Original Article

A comparison of the efficacy of naftopidil and tamsulosin hydrochloride in medical treatment of benign prostatic enlargement

Chenthil Perumal, Puskar Shyam Chowdhury, N. Ananthakrishnan, Prasant Nayak, Srinivasan Gurumurthy

Department of Urology, MGMC and RI, Puducherry, India

Abstract

Introduction: Lower urinary tract symptoms in men, over age of 50 years is suggestive of benign prostatic enlargement (BPE). Different alpha-blockers have been evaluated for the treatment of benign prostatic hyperplasia for over last 30 years. This study was conducted in a tertiary care institution during the period of year between June 2011 and August 2013 to compare the effect of naftopidil and tamsulosin in reducing the obstructive and irritable symptoms of BPE.

Subjects and Methods: A prospective randomized comparative study was carried on 60 patients of BPE by assigning half of them to treatment with tamsulosin and rest with naftopidil. Pre- and post-treatment uroflowmetry (UFM), post-void residue (PVR), International Prostate Symptoms Score (IPSS), were obtained at 15 and 30 days after starting treatment.

Results: The age of patients ranged from 51 to 78. At base line there was no statistical difference between UFM parameter, PVR and IPSS in the two groups. UFM and PVR showed significantly better response at both intervals with naftopidil. Comparison of IPSS showed better improvement in Group A both at 15 and 30 days. It was seen that the obstructive symptoms showed a significantly better response with tamsulosin and symptoms of irritability was seen better response with naftopidil.

Conclusion: It was seen that during the period of follow-up of 30 days naftopidil had a better effect on UFM, PVR, IPSS compared with tamsulosin. In general, obstructive symptoms showed better improvement in tamsulosin and irritative symptoms showed better improvement in naftopidil.

Key Words: Alpha-1D blockers, benign prostatic hyperplasia, lower urinary tract symptoms, naftopidil

Address for correspondence:
Dr. Chenthil Perumal, Department of General Surgery, MGMC and RI, Puducherry - 607 402, India. E-mail: drchen03@gmail.com
Received: 16.12.2013, **Accepted:** 10.02.2014

INTRODUCTION

Various alpha-blockers are being used for the treatment of benign prostatic hyperplasia (BPH) for the past 30 years.[1,2]

Access this article online	
Quick Response Code:	Website: www.urologyannals.com
	DOI: 10.4103/0974-7796.148624

Alpha-adrenoreceptor antagonists are the most common initial pharmacological treatment of benign prostatic enlargement (BPE).[3,4] Alpha-adrenoreceptor blockers have evolved from non-selective short-acting blockers to long-acting selective α_1 antagonists.[3] Three subtypes of alpha-1-adrenoreceptor have been identified, normally as α-1-A, α-1-B, α-1-D. Various α-1-adrenoreceptor antagonists are available world-wide for treating BPE with difference in selectivity for alpha receptor subtype with variation in efficacy and side-effect profile. Commonly used alpha blockers are tamsulosin (alpha 1a-receptor blocker) and alfuzosin (non-selective alpha 1blocker). Naftopidil is a novel alpha-blocker which exerts

its action by selective blockade of alpha-1D receptor.[5,6] However, the superiority of these agents over one another regarding clinical efficacy and adverse effects are yet to be established.[7-10] Most of the elderly men with BPE/lower urinary tract symptoms (LUTS) have storage symptoms more than the voiding symptoms, of which the most bothering symptoms of LUTS is Nocturia.[11] Interestingly, role of naftopidil in improving nocturia has been emphasized in certain studies. Alpha-1-adrenoreceptor reduces the storage symptoms probably by reducing bladder over activity by releasing of bladder outlet obstruction and blocking directly the unregulated α-1-D adrenoreceptor subtypes in detrusor muscle or spinal cord.[12-15] There is a paucity of data comparing standard doses for naftopidil and tamsulosin head to head in Indian subcontinent.

