ORIGINAL ARTICLE

Efficacy and Tolerability of Tamsulosin Alone and in Combination with Dutasteride in Patients of Benign Prostatic Hyperplasia

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Abstract

The present prospective randomized study was conducted to find out efficacy and tolerability of tamsulosin alone (0.4mg) and tamsulosin (0.4mg) in combination with dutasteride (0.5mg) in patients of BHP. Two groups of 20 patients each received either of the regimes for 24 weeks. Both groups were evaluated for uroflowmetric, ultrasonography and AUASS parameters. Both regimes caused significant increase in Qmax, Qave, voided volume and concomitant decrease in voiding time, flow time and time to peak flow($P<0.0001$). Ultrasonographically assessed prostate volume and residual urine volume decreased significantly with combination group, whereas only residual urine volume was decreased in tamsulosin group. Both groups caused improved AUASS ($P<0.0001$).Combination group produced more improvement than tamsulosin alone on Qmax, Qave and flow time ($P<0.05$) and decrease in prostate volume ($P<0.001$). Both regimes were well tolerated.The combination appears to have an additive effect

Key Words

BHP, AUA symptom score, Tamsulosin, Dutasteride

Introduction

Benign Prostatic Hyperplasia (BPH) symptoms result from two different components. The static component that results in obstructive features is because of androgens that stimulate the growth of acinar and stromal cells. While the dynamic component is responsibe for irritative symptoms due to alpha 1 receptor regulated smooth muscle tone .

Alpha 1 adrenergic blockers target the dynamic component that accounts for upto 40 percent of the obstruction (1). Tamsulosin is a specific recent alpha-1A blocker having less systemic side effects than non-specific alpha-adrenergic blockers. 5 ARIs are the only class of drugs that reduce the size of the prostate as they impede the conversion of testosterone to it's active form DHT the primary androgen driving both normal prostate development and the hyperplasia and result in reduction of prostate volume and improve lower urinary tract symptoms (2). Dutasteride a new dual 5 - ARI inhibits both isoforms of 5 alpha-reductase, In view of scanty existing data from India, the present study evaluated the efficacy and tolerability of tamsulosin alone and tamsulosin with dutasteride combination in patients of BPH.

Material & Methods

The present prospective randomized parallel study was conducted for a period of one year in patients of BPH after IEC approval. Written informed consent was obtained

Inclusion/Exclusion Criteria: included men > 50 years of age of , AUA symptom score of 8 or more, prostate volume of > 30 ml, voided volume between 125 ml to 180 ml, residual urine volume between 50 ml to 200 ml and prostate specific antigen (PSA) between 1.5 ng/ml to 4 ng/ml. Exclusion criteria included carcinoma of prostate, PSA more than 4 ng/ml, history of pelvic irradiation, orthostatic hypotension, syncope, blood pressure less than 90/70 mm of Hg , use of alpha-adrenergic agonist or antagonist, cholinergic agonist or antagonist, alpha-adrenergic antagonist or any anti-hypertensive drug within two weeks, estrogen, androgen or androgen inhibitors within preceding three months.

Study Design: A total of 40 patients comprised of two groups, who fulfilled the criterion and had normal bio-chemical and hematological values. All selected patients were assessed as per the following schedule:

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At day 0 the baseline score was obtained for uroflowmetric ultrasonographic parameters and AUA symptom score . The patients then were assigned to either of the two medications for 24 weeks Group 1 received Tamsulosin 0.4 mg orally, once a day. (Urimax ®.cipla) while the group 2 received Tamsulosin 0.4mg+Dutasteride0.5 mg combination orally, once a day.(DutasT®Dr.Reddy's laboratories). The patients then underwent five follow-up visits at 2, 4, 8, 12 and 24 weeks. Uroflowmetric parameters and AUA SS were recorded at 2,4,12 and 24 weeks, whereas ultrasonographic parameters were reassessed at 12 weeks and 24 weeks. Adverse effects were recorded at all the visits. Uroflowmetry determines non-invasive characteristic of urine flow. Peak flow rates less than 12 to 15 ml/s were taken as suggestive of obstruction .The uroflometery was performed on the clinical urodynamic testing system (Menuet ®). Parameters of uroflometry like Maximum flow rate (Qmax), Average flow rate (Qave) voided volume, voiding time, flow time and time to peak flow were recorded as they were directly displayed on computer screen. Ultrasonography: Transabdominal USG was performed using 3.5 MHz curvilinear abdominal transducer and prostatic volume, residual urine were estimated. AUA symptom score (AUASS)- American Urological Association symptom index was assessed (3). Score points 0-7 indicated mild, while 8-19 moderate whereas 20-35 were suggestive of severe symptoms of BPH.

