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Pharmacology

A Comparative Study to Monitor the Efficacy and Tolerability in Benign Prostatic Hyperplasia Patients Treated With Tamsulosin or Alfuzosin

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Abstract		Original Research Article

Introduction: Alpha1-Adrenoceptor antagonists are now well established as the most common treatment for lower urinary tract symptoms (LUTS) suggestive of bladder outflow obstruction associated with benign prostatic hyperplasia (BPH). We compared the incidence of postural hypotension symptoms BPH treated with tamsulosin or alfuzosin. *Material and methods:* A single centre, open label, double arm, observational study to evaluate International Prostatic Symptom Scored (IPSS) LUTS scores, quality of life (QoL), Maximum flow rate (Qmax) and post void residue (PVR) from baseline at 1st day, after 1 month and 2 after months. The secondary endpoints were ADE to the drugs. This is comparative study was conducted on patient attending urology department with BPH. A total number of 60 patients were divided into two arms, one arm received Tamsulosin (10mg) and the other arm received Alfuzosin (0.4mg). The study design was mainly based on the analysis of questions answered by each patient for the occurrence of the symptoms. Patients were enrolled in this study according to the following Inclusion/Exclusion criteria. *Results: During* the analysis of the study, the data generated showed that the percentage IPSS, QOL, Qmax and PVR showed significant improvement in Alfuzosin after 1 & 2 months. Adverse drug events (ADE) were observed in 45% (27/60) patients, most importantly occurrence of *postural* hypotension symptoms was found to be more in subjects treated with Alfuzosin as *compared to that of* Tamsulosin. *The various postural hypotension symptoms* observed were dizziness, bodily dissociation, lightheadedness, nausea, headache, blurred or dimmed vision and fainting. *Conclusions:* It was found that Tamsulosin and Alfuzosin were both well tolerated. In the present study, most efficacious Alfuzosin with rapid onset of action. Alfuzosin also improves the quality of life in patients with LUTS due to BPH and objectively improves maximum flow rate. It was also observed that the percentage occurrence of the postural hypotension symptoms was more in the subjects receiving Alfuzosin than the ones receiving Tamsulosin.
Keywords: Alfuzosin, Tamsulosin and benign prostatic hyperplasia.

INTRODUCTION

In both ageing men and women, lower urinary tract symptoms (LUTS) are increasing. These infections have many possible causes, including smooth muscle dysfunction, neurological factors and benign prostatic hyperplasia (BPH). Up to 15% to 25% of men aged 50-65 years have LUTS of sufficient severity to interfere with their quality of life [1].

The prostate is part of the male reproductive system. Prostate enlargement is very common as men age - symptoms usually develop around age 50 and by age 60, most men have some degree of BPH. At age 85, men have a 90% chance of having urination problems caused by BPH. It's important to note that BPH is not cancer, and it does not put you at increased risk for developing prostate cancer [2].

Benign prostatic hyperplasia (BPH) is a complex disease that is progressive in many men. BPH is commonly associated with bothersome lower urinary tract symptoms [3]. BPH is a pathologic disorder that develops in response to the action of dihydrotestosterone on the aging prostate and to changes in stromal and epithelial cells in this exocrine gland. Mild to moderate symptoms can be controlled, at least temporarily, with a-adrenergic blockers [4]. As the elderly constitutes the major proportion of the

population, this results in a major impact on the medical practice nowadays [5].

The enlargement of the prostate can produce voiding symptoms, which can lead to pathological changes in the urinary bladder and the kidney. Management of BPH has also changed significantly with a considerable advance in the understanding of the demographics and natural history of the disease [6].

The pharmacotherapy of BPH comprises of alpha-1 receptor antagonists, 5-alpha reductase inhibitors, Gonadotropin releasing hormone analogues and androgen receptor blockers [7]. Alpha blockers begin to work quickly and are usually recommended as a first-line treatment for men with mild to moderate symptoms [8].