We therefore conducted a prospective randomized controlled study to compare naftopidil and tamsulosin hydrochloride, the current drug of choice for BPE and analyzed early outcomes with regard to changes in International Prostate Symptoms Score (IPSS), uroflowmetry (UFM) and post-void residual (PVR) volume at 15th and 30th day of treatment.

SUBJECTS AND METHODS

This study was performed after getting approval from the human ethical committee and the post graduate coordinating committee of Mahatma Gandhi Medical College and Research Institute, Pondicherry, India. A prospective randomized comparative study was carried out in patients, attending Out-Patient Department of General Surgery and Urology, Mahatma Gandhi Medical College and Research Institute from September 2011 to June 2013.

Men with age over 50 years with the clinical symptoms of BPE, LUTS, with or without raised PVR urine were included in the study. Patients with untreated urinary tract infection, palpable nodule in the prostate, associated upper urinary tract changes and prostate size greater than 60cc were excluded from the study.

All the patients participating in the study were informed about the merits and demerits of the study and informed consent was obtained. A total of 60 symptomatic cases of BPE were randomized into two groups of 30 patients each; patients who presented on odd numbered days were placed in Group A and were treated with naftopidil (50 mg), whereas, patients who presented on even number days were placed in study Group B and were treated with tamsulosin hydrochloride (0.4 mg). The drugs were administered once a day for 30 days. Prior to study, UFM was done to calculate the peak flow rate. Ultrasonography (USG) kidneys, ureters and bladder was carried out on all patients enrolled for the study to identify the prostate size and PVR.

Patients were followed-up at 15th and 30th days with reassessment of IPSS to identify response with regards to obstructive and irritative symptoms, USG was done to look for improvement in PVR volume and UFM was done to find out if there was any improvement inflow rate.

Statistical analysis was carried out using the Statistical softwares namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver. 2.11.1 and Microsoft word and Excel have been used to generate graphs, tables etc. Results on continuous measurements are presented on mean ± standard deviation (Min-Max) and results on categorical measurements are presented in number (%).

RESULTS

The mean age in Group A was 59.9 ± 5.5 years and was not significantly different from Group B which was 60.1 ± 5 years ($P = 0.864$). Majority of patients (96.7%) in Group A and all patients in Group B were in the 51-70 years age group.

Pre-treatment baseline data on UFM, PVR and IPSS are shown in Table 1. It was seen that there were no significant differences between Group A and Group B in any of the three parameters.

Table 2 depicts a comparative evaluation of data on UFM in the two groups at baseline and on follow-up at 15 and 30 days after treatment. It is seen from Table 2, both at 15 and 30 days, that the flow rates were significantly lower in Group B compared to Group A ($P < 0.001$**). Individually, it was seen in both Group A and Group B that there was

Table 1: Comparative evaluation of pre-treatment baseline in uroflowmetry, PVR, IPSS

Baseline parameters	Group A	Group B	*P* value
Uroflowmetry	8.12-9.15	7.91-8.82	0.430
PVR	94.62-103.78	98.86-106.94	0.220
IPSS	19.02-20.91	20.24-22.36	0.060#

PVR: Post-void residue, IPSS: International prostate symptoms score, #Suggestive of significance (*P>0.05, P<0.10*)

Table 2: Comparative evaluation of uroflowmetry in two groups studied

Uroflowmetry	Base line	15 days	30 days	*F* value	*P* value
Group A					
Mean±SD	8.63±1.38	14.30±0.70	17.83±0.83	775.77	<0.001**
95% CI	8.12-9.15	14.04-14.56	17.52-18.14		
Group B					
Mean±SD	8.37±1.22	12.43±1.31	15.57±0.94	693.42	<0.001**
95% CI	7.91-8.82	11.95-12.92	15.22-15.92		
P value	0.430	<0.001**	<0.001**	-	-

F values are obtained by repeated measures ANOVA, SD: Standard deviation, CI: Confidence interval. **Strongly significant (P≤0.01)

significant increase in flow rate after treatment both at 15 and 30 days. Of the two as mentioned above, the effect was better in Group A, where it showed marked improvement from a baseline value of 8.63 ± 1.38 ml to 17.83 ± 0.83 ml at 30 days compared with Group B in which the improvement was only from 8.37 ± 1.22 ml to 15.57 ± 0.94 ml.