Statistical Analysis

Results were analyzed by applying unpaired t-test for intergroup significance. The intragroup significance was assessed using paired t test. The data was expressed as Mean ± SEM and P value <0.05 was taken as significant. Tolerability was analysed using chi-square test.

Results

The average age in Group 1 was 59.85 yrs and 60.15 years in group 2.

Uroflowmetry Parameters: Tamsulosin caused a significant increase in Qmax, Qave and voided volume (P<0.0001) during the entire duration of the study. Tamsulosin monotherapy significantly decreased voiding time, flow time and time to peak flow (P<0.0001) throughout with maximum decrease at 24 weeks. Combination therapy caused a significant increase in Qmax, Qave and voided volume (P<0.0001) with maximum increase at 24 weeks. There was a significant decrease in voiding time, flow time and time to peak flow (P<0.0001) with maximum fall seen at 24 week

When compared Qmax in both regimes had similar effect upto 12 weeks. However at 24 weeks, the combination therapy caused significant increase in Qmax than Tamsulosin alone (P<0.05). Qave was affected in same magnitude by both regimes till 4 weeks. However combination therapy showed greater improvement in Qave at 12 weeks(P<0.01) ,24weeks(P<0.05).Both the groups affected the voided volume ,voiding time and time to peak flow in a similar fashion .The decrease in flow time was similar in two groups except at 24 weeks (P<0.05) in favour of combination therapy. (*Table 1*)

Ultrasound Findings: Ultrasonography did not reveal any reduction in prostate volume with tamsulosin. However statistically significant decrease in residual volume was observed at 12 and 24 weeks with maximum reduction at 24 weeks (P<0.0001). With combination therapy the Prostate volume decreased significantly from 12 weeks onwards with maximum reduction at 24 weeks (P<0.0001).Concurrently the residual volume also showed reduction from 12 weeks onwards (P<0.0001). On comparison, the combination group caused significant decrease in the prostate volume than Tamsulosin alone at 12 weeks (P<0.05) and 24 weeks (P<0.001) (*Table 2*)

AUA Symptom Score: Tamsulosin showed an improvement in AUA symptom score throughout the trial. A significant effect was observed from 4 weeks onwards with peak at 24 weeks(P<0.0001). AUA symptom score also improved significantly with combination from 2 weeks onwards till the end of the trial with maximum reduction at 24 weeks (P<0.0001). When compared the improvement was numerically more in the combination group. though the intergroup comparison did not reach any statistical significance. (*Table 3*)

Tolerability : Both regimens were well tolerated. Vital signs were maintained in both the groups throughout the entire study. Six patients reported adverse effects out of which four patients in the Tamsulosin group had dizziness, headache, stuffy nose and abnormal ejaculation (one each). Whereas, two patients in combination group (one each) complained abnormal ejaculation and decreased libido. These adverse effects were reported at 4 weeks in both groups and these symptoms subsided with the continuation of the therapy upto 24 weeks. None of these adverse effects were serious enough to warrant discontinuation of the therapy.

Discussion

Currently alpha-adrenergic receptor blockers and 5 alpha- reductase inhibitors [5 ARIs] with different modes of action provide the mainstay of pharmacotherapy of BPH. All the three subtypes of alpha-adreneceptors have been identified in the prostatic stromal tissue, however alpha-1A predominates in the prostate, bladder neck and

