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A PROSPECTIVE STUDY ON EFFICACY OF SELECTIVE ALPHA 1A ADRENOCEPTOR ANTAGONIST AND SELECTIVE ALPHA 1D ADRENORECEPTOR ANTAGONIST VERSUS WITH ANTICHOLINERGICS IN MANAGEMENT OF LUTS IN BENIGN ENLARGEMENT OF PROSTATE.

1. Nookinaidu Chitekela, Senior resident, Department of Urology, Sri Venkateswara Institute of Medical Sciences, Tirupati, India. Email ID: naidudr80@gmail.com
2. Bhavatej Enganti, Senior resident, Department of Urology, Sri Venkateswara Institute of Medical Sciences, Tirupati, India. Email ID: bhavatej@gmail.com
3. Shyam Sundar, Senior resident, Department of Urology,Sri Venkateswara Institute of Medical Sciences, Tirupati, India. Email ID : syam.t.sundar@gmail.com
4. Anil Kumar Nallabothula, Associate professor, Department of Urology, Sri Venkateswara Institute of Medical Sciences, Tirupati, India. Email ID: drak_90@yahoo.co.in
5. Srinivasan Subramanian, Professor, Department of Urology, Sri Venkateswara Institute of Medical Sciences, Tirupati, India. Email ID: suburotransplant@gmail.com
6. Rambabu Dandu, Associate Professor, Department of Urology, Sri Venkateswara Institute of Medical Sciences, Tirupati, India. Email ID: rambabudvs03@gmail.com

Article Info

***Corresponding Author:**

Dr. NookiNaidu Chitikela

Email: naidudr80@gmail.com

Abstract

Objectives

- To compare the clinical efficacy of naftopidil and tamsulosin versus tolterodine and tamsulosin in treatment of lower urinary tract symptoms (storage) associated with benign prostatic enlargement.

Patients and Methods

- A prospective randomized study from January 2011 to December 2012; with a minimum follow up period of 6 months was conducted in men with lower urinary tract symptoms (Storage) due to benign prostatic enlargement.
- The study cohort was randomized into two treatment groups: Group 1 receiving 25 mg Naftopidil + 0.4 mg tamsulosin daily (n-50), and Group 2 receiving 0.4 mg Tamsulosin + 2mg tolterodine daily (n-50).
- Baseline symptom scores (IPSS) were compared with those

at 4 weeks and 12 weeks.

Results

- At 4 weeks in group 1, daytime frequency score significantly improved from 4.06 to 2.96 ($P < 0.0001$), and nocturia score improved significantly from 3.66 to 2.84 ($P < 0.0001$).
- In group 2 at 4 weeks, there was significant improvement noted in the score of daytime frequency score (4.02 to 3.24, P <00 0.1) only.
- In group 1, storage and obstructive voiding symptoms improved significantly (p =0.003) compared to group 2 (p=0.019).
- Group 1 had an early response to improvement of storage symptoms compared to Group 2.

Conclusion

- Both the treatment groups showed good results in improving storage symptoms associated with benign prostatic enlargement.
- Among these two groups, group 1 showed significant improvement in treating nocturia, postvoid residual urine and peak flow rate.

Key words: Benign prostatic hypertrophy, International Prostatic Symptom Score, lower urinary tract symptoms, Naftopidil, Tamsulosin, Tolterodine.

Introduction :

Benign prostatic hyperplasia (BPH) is a progressive disease that is commonly associated with bothersome lower urinary tract symptoms (LUTS) such as obstructive symptoms (decreased and intermittent force of stream and the sensation of incomplete bladder emptying) and storage symptoms (frequency, urgency and nocturia). Longstanding bladder outlet obstruction (BOO) and bladder over distension may cause fibrotic changes of the bladder wall leading to changes in detrusor function. Detrusor instability is thought to be a contributor to the storage symptoms seen in LUTS [1, 2].