Tamsulosin is a subtype-selective alpha (lA)- and alpha (lD)-adrenoceptor antagonist. Alpha(l)-receptors predominate in the prostate gland, prostatic capsule, prostatic urethra and bladder, and the relaxation of prostate and bladder smooth muscles is associated with improved maximal urine flow (Q(max)) and alleviation of lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH). Tamsulosin 0.4 mg once daily in a modified-release formulation increased Q (max) and improved symptom scores. Tamsulosin is effective in patients with mild to severe LUTS associated with BPH, in patients with diabetes mellitus and in the elderly, and does not interfere with concomitant antihypertensive therapy [9]. Tamsulosin is an improvement over other alpha-adrenergic antagonists for the management of symptoms of benign prostatic hyperplasia. It is a more convenient alternative that does not require initial dosage titration, has a fast onset of action, and has a low potential to cause hypotension when used alone or in combination with commonly used antihypertensive agents. It is costlier than some of the other second-generation alpha-adrenergic antagonists [10].

Alfuzosin is used in men to treat symptoms of an enlarged prostate (benign prostatic hyperplasia or BPH), which include difficulty urinating (hesitation, dribbling, weak stream, and incomplete bladder emptying), painful urination, and urinary frequency and urgency. It works by relaxing the muscles in the prostate and bladder to allow urine to flow more easily [11]. A once-daily formulation of alfuzosin has recently been developed in order to improve the convenience of dosing and to provide optimal pharmacokinetic coverage over a 24-h period. In addition, alfuzosin is the only alpha 1-blocker that has demonstrated a significant decrease in post-void residual urine, a known risk factor for acute urinary retention, as well as the incidence of acute urinary retention [12].

According to the data available, a higher rate of vasodilatory, cardiovascular side effects (dizziness, fatigue, and hypotension) is observed with terazosin and doxazosin, when compared with the alfuzosin and tamsulosin. Of the latter two, hypotension was more frequent with alfuzosin, while ejaculatory dysfunction was more frequent with tamsulosin. In conclusion, each of the four medications is a possible treatment option for BPH, but it is believed that alfuzosin and tamsulosin are the better choice. In light of an identical efficacy, these medications offer better tolerability, and ease of use of a once daily treatment without dose titration. The choice between the two should be tailored to the individual patient, with alfuzosin associate with hypotensive side effects, and tamsulosin causing ejaculatory dysfunction [13].

The standard medical therapy for symptomatic benign prostatic hyperplasia is alpha-blockers and 5-alpha-reductase inhibitors. Ongoing studies demonstrate the long-term safety and efficacy of these two classes of therapeutic approaches [14].

Hence, the present study of comparing the above two drugs for the improvement in International Prostatic Symptom Scored (IPSS) LUTS scores, quality of life (QoL), Maximum flow rate (Qmax) and post void residue (PVR) from baseline at 1st day, after 1 month and 2 after months. The secondary endpoints were ADE to the drugs.

STUDY DESIGN

This is comparative study was conducted on patient attending medicine department of NC Medical & Hospital with BPH. The study was carried out as per the ICH, 'Guidance for Good Clinical Practices (GCP)' and the principles of Declaration of Helsinki. The Independent Ethics Review Committee (IERC) has reviewed and approved the protocol synopsis and the Informed Consent Form (ICF).

A single center, open label, double arm, observational study to evaluate the occurrence of postural hypotension symptoms in patients with benign prostatic hyperplasia was used. Patients were divided into two arms, one arm received tamsulosin (10mg) and the other arm received alfuzosin (0.4mg). The study design was mainly based on the analysis of questions answered by each patient for the occurrence of the symptoms.

STUDY POPULATION

A total number of 60 patients who were being prescribed alfuzosin or tamsulosin were selected for the study. The informed consent of each patient was taken prior to their enrollment in the study- Thereafter, the inclusion-exclusion criteria of the patients were checked and found to be in accordance with that mentioned in the protocol approved by IERC. The past medical history of the patients was duly recorded in the Case Report Form (CRF).

Patients were enrolled in this study according to the following Inclusion/Exclusion criteria

Inclusion Criteria
- Male patients above 45 years of age.
- Patients showing lower urinary tract symptoms (LUTS).
- Patients willing to participate in the study.
- All newly diagnosed and old patients receiving tamsulosin or alfuzosin.