Table 1: Urollowmetry Parameters

UFM Parameters G1 vs G2	Baseline	2 weeks	4 weeks	12 weeks	24 weeks
	9.45±0.51	9.83±0.50**	10.61±0.47**	10.86±0.48**	11.12±0.46**
Qmax(ml/s)	9.26±0.46	9.58±0.45**	10.69±0.44**	11.64±0.41**	12.48±0.45** #
	4.34±0.09	4.55±0.10**	4.77±0.09**	5.09±0.09**	5.43±0.09**
Qave(ml/s)	4.40±0.10	4.60±0.10**	4.88±0.10**	5.46±0.09** #	5.87±0.09**# #
	143.25±2.55	144.40±2.58**	158.70±2.31**	160.55±2.41**	162.35±2.39**
Voided Volume (ml)	143.7±2.56	144.0±2.60	159.0±2.79**	164.55±2.77**	167.25±2.81**
	33.05±1.07	32.05±1.06	25.35±0.75**	23.20±0.67**	21.30±0.61**
Voiding time(s)	33.15±0.95	31.85±0.97**	24.80±0.99**	22.45±1.02**	20.15±0.99**
	30.60±1.03	29.80±0.99**	23.90±0.79**	21.45±0.69**	19.20±0.61**
Flow Time(s)	30.80±1.04	29.60±0.99**	22.20±0.81**	19.95±0.84**	16.95±0.92** #
	18.85±1.45	18.85±1.45	17.45±1.46**	16.65±1.42**	15.45±1.36**
Time to Peak flow(s)	19.90±1.56	19.90±1.56	17.90±1.51**	15.65±1.57**	14.0±1.54**

*P value<0.001; **P value<0.0001 (intra group) #P value<0.05; ##P value<0.01 (inter group)

Table-2. USG Parameters

USG Parameters Group-1	Baseline	12 weeks	24 weeks
Prostate Volume (ml)	53.35 ± 2.87	53.40 ± 2.88	53.30 ± 2.86
Residual urine volume(ml)	96.00 ± 4.77	69.25 ±3.14**	57.25 ± 2.77**
Group - 2			
Prostate Volume (ml)	53.40 ± 2.64	45.20±2.34** #	40.10±2.23** # #
Residual urine volume(ml)	96.20±3.16	67.40±1.97**	53.40±1.59**

*P value<0.001; **P value<0.0001 (intra group) #P value<0.05; ##P value<0.01 (inter group)

Table 2. AUASS Score

Baseline	2 weeks	4 weeks	12 weeks	24 weeks
Group 1				
15.5±1.09	15.4±1.08	14.7±0.93 *	10.0±0.59**	8.85±0.51**.
Group 2				
15.7±0.91	15.45±0.85*	13.9±0.81	9.35±0.51**	7.85±0.52**

urethra (4). Thus alpha-1A adrenoceptor antagonists more effectively tackle the dynamic component of BPH while 5 ARIs are the sole hormonal therapy to date that reduce prostate bulk by decreasing the level of DHT (5).

Therefore in current study Tamsulosin a specific alpha-1A blocker and Dutasteride a new dual 5 ARI were extensively evaluated in patients of BHP by a test battery chosen to obtain the effects of these two drugs on both static and dynamic components of BHP.

Maximum Flow Rate (Qmax) has a curvi-linear relation to bladder volume which affects peak flow rate in the normal as well as the obstructed individual. Results of the present study revealed that tamsulosin (0.4mg) caused a significant improvement in Qmax from 2 weeks onwards till 24 weeks (P<0.0001).It suggests that tamsulosin rapidly exerted effect on Qmax. Our results are in accordance with the previous studies (6,7,8,9). However our results are contrary to some studies (10,11) who used 0.2 mg of Tamsulosin, different from our study dose. This might be because of larger sample size and different baseline characteristics .The favourable effect of tamsulosin on Qmax is compatible with the action of alpha-1adrenoreceptor antagonist in causing relaxation of bladder neck and prostate smooth muscle and hence decreasing the pressure on the prostatic urethra and bladder neck.

The combination of tamsulosin and dutasteride affected Qmax in a similar fashion to tamsulosin but the increase was statistically more significant at 24 weeks (p<0.05). alpha-AR antagonists and their combination with 5 ARI have been reported to cause better improvement in Qmax (12,13,14). It is thus clear from current study that co-administration of dutasteride with tamsulosin did modify Qmax more favorably than tamsulosin. It can be attributed to the probable additive effect of tamsulosin on relaxing the bladder neck and dutasteride on reducing the prostate bulk. Qave, that too depends on bladder volume. showed an upward trend in the same way as Qmax in both the groups. Tamsulosin caused a significant increase at 2 weeks(P<0.0001) onwards, and this in conformity with previous research work (6,9,13).