For years, the primary treatment options for BPH were surgical. Since the past 2 decades, medical therapy has become the most common modality of treatment. Therapy may be targeted at treatment of symptoms and/or preventing progression of disease. Many medications were used in treatment of BPH, which includes alpha – adrenergic antagonists, 5α reductase inhibitors, antimuscarinics, phytotherapeutics and hormonal therapies [2, 3].

There is emerging evidence that LUTS in men occur as a result of both bladder and prostate conditions. Theoretically the combined antagonism of alpha 1A and alpha 1D receptors are a great option for the management of BPH as it combines a reduction of prostatic smooth muscle tone with decreased detrusor instability [4]. In our study, we compared the efficacy of combination of alpha 1A blocker and alpha 1D blocker with combination alpha 1A blocker and anticholinergic in patients with storage symptoms due to BPH.

Objectives:

To compare the clinical efficacy of combination of naftopidil (Naf) and tamsulosin (Tam) with tolterodine (Tolt) and tamsulosin (Tam) in improving the storage symptoms associated with BPH.

Patients and methods:

A prospective randomized study from January 2011 to December 2012; with a minimum follow up period of 6 months was conducted in men with lower urinary tract symptoms (Storage) due to benign prostatic enlargement at the outpatient department after an informed consent. The study cohort was randomized into two treatment groups: Group 1 receiving 25 mg Naf + 0.4 mg Tam daily and Group 2 receiving 0.4 mg Tam + 2mg Tolt daily for a period of 12 weeks. Men 40 yrs and older with a IPSS score 8 or higher, IPSS quality of life (QOL) score of 2 or more for more than 3 months were included in the study. Men with clinically significant BOO (defined as a PVR > 200ml and Qmax < 5 ml/s), BOO due to causes other than BPH, Serum PSA >10 ng/ml and history of prostate surgery were excluded from the study.

Therapeutic efficacy were analyzed by using IPSS score, QOL index, maximum flow rate (Qmax), and residual urine volume (measured by transabdominal ultrasonography). Overall efficacy is determined using the IPSS, QOL index, Qmax and efficacy grade was evaluated as excellent, good, and poor. The therapeutic effect and safety were evaluated at 4 weeks and 12 weeks after the beginning of the treatments and at the end of observation. At the beginning of administration, 4 weeks after the beginning of administration, and at the end of observation, the total IPSS and QOL score and the scores of individual IPSS items, storage symptoms, and voiding symptoms were evaluated. Combined variables to represent storage or voiding symptoms were also evaluated as the combined score of two or three items among storage or voiding symptoms. At the beginning of administration and at the end of observation, the urination volume, maximum flow rate (Qmax), residual urine volume was evaluated.

Statistical analysis:

Unpaired t-test (Mann-Whitney U-test) was used to compare age, estimated prostate volume, Q max and residual urine between groups. The intragroup comparison between baseline and post treatment scores, Wilcox on signed rank test was done. The intergroup comparison was done by Mann-Whitney U-test. Results were expressed as mean± SD with statistical significance of $p < 0.05$. Statistical analysis was performed using SPSS 17 (Statistical Packages for Social Sciences, SPSS, Chicago, IL, USA).

Results:

Total of 123 subjects were enrolled to the study, 100 subjects were included and were randomized into two groups: Group 1(n- 50) and Group 2 (n-50) were analyzed. 23 patients were excluded from the study due to missed data and lack of follow up. Patient's characteristics were noted as in Table 1. At baseline, there was no significant difference between two groups with regard to age, prostate volume; maximum voiding flow rate and post void residual urine. The total IPSS score decreased significantly 4 weeks after the beginning of administration and at the end of observation in both groups (Table 2). IPSS score significantly decreased in group 1 from 16.42±3.03 to 12.6+2.5 after 4 weeks ($p < 0.0001$) and 9.7 at the end of administration ($p < 0.0001$). In the group 2, total IPSS significantly decreased from 15.52 to 12.04 after 4 weeks ($P < 0.0001$) and 10.5 at the end of administration ($P < 0.0001$). The QOL index also improved in both groups similarly to the total IPSS score. However, significant difference was noted in these scores between the two groups after 4 weeks but no difference at the end of administration (Table 2). In both groups storage symptoms significantly ($P<0.0001$) improved after the end of study but voiding symptoms improved significantly (p-0.0003) in group 1 compared to group 2 (p-0.019). After 12 wks significant improvement noted in Q max ($P=0.009$) in group I where as in group II no significant improvement noted ($P=0.15$), Post void residue significantly decreased in both groups (Table 3). At 4 weeks in group 1, daytime frequency score significantly improved from 4.06 to 2.96 ($p < 0.0001$), and nocturia score improved significantly from 3.66 to 2.84 ($P < 0.0001$) (Table 4). In group 2 at 4 weeks, significant improvement was noted in the daytime frequency score (4.02 to 3.24, p <00 0.1) but no significant improvement seen in the Nocturia score (3.3 to 3.04, $P = 0.051$). In group 1