Exclusion Criteria
- Patients below 45 years of age.
- Patients which have been previously operated for prostate surgery.
- Patients having CA prostate.
- Patients participating in other clinical trial.
- Patients having any kind of disorder that hinders the subject to give written informed consent and/or to comply with study procedures.
- Any major medical or psychiatric disorder that may prevent the subject from completing the study or showing interference with the interpretation of the study results.
- Over prescribing, over dosage, and excess consumption.
- Unconscious patients and those unable to respond to verbal questions will also excluded from the study.

DATA COLLECTION

A proforma containing detailed information on each patient was prepared according to the protocol designed for the study. Informed consent was taken from all the patients included in the duty

Relevant data were taken from the patients with benign prostatic hyperplasia. The data included name, address, age of the patient, date of birth and history of presenting illness. The proforma also enlisted general clinical examination like blood pressure, pulse and abdomen examination including digital per rectal examination and urological examination including urine routine, ultrasound and serum prostate specific antigen (PSA).

The ultrasonography investigations were done to measure the size of the prostate and post void residual urine (PVR).

The assessment of the symptoms was done by using International Prostatic Symptom Scored (IPSS) which was given to patient on the very first visit to the OPD. The severity of LUTS was also assessed by the IPSS, based on the answers to seven questions regarding urinary symptoms (incomplete emptying, frequency, intermittency, urgency, weak stream, straining, and nocturia). The seven questions were as follows:

- Incomplete emptying: How often have you had the sensation of not emptying your bladder?
- Frequency: How often have you had to urinate less than every 2 h?
- Intermittency: How often have you found you stopped and started again several times when you urinated?
- Urgency: How often have you found it difficult to postpone urination?
- Weak stream: How often have you had a weak urinary stream?
- Straining: How often have you had to strain to start urination? (scores: 0 - not at all; 1 - <1 in 5 times; 2 - less than half the time; 3 - about half the time; 4 - more than half the time; 5 - almost always) •
- Nocturia: How many times did you typically get up at night to urinate? (scores: 0 - none; 1 - 1 time; 2 - 2 times; 3 - 3 times; 4 - 4 times; 5 - 5 times)
- (total IPSS score: 1–7: Mild; 8–19: Moderate: 20–35: Severe)
- QOL: If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about it?
- (QLSs based on Likert scale: 0 - delighted; 1 - pleased; 2 - mostly satisfied; 3 - mixed; 4 - mostly dissatisfied; 5 - unhappy; 6 - terrible). The QLS is used to assess the impairment in QOL due to urinary symptoms.
- The drugs i.e. Alfuzosin 10 mg or Tamsulosin 0.4 mg once daily were given to the patients randomly. The patients were advised to come for the follow up after first month of the treatment. The occurrence of the postural hypotension symptoms, if present was noted.

Study Endpoints
The primary endpoints were improvement in IPSS LUTS scores, QoL, Qmax in ml/s and PVR from baseline at 1st day, after 1 month and 2 after months. The secondary endpoints were ADE to the drugs.

Statistical Analysis
Data was analyzed by SPSS 24th version software. The variables were summarized using mean and standard deviation based on the characteristics of the variable. Oneway ANOVA and the Kruskal-Wallis test were used as appropriate for the analysis of continuous variables based on the normality of the distribution. Chi-Square test was used for categorical variables. The p value of <0.05 was considered statistically significant. Postural hypotension symptoms were analyzed by using percentile for the percent of the occurrence of the postural hypotension symptoms. The result was expressed as percentage and conclusions were drawn from the same.

RESULT

In this study, total 60 subjects were involved with 30 in each treatment arm for the comparison, there were no drop-outs or protocol violations during the study.

Table-1: Comparison of Alfuzosin and Tamsulosin in benign prostatic hyperplasia: Demographic and baseline characteristics of the study subjects

Parameters	Alfozosin	Tamsulosin
Age (years) Mean ± SD	62.23 ± 7.82	61.98 ± 6.81
Weight (kg) Mean ± SD	66.33 ± 6. 21	68.83 ± 6.35
Height (cm) Mean ± SD	165.23 ± 7.32	167.33 ± 8.31
Serum Creatinine in mg/dl Mean ± SD	0.93 ± 0.12	0.90 ± 0.11
PSA in ng/ml Mean ± SD	2.31 ± 0.24	2.42 ± 0.27

Table-1 shows the baseline demographic and clinical characteristics of the study subjects. Mean age of patients were 62.23 ± 7.82 and 61.98 ± 6.81 years (mean ± standard deviation [SD]) Alfozosin and Tamsulosin respectively.