Table 3 shows a comparison of PVR with treatment in Groups A and B. In Group A the mean PVR reduced from 99.20 ± 12.28 ml to 22.77 ± 5.32 ml at 30 days. This difference was statistically significant ($P < 0.001$**). In Group B, the baseline PVR showed improvement from 102.90 ± 10.81 to 27.13 ± 5.47 at 30 days. This again was significant. A comparative evaluation, however, between Group A and B showed that both at 15 and at 30 days, the effect was better in Group A.

Table 4 shows the comparison of IPSS in the two groups. In Group A, the mean IPSS improved from 19.97 ± 2.53 to 5.67 ± 0.99 at 30 days. This change was significant ($P < 0.001$**). In Group B, IPSS score changed from 21.30 ± 2.84 to 6.47 ± 1.14 at 30 days. This change was also significant. However, a comparison of two groups showed that the symptoms score improved more in Group A compared to Group B. This was significant both at 15 days and 30 days.

Table 5 shows individual symptoms which contribute to IPSS. It is seen that all the symptoms show significant improvement with treatment both at 15 days and 30 days in both groups. However, when the two groups were compared it was seen that the observations were slightly different. It is seen from the table that obstructive symptoms such as poor stream, intermittency and straining showed better response in Group B. This difference was significant both at 15 days and 30 days for intermittency and straining and only at 15 days for poor stream. The obstructive symptoms of incomplete voiding disappeared in both group in all patients at 15 days itself.

Table 3: Comparative evaluation of PVR in two groups studied

PVR	Base line	15 days	30 days	*F* value	*P* value
Group A					
Mean±SD	99.20±12.28	43.03±9.53	22.77±5.32	1395.00	<0.001**
95% CI	94.62-103.78	39.47-46.59	20.78-24.75		
Group B					
Mean±SD	102.90±10.81	49.67±10.17	27.13±5.47	1408.91	<0.001**
95% CI	98.86-106.94	45.87-53-46	25.09-29.18		
P value	0.220	0.012*	0.003**	-	-

F values are obtained by repeated measures ANOVA, SD: Standard deviation, CI: Confidence interval, PVR: Post-void residue, *Moderately significant ($P>0.01$, $P\leq0.05$), **Strongly significant ($P\leq0.01$)

Table 4: Comparative evaluation of IPSS in two groups studied

IPSS	Base line	15 days	30 days	*F* value	*P* value
Group A					
Mean±SD	19.97±2.53	8.77±1.22	5.67±0.99	869.33	<0.001**
95% CI	19.02-20.91	8.31-9.22	5.30-6.04		
Group B					
Mean±SD	21.30±2.84	10.03±1.59	6.47±1.14	783.44	<0.001**
95% CI	20.24-22.36	9.44-10.63	6.04-6.89		
P value	0.060#	0.001**	0.005**	-	-

IPSS: International prostate symptoms score, SD: Standard deviation, CI: Confidence interval, #Suggestive significance ($P>0.05$, $P<0.10$), **Strongly significant ($P\leq0.01$)

Regarding symptoms of irritability such as urgency, frequency and nocturia, it is seen that there was no significant difference in the two groups as regards urgency. However, as regards frequency and nocturia the response was significantly better in Group A.