Tamsulosin affected voided volume favourably (p<0.0001), these results are in accordance with the work done by various authors (6,7). Improvement shown by the combination therapy on voided volume and Qave followed a similar pattern as tamsulosin except at 12 and 24 weeks, when a statistical significance was obtained in Qave in favor of combination therapy. However the scan of literature failed to reveal any study regarding effect of combination therapy on voided volume and Qave. Our results imply that addition of 5 alpha-reductase inhibitors to alpha-blocker has a potential additive effect which can be explained on the basis of similar action of these drugs with different mechanism of action. Tamsulosin acted faster, resulted in increased the flow rates and voided volume in both the groups from 2 weeks onwards by reducing the impedance at the bladder neck, whereas 5 alpha-reductase inhibitors took time to show their effect.

Voiding time indicative of the total time during which the flow exists has a linear relation to the voided volume. It decreased with tamsulosin in our study is similar to the already reported (6). Much in a similar way flow time decreased and so did the 'time to peak flow'. Combination therapy significantly decreased voiding time, flow time and 'time to peak flow', though only flow time reached an inter group, statistically significance at 24 weeks. As tamsulosin relieves the obstruction by blocking the alpha-1adrenoreceptors and therefore the patient takes less time to void. Addition of dutasteride causes a decrease in the prostate volume thereby decreasing the compression on prostatic urethra and this effect is discernible from 12 weeks onwards.

AUA symptom index quantify the urinary symptoms in men with BPH and the score over time tracks disease progression and response to the treatment.Tamsulosin improved the AUA symptom score, this is in accordance with the previous trials [8,16,17]. The decline in AUA symptom score is attributed to alpha-blockade, leading to decrease urethral resistance and relief of obstruction. Combination therapy also reduced AUA symptom score as tamsulosin alone. As reported in earlier study the Tamsulosin and dutasteride combination had similarly

reduced AUA symptom score (18) .Prostate volume did not show any reduction with tamsulosin. A similar observation reported with doxazosin,another 5 AR antagonist (12).

Comparative data of tamsulosin and tamsulosin with dutasteride on prostate volume is sparse. In present study the combination therapy reduced the prostate volume significantly. Our results are comparable to the work done in previous studies (12,13,14,19). The shrinkage of prostate bulk with dutasteride helps in further increasing the urinary flow rates in patients already on tamsulosin. In present study, tamsulosin showed a significant decrease in residual urine volume($P<0.0001$).Such results are in conformity with already reported work (9,10,1). Combination therapy also reduced the residual volume and the reduction was numerically more than tamsulosin. Therefore, it suggests that addition of dutasteride further induce reduction in the prostate volume that helps in reducing the residual urine volume further. No new safety issue emerged during 24 weeks trial in Tamsulosin and combination group. Both regimes were well tolerated and reported transient adverse effects were not severe enough to warrant discontinuation of therapy. Our findings are in agreement with various previously published reports (7,18,20,21).Though it is not possible to separate the adverse events associated with Tamsulosin and Dutasteride,as both cause sexual dysfunction. Impotence (4.7%), decreased libido (3.0%), ejaculation disorder (1.4%) and gynaecomastia (0.5%) have been reported in past with Dutasteride andTamsulosin (22).

Conclusion

Current study thus demonstrates that Tamsulosin, favourably affects the urinary flow rates by removing the impedance at the bladder neck leading to improved symptom score and a concurrent decrease in residual volume. Dutasteride, a 5 alpha-reductase inhibitor decreases the prostate bulk, thus improving flow rates and AUA symptom score.When both drugs are combined, the combination appears to have an additive effect benefiting the patient more than the single drug alone.

