Alfuzosin the mean IPPS was 10.4±4.7 points, which is comparable with the present study. Van et al showed the improvement in IPPS was statistically greater with Alfuzosin bid alone (6.3±5.8) and in Finasteride (5.2±5.7) respectively[14]. Hofner showed in his study that mean changes in IPSS were significantly higher with Alfuzosin, alone (6.3) which is consistent with the present study[15].

In our study, Qmax improvement was the maximum after first three months with both regimens and the changes persisted for rest of the study period. Roehrborn, found in their studies that Qmax increased 2.3 ml/s from baseline in Alfuzosin treated group[16]. Similar finding was observed by Lee et al where they found Qmax increased 2.7 ml/s from baseline in this group[17]. The result obtained in the current study is comparable with the above mentioned study. Kirby et al showed in their study that combined therapy produce statistically significant (p<0.05)

improvements in total Qmax[18]. Hofner reported in their patients likely to be obstructed, increases in Qmax were significantly higher in both groups (2.9 ml/s) which is closely resemble with the present study[15].

The mean PVR (ml) decreased after receiving treatment in both group in three months follow-up and the remaining follow-up PVR change was almost steady between both groups. No statistically significant ($p>0.05$) difference were observed between two groups of patients in each follow-up. Djavan et al showed 30.0% reduction in PVR after treated by Alfuzosin, which closely resemble with the present study[19].

The primary specific ADE reported for AB was dizziness, headache and asthenia. However, we observed that ADE was almost similar in both groups. Zhang et al observed that Alfuzosin with antihypertensive medication decreases systolic and diastolic blood pressure. Orthostatic hypotension was observed only with tamsulosin in 3% patients, but not with Alfuzosin and silodosin[13]. The incidence of dizziness, orthostatic hypotension and cardiovascular ADE was similar to placebo[20]. In different studies dizziness was the most significant side effect in Alfuzosin-treated patients and hypotension were approximately 1%, dizziness 5.7%, upper respiratory tract infection 3.0% with Alfuzosin[14]. Hofner showed postural hypotension, asthenia and dizziness with the sustained-release formulation of Alfuzosin alone, which is completely devoid of cardiovascular effects[15]. Regarding the adverse effects in this study it was found that hypotension, dizziness, headache, abnormal ejaculation and others were found in both groups, but no statistically significant ($p<0.05$) difference was found between two groups.

Conclusion

In this comparative study, the combination of Alfuzosin and Finasteride was no more effective than Alfuzosin alone with regard to both primary outcome measures symptom scores and urinary-flow rate. Moreover, there was no statistically significant difference in ADE rates between two regimens. However, large, multicentered, double-blind, placebo-controlled, randomized trials are needed to establish the effect of this regimens in the treatment of LUTS due to BPH. The persistency of the treatment effects will have to be addressed with more frequent and longer follow up period.

Disclosure

All the authors declared no competing interest.

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