DISCUSSION

α1-adrenoreceptor antagonists such as naftopidil and tamsulosin are widely used as the first choices for the treatment of LUTS associated with BPE because of the fast action and safety of these agents.[16,17] Naftopidil was developed by Boehringer Mannheim in Germany and is the latest α1-adrenoreceptor antagonist for the treatment of BPH. Clinically, naftopidil relaxes the prostate and lower urinary tract and its effectiveness on the LUTS associated with BPH has been confirmed.[2] A basic study investigating the affinity of human α1-adrenoreceptor subtypes (α1a, α1b and α1d) showed that, compared to α1b, which is involved in vasoconstriction and blood pressure control, naftopidil affinity is ≈3-17 times greater for α1a and α1d, which are involved in intraprostatic urethral pressure.[7] Furthermore, α1d-adrenoreceptors appear to be involved in improving bladder stimulation at the spinal level.[8] in addition, Kojima *et al*., recently reported that naftopidil was effective in patients with dominant expression of α1d-adrenoreceptor messenger ribonucleic acid in the prostate.[9] Although the difference in affinity to the alpha-1D receptor between these two drugs seems not much *in vitro*, there is still controversy over the possible differences in their therapeutic effects.[18]

In our study, naftopidil showed significant improvement in irritative components of IPSS mainly Frequency and Nocturia at 15 and 30 days of treatment which was supported by a recent comparative study conducted by Iqbal *et al*.[19] Tamsulosin showed better response in obstructive symptoms such as poor stream, intermittency and straining at 15 and 30 days of treatment which is similar to a comparative study reported by Ukimura *et al*.[18] and Nishino and Deguchi[16] in Japan. The difference between naftopidil and tamsulosin in improvement of IPSS may be explained by the recent studies showing the difference in distribution of receptor subtypes not only in prostate but also in bladder and nervous system. Involvement of neuromuscular receptor, mainly alpha-1D receptor present in detrusor muscle and bladder epithelium may be the reason for over active bladder.[4,14,18,20] Inhibition of rhythmic

Table 5: Comparative evaluation of IPSS (independent items) in two groups studied

Items: IPSS	Group	Base line	15 days	30 days	*F* value	*P* value
Poor stream	A	2.47±0.10	1.37±0.09	1.10±0.06	107.292	<0.001**
	B	2.87±0.13	1.07±0.05	1.00±0.00	182.18	<0.001**
	P value	0.022*	0.004**	0.078#	-	-
Intermittency	A	2.03±0.16	0.60±0.09	0.27±0.08	101.308	<0.001**
	B	2.27±0.16	0.20±0.07	0.07±0.05	172.16	<0.001**
	P value	0.297	0.001**	0.038*	-	-
Straining	A	2.43±0.09	1.07±0.07	0.90±0.06	150.87	<0.001**
	B	2.73±0.11	0.77±0.11	0.37±0.09	194.12	<0.001**
	P value	0.037*	0.027*	<0.001**	-	-
Sense of incomplete voiding	A	1.00±0.19	0±0	0±0	-	-
	B	1.17±0.20	0±0	0±0	-	-
	P value	0.548	-	-		
Urgency	A	3.03±0.13	1.30±0.10	0.87±0.08	193.826	<0.001**
	B	3.20±0.13	1.43±0.10	0.77±0.08	209.477	<0.001**
	P value	0.371	0.353	0.374	-	-
Frequency	A	4.00±0.07	1.90±0.07	1.00±0.00	1085.11	<0.001**
	B	4.07±0.05	2.77±0.10	1.53±0.09	396.394	<0.001**
	P value	0.420	<0.001**	<0.001**	-	-
Nocturia	A	5.00±0.00	2.53±0.09	1.53±0.11	504.33	<0.001**
	B	5.00±0.00	3.80±0.07	2.77±0.08	430.912	<0.001**
	P value	-	<0.001**	<0.001**	-	-

IPSS: International prostate symptoms score, #Suggestive significance (P>0.05, P<0.10), *Moderately significant (*P>0.01, P≤0.05*).,**Strongly significant (*P≤0.01*)

contraction in rat's bladder and increased capacity of bladder by inhibition of C fibers in rats with cerebrovascular disease was demonstrated by Sugaya *et al*.[15] and Yokoyama *et al*.,[4] respectively. The early improvement in irritative symptoms by naftopidil may be attributed to its stronger action on the central nervous system due to its effect on nerves with alpha-1D receptors which cause effective inhibition of afferent stimulation to detrusor muscles of bladder. Tamsulosin on the other hand, causes relaxation of smooth muscle of the bladder outlet including the prostatic urethra and relieves functional obstruction of the lower urinary tract. This causes an improvement in the urinary flow and indirectly decreases the frequency of urination.