Table-2: Comparison of IPSS treatment with Alfozosin and Tamsulosin at baseline, after 1 month and after 2 months

Duration	Alfozosin Mean ± SD	Tamsulosin Mean ± SD	p value
Baseline	18.93 ± 5.12	18.31 ± 5.31	0.832[ns]
After 1 month	14.01 ± 4.03	15.52 ± 4.56	0.047[s]
After 2 months	11.23 ± 3.78	12.64 ± 3.03	0.012 [s]

Ns: not significant, S: significant

IPSS

In Table-2 the mean and SD of IPSS scores at baseline were comparable between the two groups Alfozosin and Tamsulosin (18.93± 5.12 Vs 18.31 ± 5.31, p = 0.832). At follow-up at after 1 month (14.01 ± 4.03 Vs 15.52 ± 4.56, p = 0.047) and after 2 months (11.23 ± 3.78 Vs 12.64 ± 3.03, p = 0.012) the maximum improvement was observed in Afluzosin and this was statistically significant. At end of the first month and after 2 months.

Table-3: Comparison of QoL treatment with Alfozosin and Tamsulosin at baseline, after 1 month and after 2 months

Duration	Alfozosin	Tamsulosin	p value
Baseline	3.81 ± 0.83	3.72 ± 0.71	0.730
After 1 month	3.03 ± 0.78	3.31 ± 0.64	0.042[s]
After 2 months	2.37 ± 0.53	2.83 ± 0.48	0.008[s]

In Table-3 the mean QoL scores at baseline were comparable between the two groups Alfozosin and Tamsulosin (3.81 ± 0.83 Vs 3.72 ± 0.71; p = 0.730) at baseline. After 1 month between two groups (3.03 ± 0.78 Vs 3.31 ± 0.64, p = 0.042) and After 2 months (2.37 ± 0.53 Vs 2.83 ± 0.48, p =0.008), improvement in QoL was the maximum in Afluzosin Group and this was statistically significant.

Table-4: Comparison of Qmax treatment with Alfozosin and Tamsulosin at baseline, after 1 month and after 2 months

Duration	Alfozosin	Tamsulosin	p value
Baseline	13.63 ± 0.74	13.81 ± 0.79	0.843
After 1 month	15.03 ± 0.93	14.23 ± 0.73	0.048[s]
After 2 months	15.87 ± 1.35	14.83 ± 1.55	0.006[s]

In Table-4, the mean Qmax at baseline was comparable between Alfozosin and Tamsulosin groups (13.63 ± 0.74 Vs 13.81 ± 0.79, p = 0.843). At follow-up, the improvement was the maximum in Alfozosin and it was statistically significant at after 1 month (15.03 ± 0.93 Vs 14.23 ± 0.73, p = 0.048). At after 2 months after starting the drug, the improvement was the maximum in Alfozosin; however, it was statistically significant.

Table-5: Comparison of PVR treatment with Alfozosin and Tamsulosin at baseline, after 1 month and after 2 months

Duration	Alfozosin	Tamsulosin	p value
Baseline	34.52 ± 9.63	34.01 ± 9.54	0.936
After 1 month	27.21 ± 8.86	27.89 ± 7.67	0.719[ns]
After 2 months	21.73 ± 6.26	22.03 ± 5.42	0.593[ns]

In Table-5, the PVR was similar in two groups at baseline. Though the PVR was reduced in Alfozosin at after 1 and 2 months, but when it was compared between in two groups it was not significant.

Adverse Drug Reaction (ADR)

ADR was seen in 27 patients out of 60 patients. Upper respiratory tract infection was the most common AE (n = 6 and 4 with alfuzosin and tamsulosin respectively) followed by dizziness (n = 5 and 2 with alfuzosin and tamsulosin respectively). 1 patients with alfuzosin and 2 patients with tamsulosin had a significant QTc prolongation (>45 ms). The incidence of ejaculatory dysfunction was seen in tamsulosin (n = 2). 2 patients tamsulosin and 3 patients alfuzosin group had orthostatic hypotension. Compliance, as mentioned in methodology section, was assessed by daily drug reminder chart and pill count method.