there was significant improvement in poor stream, straining and incomplete emptying compared to group 2.

At the end of study, both the groups responded well to treatment, but in comparison group 1 showed significant improvement in total IPSS and quality of life index compared to group 2. Non responders are more in group 2 compared to group 1(Table 5). Side effects were less in both the groups. Group 1 had dizziness, headache, hypotension and erectile dysfunction, where as group 2 had dry mouth and urinary retention along with dizziness and hypotension.

Table 1: Patient characteristics at base line

Feature	Group 1	Group 2	P value
Age (years)	62.74± 7.3	61.02±7.2	0.24
Prostatic volume	36.7±6.47	35.88±6.35	0.52
Q max (ml/sec)	14.75±4.46	14.69± 3.16	0.93
PVR (ml)	25.98±25.56	23.64±17.4	0.56

PVR, post void residual urine; Qmax, maximum urinary flow rate; SD, standard deviation.

Table 2: Comparison of Baseline subjective symptoms and changes after 4 &12 weeks among the Groups.

	Baseline (A)	After 4 wks (B)	P value (A& B)	After 12wks (C)	P value (A&C)
Storage symptoms					
Group I	11.48±1.40	8.96±1.80	<0.0001	6.48±2.03	<0.0001
Group II	11.06±1.33	9.46±1.19	<0.0001	7.26±2.14	<0.0001
P value	0.13	0.10		0.06	
Voiding symptoms					
Group I	4.88±2.40	3.74±1.72	0.0075	3.28±1.86	0.0003
Group II	3.96±2.21	3.58±1.58	0.32	3.08±1.40	0.019
P value	0.048	0.629		0.54	
Total IPSS					
Group I	16.42±3.03	12.66±2.5	<0.0001	9.74±3.10	<0.0001
Group II	15.52±2.6	12.04±2.5	<0.0001	10.52±3.23	<0.0001
P value	0.033	0.22		0.22	
QOL index					
Group I	4.04±0.83	3.1±0.86	<0.0001	2.44±0.86	<0.0001
Group II	3.36±0.87	2.96±0.87	0.002	2.44±1.03	<0.0001
P value	0.0001	0.42		0.1	

TABLE 3: Baseline of Qmax & PVR, and changes after 12 weeks of treatment with Group 1 (n-50) and Group 2(n-50)

	Baseline (A)	After 12 weeks(B)	P value
Qmax(ml/sec)			
Group I	14.75±4.46	16.94±3.74	0.009
Group II	14.69±3.16	15.55±2.85	0.15
P value	0.93	0.039	
PVR			
Group I	25.98±25.56	13.20±18.8	0.005
Group II	23.62±17.4	15.6±15.6	0.017
P value	0.59	0.49	

Table 4: Comparison of Baseline values of IPSS to changes after 4 & 12 weeks of treatment between the treatment groups.