The peak flow rate (Qmax) represents one of the key items for assessing voiding symptoms. In the present study, the degree of improvement in the Qmax was significantly better for Group A naftopidil than for Group B tamsulosin at 15 days as well as 30 days of follow-up. Ukimura *et al*.[18] and Nishino and Deguchi[16] showed a similar response of flow rate improvement with naftopidil and tamsulosin in their study.

Improvement in PVR was significantly better with naftopidil at 30 days. This better response by naftopidil in improving PVR was supported by Ukimura *et al*.[18] and Iqbal *et al*.[19] Alpha-1D receptors have been found to be involved in the storage of urine in the bladder as was suggested by Chen *et al*., the bladder capacity and urine volume per urination were significantly higher in alpha-1D knock-out mice than wild mice.[21] Thus, this report suggests that with relatively greater affinity to alpha-1D receptors, naftopidil can affect the storage function. This does not contradict the clinical reports that the improvements in storage symptoms by naftopidil administration are caused by an improvement in bladder compliance.[7] However the difference in the effects of the two drugs on voiding and storage symptoms were found to be in apparent after 6 or more weeks in earlier studies.[18]

In general, obstructive symptoms showed better improvement in tamsulosin and irritative symptoms showed better improvement in naftopidil. Naftopidil may be considered a better option for patients with predominantly irritative LUTS.

CONCLUSIONS

It was seen that during the period of follow-up of 30 days naftopidil (Group A) had a better objective improvement on maximum flow rate, PVR, International prostate symptom score compared with tamsulosin. In general, obstructive symptoms showed better improvement in tamsulosin group and irritative symptoms showed better improvement in naftopidil group. Naftopidil may be considered a better option for patients with predominantly irritative LUTS.

ACKNOWLEDGMENT

The authors are highly thankful to the patients enrolled in this study and to all who worked hard in collecting the data for this study. Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript.

REFERENCES

1. Homma Y, Kawabe K, Tsukamoto T, Yamaguchi O, Okada K, Aso Y, *et al*. Estimate criteria for efficacy of treatment in benign prostatic hyperplasia. Int J Urol 1996;3:267-73.
2. Nishino Y, Masue T, Miwa K, Takahashi Y, Ishihara S, Deguchi T. Comparison of two alpha1-adrenoceptor antagonists, naftopidil and tamsulosin hydrochloride,