References

1. De la Rosette JJ, Kortmann BB, Rossi C, *et al.* Long-term risk of retreatment of patients using alpha blockers for lower urinary tract symptoms. *J Urol* 2002;167: 1734-9
2. Horvath K, Walter G, Varga A and Romics I. A novel approach to the treatment of BPH. *BJU* 2006; 97: 1252-55
3. BarryMJ, FowlerFJ Jr, O'Leary MP,Bruskewitz RC, *et al.* The American Urological Association symptom index for benign prostatic hyperplasia. The measurement Committee of the American Urological Association. *J Urol* 1992;148:1549-57
4. Nehra A. Selecting therapy for maintaining sexual function in patients with BPH. *BJU Int* 2005; 96: 237-43
5. Foley C L , Kirby R S. 5 ARI: What is new? *Curr Opin Urol* 2003; 13(1): 31-37
6. Abrams P, Schulman C C, Voage S. Tamsulosin, a selective ?-1A adrenergic antagonist. A randomized controlled trial in patients with BPH. The European Tamsulosin Study Group. *Br J Urol* 1995; 76: 325-26
7. Chappel CR. Selective alpha 1-adrenoceptor antagonists in BPH. Rationale and clinical experience. *Eur Urol* 1996; 29: 129-44
8. Narayan P, Lepor H. Long term open label phase III multicenter study of tamsulosin in BPH. *Urology* 2001; 57: 466-70
9. Yanardag H, Goktas S, Kibar Y, Kilic S, Erduran D. Intermittent tamsulosin therapy in men with LUTS. *J Urol* 2005; 173: 155-57
10. Kurita Y, Ushiyama T, Suzuki K, Fujita K, Kawabe K. Transition zone ratio and PSA density. The index of response of BPH to an alpha-blocker. *Int J Urol* 1996; 3: 361-66
11. Gotoh M, Kamihira O, Kinukawa T, Ono Y, Ohshima S, Origasa H. Comparison of tamsulosin and naftopidil for efficacy and safety in the treatment of BPH; a randomized controlled trial. *BJU Int* 2005; 96: 581-86
12. Lepor H, William O W, Barry M J, *et al*. The efficacy of Terazosin, Finasteride or both in BPH. *N Engl J Med* 1996; 335: 533-39
13. Debruyne F M J, Jardin A, Collol D, *et al*. Sustained release Alfuzosin, Finasteride and the combination of both in the treatment of BPH. *Eur Urol* 1998; 34: 169-75
14. Kirby RS, Roehrborn C, Boyle P, *et al.* Efficacy and tolerability of doxazosin and finasteride alone or in combination in the treatment of symptomatic BPH- the PREDICT trial. *Urology* 2003; 61: 119-26
15. Chapple C R, Wyndaele J J, Nordling J, *et al.* Tamsulosin The first prostate selective ?1A-adrenoceptor antagonists. *Eur Urol* 1996; 29; 155-67
16. Milani S, Djavan B. Lower Urinary tract symptoms suggestive of BPH: latest update on ?1-adrenoceptor antagonists. *BJU Int* 2005; 95(4): 29-36
17. Flannery M T, Ramsdell J, Ranhosky A, Davidai G, Ruoff G. Efficacy and safety of Tamsulosin for BPH: Clinical experience in primary care setting. *Curr Med Res Opin* 2006; 22(4); 721-30
18. Barkin J, Guimaraes M, Jacobi G, Pushkar D, Taylor S, Van Vierssen OB on behalf of the SMART-1 investigator group. Alpha-blocker therapy can be withdrawn in the majority of men following initial combination therapy with the dual 5alpha-reductase inhibitor-dutasteride. *Eur Urol* 2003; 44: 461-66
19. Gittelmann M, Ramsdell J, Young J, McNicholas T. Dutasteride improves objective and subjective disease measures in men with BPH and modest or severe prostate enlargement. *J Urol* 2006; 176: 1045-50
20. Kawabe KE. Efficacy and safety of Tamsulosin in the treatment of BHP. *BJU* 1995; 76(1): 63-67
21. Hofner K, Claes H, De Reijke TM, Folkestad B, Speakman MJ for the European Tamsulosin Study Group. Tamsulosin 0.4 mg once daily! Effects on sexual function in patients with LUTS suggestive of BHP. *Eur Urol* 1999; 36: 335-41
22. Giuliano F. Impact of medical treatment for BHP on sexual function. *B J U Int* 2006; 97(2): 34-38