	Baseline (a)	After 4wks (b)	P value (a&b)	After 12wks (c)	P value (a & c)

Incomplete emptying					
Group I	0.90±0.58	0.36±0.48	<0.0001	0.3±0.43	<0.0001
Group II	0.48±0.54	0.3±0.46	0.075	0.2±0.40	0.004
P value	0.0003	0.52		0.23	
Frequency					
Group I	4.06±0.79	2.96±0.65	<0.0001	2.14±0.75	<0.0001
Group II	4.02±0.89	3.24±0.82	<0.0001	2.5±0.95	<0.0001
P value	0.81	0.06		0.038	
Intermittency					
Group I	1.3±0.76	1.12±0.65	0.206	0.98±0.62	0.023
Group II	0.78±0.70	0.76±0.65	0.555	0.76±0.63	0.88
P value	0.0006	0.0017		0.081	
Urgency					
Group I	3.76±0.79	3.2±0.75	0.0004	2.44±0.86	<0.0001
Group II	3.64±0.96	3.16±0.91	0.001	2.58±0.92	<0.0001
P value	0.49	0.81		0.43	
Weak stream					
Group I	1.44±0.67	1.24±0.62	0.125	0.96±0.63	0.0004
Group II	0.82±0.62	0.78±0.61	0.74	0.8±0.63	0.87
P value	<0.0001	0.0003		0.21	
Straining					
Group I	1.3±0.70	1.02±0.5	0.031	0.9±0.64	0.003
Group II	0.9±0.67	0.89±0.6	0.939	0.88±0.68	0.87
P value	0.004	0.29		0.879	
Nocturia					
Group I	3.66±0.68	2.84±0.81	<0.0001	1.98±0.91	<0.0001
Group II	3.36±0.87	3.04±0.72	0.051	2.78±0.84	0.001
P value	0.057	0.195		<0.0001	

Table 5: Treatment efficacy after 12 wks among the groups

	Excellent	**Good**	**Fair**	**Poor/worse**
Total IPSS				
Group I	9	18	16	7
Group II	5	17	17	11
QOL Index				
Group I	8	22	14	6
Group II	4	19	17	10

Discussion:

Treatment of Lower Urinary Tract Symptoms (LUTS) from BPH has evolved from surgical therapy to medical monotherapy to combination therapy. A common goal for treating men with BPH/LUTS is to relieve bothersome symptoms and their effect on QOL [1, 2]. In our present study, we analyzed the results of combination of two selective alpha alpha-adrenergic receptor (AR) blockers with combination of a selective α-AR blocker and anticholinergic in patients with storage LUTS due to BPH. The efficacy of Tamsulosin in treating BPH due to its specific α1AR blockade was well proven; it relieves the functional obstruction by inducing relaxation of smooth muscle. Although the changes in AR subtypes are important, α1AR-mediated bladder afferent activation is another important mechanism for understanding over activity in BOO experimental models. Recently, it was reported that α1A AR antagonists are effective in the treatment of storage symptoms. This suggests that not only α1D AR antagonists but also the α1A AR antagonists may have an important role in the development of storage symptoms. With regard to the mechanisms of α1AR antagonists in the improvement of storage symptoms, recent attention has focused on the possibility that α1AR antagonists may inhibit afferent nerves from the lower urinary tract [5, 6].