in the treatment of lower urinary tract symptoms with benign prostatic hyperplasia: A randomized crossover study. BJU Int 2006; 97:747-51.
3. Lepor H. The evolution of alpha-blockers for the treatment of benign prostatic hyperplasia. Rev Urol 2006;8 Suppl 4:S3-9.
4. Yokoyama O, Yusup A, Oyama N, Aoki Y, Tanase K, Matsuta Y, *et al*. Improvement of bladder storage function by alpha1-blocker depends on the suppression of C-fiber afferent activity in rats. Neurourol Urodyn 2006; 25:461-7.
5. Kawachi Y, Sakurai T, Sugimura S, Iwata S, Noto K, Honda S e*t al*. Long-term treatment and prognostic factors of alpha 1-blockers for lower urinary tract symptoms associated with benign prostatic hyperplasia: A pilot study comparing naftopidil and tamsulosin hydrochloride**.** Scand J Urol Nephrol 2010; 44:38-45.
6. Masumori N. Naftopidil for the treatment of urinary symptoms in patients with benign prostatic hyperplasia. Ther Clin Risk Manag 2011;7:227-38.
7. Caine M, Pfau A, Perlberg S. The use of alpha-adrenergic blockers in benign prostatic obstruction. Br J Urol 1976;48:255-63.
8. Hieble JP, Bylund DB, Clarke DE, Eikenburg DC, Langer SZ, Lefkowitz RJ, *et al*. International Union of Pharmacology. X. Recommendation for nomenclature of alpha 1-adrenoceptors: Consensus update. Pharmacol Rev 1995;47:267-70.
9. Roehrborn CG, Schwinn DA. Alpha1-adrenergic receptors and their inhibitors in lower urinary tract symptoms and benign prostatic hyperplasia. J Urol 2004;171:1029-35.
10. Andersson KE, Gratzke C. Pharmacology of alpha1-adrenoceptor antagonists in the lower urinary tract and central nervous system. Nat Clin Pract Urol 2007;4:368-78.
11. Ushijima S, Ukimura O, Okihara K, Mizutani Y, Kawauchi A, Miki T. Visual analog scale questionnaire to assess quality of life specific to each symptom of the International Prostate Symptom Score. J Urol 2006;176:665-71.
12. Smith MS, Schambra UB, Wilson KH, Page SO, Schwinn DA. Alpha1-adrenergic receptors in human spinal cord: Specific localized expression of mRNA encoding alpha1-adrenergic receptor subtypes at four distinct levels. Brain Res Mol Brain Res 1999;63:254-61.
13. Price D. Potential mechanisms of action of superselective alpha (1)-adrenoceptor antagonists. Eur Urol 2001;40 Suppl 4:5-11.
14. Bouchelouche K, Andersen L, Alvarez S, Nordling J, Bouchelouche P. Increased contractile response to phenylephrine in detrusor of patients with bladder outlet obstruction: Effect of the alpha1A and alpha1D-adrenergic receptor antagonist tamsulosin. J Urol 2005;173:657-61.
15. Sugaya K, Nishijima S, Miyazato M, Ashitomi K, Hatano T, Ogawa Y. Effects of intrathecal injection of tamsulosin and naftopidil, alpha-1A and -1D adrenergic receptor antagonists, on bladder activity in rats. Neurosci Lett 2002;328:74-6.
16. Nishino Y, Deguchi T. A comparative crossover study for effectiveness of naftopidil and tamsulosin in patients with benign prostatic hyperplasia. Jpn J Neurogenic Bladder Soc 2001;12:82.
17. AUA Practice Guidelines Committee. AUA guideline on management of benign prostatic hyperplasia (2003). Chapter 1: Diagnosis and treatment recommendations. J Urol 2003;170:530-47.
18. Ukimura O, Kanazawa M, Fujihara A, Kamoi K, Okihara K, Miki T, *et al*. Naftopidil versus tamsulosin hydrochloride for lower urinary tract symptoms associated with benign prostatic hyperplasia with special reference to the storage symptom: A prospective randomized controlled study. Int J Urol 2008;15:1049-54.
19. Singh I, Gupta A, Agrawal V, Joshi M. A randomized clinical study to compare the efficacy and safety of naftopidil versus tamsulosin in symptomatic benign prostatic hyperplasia. UroToday Int J. 2013 April; 6 (2):art 17. http://dx.doi.org/10.3834/uij. 1944-5784.2013.04.04.
20. Hampel C, Dolber PC, Smith MP, Savic SL, Th roff JW, Thor KB, *et al*. Modulation of bladder alpha1-adrenergic receptor subtype expression by bladder outlet obstruction. J Urol 2002;167:1513-21.
21. Ikemoto I, Kiyota H, Ohishi Y, Abe K, Goto H, Kishimoto K, *et al*. Usefulness of tamsulosin hydrochloride and naftopidil in patients with urinary disturbances caused by benign prostatic hyperplasia: A comparative, randomized, two-drug crossover study. Int J Urol 2003;10:587-94.

How to cite this article: Perumal C, Chowdhury PS, Ananthakrishnan N, Nayak P, Gurumurthy S. A comparison of the efficacy of naftopidil and tamsulosin hydrochloride in medical treatment of benign prostatic enlargement. Urol Ann 2015;7:74-8.

Source of Support: MGMC and RI, **Conflict of Interest:** None.