DISCUSSION

There are no studies in literature comparing the following two drugs: Alfuzosin and Tamsulosin, in the medical management of LUTS due to BPH. We administered these two drugs as monotherapy in symptomatic LUTS due to BPH in 30 patients in each and observed for improvements in IPSS, QoL, Qmax, PVR and also for ADE.

We observed that two drugs had improvement in IPSS scores and it was the maximum with Alfuzosin.

In our study, the maximum improvement in QoL with Alfuzosin. In addition, Qmax improvement was the maximum at baseline with Alfuzosin. In the following weeks, similar Qmax improvement was observed in two drugs. We observed that although the baseline IPSS scores were comparable between two groups, it was lower among patients of the Alfuzosin arm.

Benign prostatic hyperplasia is one of the most common conditions affecting elderly males with are resultant impact on the medical practice as the elderly constitute an increasing population not in India but also throughout the world. A decade back, surgery and watchful-waiting were only accepted management options for BPH. Recently, there has been a drastic decline in the surgery as medication has become the pioneer for the treatment of BPH and this has been a major change in urological clinical practice.

Alpha-l blockers have become the major drugs for BPH, among which Alfuzosin has been claimed to be uroselective Alpha-1 blocker and Tamsulosin is Alpha-lA prostate specific blocker.

The adverse effect of alpha blockers i.e. postural hypotension is under study. The following symptoms can occur after sudden standing or stretching (after standing): Dizziness, Euphoria or dysphoria, Bodily dissociation, Distortions in hearing, Lightheadedness, Nausea, Headache, Temporary decrease in hearing, Blurred or dimmed vision, Seizures, Generalized (or extremity) numbness/tingling and fainting. Coat hanger pain (pain centered in the neck and shoulders) and in rare, extreme cases, vasovagal syncope.

In our study, we have compared the occurrence of postural hypotension symptoms in 30 subjects treated with Alfuzosin 10mg once daily with the 30 subjects treated with Tamsulosin 0.4mg once daily.

It was found that Tamsulosin and Alfuzosin were both well tolerated. In the present study, it was also observed that the percentage occurrence of the postural hypotension symptoms was more in the subjects receiving Alfuzosin than the ones receiving Tamsulosin. The percentage occurrence of the postural hypotension symptoms in Tamsulosin was observed to be 6.66% which was nearly the same as in observational cohort study of over 10,000 patients by Mann RD *et al.*, [15]. The percentage occurrence of the postural hypotension symptoms in the subjects receiving Alfuzosin was found to be 10% which was nearly the same to the value observed in the study carried out on 360 patients by Van Kerrebroec P *et al.*, [16].

Another study conducted by Nordling J compared both these drugs and concluded that doses of Alfuzosin and Tamsulosin were well tolerated, with dizziness the most frequent adverse event /placebo, 4%;

alfuzosin 10 mg, 6%; 15 mg, 7%; tamsulosin, *2%)* [17]. According to the study by Lee M., Tamsulosin has low potential to cause hypotension when used alone or in combination [18].

With the limited study period, as in the present study, it may be concluded that either of the two drugs may be used in BPH with almost equal effectiveness, except better tolerability of tamsulosin because of lesser occurrence of postural hypotension symptoms than Alfuzosin.

The standard medical therapy for symptomatic benign prostatic hyperplasia is still alpha- blockers and 5-alpha-reductase inhibitors. Many ongoing studies have demonstrated the longterm safety and efficacy of these two classes of therapeutic approaches. Although there have been no new Food and Drug Administration approved medical therapies for the treatment of benign prostatic hyperplasia over the past year, interest in and the use of alpha blockers continues to increase.

CONCLUSION

From the above study, Alfuzosin is the most efficacious drug with a rapid onset of action and had consistent improvement in LUTS after 2 months in Indian men. Alfuzosin also improves the quality of life of patient with LUTS due to BPH and objectively improves maximum flow rate. However, Alfuzosin has more adverse events when compared to tamsulosin.