With regard to α1AR-mediated bladder afferent activation, the expression of α1ARs in the urothelium has been well documented. Up-regulation of these receptors can trigger the release of a number of mediators including ATP and nitric oxide, which may modulate bladder afferent nerve activity [7]. Alpha 1 ARs located in the bladder urothelium, primary sensory nerve and bladder vessels are involved in afferent signalling. It is suggested that α1AR antagonists may decrease bladder afferent activity by blocking α1ARs in these sites, thereby reducing the storage dysfunction associated with BOO [6, 7]. Previously storage voiding symptoms were treated effectively using combination of α1AR and anticholinergics. Recent studies on alpha-1 receptors have shown the presence of three subtypes: α1A, α 1B, and α1D [8]. There have been reports that α1A and α1D receptors are expressed at high levels in hyperplastic human prostates and that their distribution shows wide individual variation. Concerning the quantity of each of α 1 subtype in the human prostate, a recent study showed that 69%, 3.3%, and 27% of the α 1ARs are subtypes of α 1A, α1B and α 1D respectively. In patients with BPH it was reported that α 1A subtype increased to 85%, α 1D decreased to 14% and the amount of α 1B was negligible. Recent studies provided further interesting evidence on the difference in the receptors not only in the prostate but also in the bladder or nervous system. In terms of α1AR distribution in the human bladder, in contrast to the bladder trigone that contains only α1A AR, the detrusor mainly contains α1D subtypes (66%) and, to a lesser extent, the α1A subtypes (34%) but no α1B subtypes. α 1D ARs mostly seen on bladder dome and spinal cord. Theoretically, α1D receptor blockade in the bladder results in improvement of storage voiding symptoms [8, 9]. Naftopidil is a third generation alpha blocker selectively blocks α1-D receptors along with α1A adrenoreceptors. Naftopidil and Tamsulosin are widely used as the first choices for the treatment of LUTS associated with BPH. Although both Tamsulosin and Naftopidil are categorized as α 1A/ α1D antagonists, Tamsulosin seems to have a relatively higher affinity and selectivity to α1A receptor subtype while Naftopidil seems to have a relatively higher affinity to α 1D receptor subtype [10, 11]. Although the difference in affinity to the α 1D receptor between these two drugs seems not so much in vitro, there is still controversy over the possible differences in their therapeutic effects. There have been some reports that the effectiveness of the two drugs on voiding symptoms as a whole was comparable at 4 or more weeks of administration. Authors reported that Naftopidil showed better effects on storage symptoms especially on increased daytime frequency at 8 weeks or on nocturia at 4 weeks [11].

Naftopidil and Tamsulosin are characterized by effectiveness for storage symptoms and voiding symptoms, respectively, in a clinical study conducted by Yoshio Kawachi et al. In the Naftopidil group, the failure rate was higher with a positive history of acute urine retention, whereas in the Tamsulosin group, the failure rate was higher in the presence of OAB symptoms [12].

In recent years it was reported that the prevalence of overactive bladder (OAB) increases with age. Anticholinergic agents are currently used to treat OAB, but elderly men mostly have composite LUTS with both OAB and BOO [13]. Therefore, Ouslander et al proposed that men be treated initially with α1AR antagonists, and those not responding or tolerating to these agents, and who are not candidates for surgical intervention, may benefit from a trial of an anticholinergic agent, provided they are carefully monitored for the development of urinary retention [14]. Although Athanasopoulos et al and Maruyama et al reported that treatment combining an anticholinergic agent with α1AR antagonists is useful for OAB in men with BPH; general consensus has not yet confirmed their clinical effects on BPH with OAB in men [15, 16].

Based on this theoretical background we combined tamsulosin and naftopidil for treating storage symptoms with BPH. In order to avoid postural hypotension and other side effects due to alpha blockade we have given spacing to both the drugs and reduced the dosage (25mg

naftopidil and 0.4 mg tamsulosin). Many studies reported on storage symptoms in BPH effectively treated by combination of alpha blockers and anticholinergics. In our study both these combinations are useful in treating storage symptoms effectively with no statistically significant difference but among storage symptoms nocturia improved significantly in group 1 compared to Group 2. Voiding symptoms improved better in group 1 compared to group 2. In our study, early improvement of storage symptoms was noted in group 1 patients compared to group 2. Adverse effects and compliance are same in both the groups, improvement in maximum voiding flow rate and post void residue are good in Naftopidil and tamsulosin group compared with tamsulosin and tolterodine group. Our study had limitations with regard to small size of study cohort and short follow up.

Conclusion:

Treatment of BPH with predominant storage symptoms can be achieved by combination of drugs. Among medical management combination of two selective alpha blockers (naftopidil and tamsulosin) and combination of selective alpha blocker, anticholinergic gives good results. Among these two combinations naftopidil+tamsulosin gives better results in treating nocturia, residual urine and improvement of peak flow rate. Patients with BPH associated with storage symptoms any of the above combinations can be used to achieve good QOL. No significant side effects and compliance was noted with any of the above combination of drugs. To our knowledge, our prospective study was first to clarify that proper use of Naf + Tam is effective in treating storage symptoms in benign prostatic hyperplasia, and gives best results when storage symptoms associated with obstructed voiding symptoms.

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