It can be also concluded that, the frequency of postural hypotension symptoms attributed to Alfuzosin and Tamsulosin showed significant difference (10% and 6.66%, respectively). It was observed that both the treatment arms had low percentage rates of postural hypotension symptoms.

The results of the study showed that Tamsulosin 0.4mg once daily and Alfuzosin 10 mg once daily in the treatment of BPH were well tolerated, thus maintaining the improvement in the lower urinary tract symptoms.

However, Alfuzosin significantly showed a greater occurrence of postural hypotension symptoms when analysed with Tamsulosin.

REFERENCES

1. Thorpe A, Neal D. Benign prostatic hyperplasia. The Lancet. 2003; 361(9366):1359 1367.
2. Benign Prostatic Hyperplasia. http://umm.edu/health/medical/altmed/condition /bemgn ~ pros —hyperplasia, doa-4/1/2014.
3. Emberton M, Cornel EB, Bassi PF, Fourcade RO, Gomez JM, Castro R. Benign prostatic hyperplasia as a progressive disease: a guide to the risk factors and options for medical management. International journal of clinical practice. 2008 Jul;62(7):1076-

1086.

4. Steers WD, Zorn B. Benign prostatic hyperplasia. Elsevier. 1995; 41(7):437-497.

5. Marberger M, Harkaway R. Optimising the medical management of benign prostatic hyperplasia. European urology. 2004 Apr;45(4):411-9.

6. Tanaka Y, Masumori N, Itoh N, Sato Y, Takahashi A, Ogura H, Furuya S, Tsukamoto T. Urodynamic effects of terazosin treatment for Japanese patients with symptomatic benign prostatic hyperplasia. The Journal of urology. 2002 Jun;167(6):2492-2495.

7. Höfner K, Jonas U. Alfuzosin: a clinically uroselective α 1-blocker. World journal of urology. 2002 Apr 1;19(6):405-412.

8. Patient information: Benign prostatic hyperplasia (BPH) (Beyond the Basics). http://www.uptodate.com/contents/benign-prostatic-hyperplasia-bph-beyond-th basics. doa-7/1/2014.

9. *Dunn CJ,* Matheson A, Faulds DM. Tamsulosin: a review of its pharmacology and therapeutic efficacy in the management of lower urinary tract symptoms. Drugs Aging. 2002; 19(2): 135-161.

10. *Lee M. Tamsulosin* for the treatment of benign prostatic hypertrophy. Ann Pharmacother. 2000*;34(2): 188-199.*

11. *Alfuzosin.* *2012* http://www.nim.nih.gov/medlineplus/druginfo/meds/a604002. *Html doa 12/1/2014.*

12. Hofncr K, Jonaw U. Alliizonin: a clinically uroseleclive alpha I -blocker. World *I* Urol. 2002; l9(6):405-412.

13. Bar-Yosef Y, Mabjcesh NJ, Laufer M, Neulander EZ, Kaver I, Matzkin H. Alpha blockers in or symptomatic benign prostatic hyperplasia—are all drugs bom equal?. Harefuah. 2008; 147(6):514-519.

14. Cuellar DC, Kyprianou N. Future concepts in the medical therapy of benign prostatic hyperplasia. Current opinion in urology. 2001 Jan 1;11(1):27-33.

15. Mann RD, Biswas P, Freemantle S, Pearce G, Wilton L. The pharmacovigilance of tamsulosin: event data on 12 484 patients. BJU international. 2000 Mar;85(4):446-450.

16. Van Kerrebroeck P, Jardin A, Van Cangh P, Laval KU, ALFORTI Study Group. Long-term safety and efficacy of a once-daily formulation of alfuzosin 10 mg in patients with symptomatic benign prostatic hyperplasia: open-label extension study. European urology. 2002 Jan 1;41(1):54-61.

17. Nordling J. Efficacy and safety of two doses (10 and 15 mg) of alfuzosin or tamsulosin (0.4 mg) once daily for treating symptomatic benign prostatic hyperplasia. BJU international. 2005; 95(7):1006-12.

18. Lee M. Tamsulosin for the treatment of benign prostatic hypertrophy. Ann Pharmacother. 2000 Feb; 34(2): 188-99.