IS DOUBLE DOSE OF TAMSULOSIN MONOTHERAPY SUPERIOR TO COMBINATION OF CONVENTIONAL DOSE OF TAMSULOSIN AND FINASTERIDE IN SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA

MZ HUSSAIN[1], S M KHAN[2], AKMA ISLAM[3], S AKHTER[2], SUHEL AL-MUJAHID REZA[4], MD. REZAUL KARIM[5]

[1]Department of Urology, Sheikh Abu Naser Specialized Hospital, Khulna, [2]Department of of Urology, Chittagong Medical College, Chittagong, [3]Department of Urology, Bangabandhu Sheikh Mujib Medical University , Dhaka, [4]Department of Urology, Sheikh Hasina Medical College Tangail, [5]Department of Urology, Shaheed Ziaur Rahman Medical College, Bogra

Abstract

Background: *The primary aim of the medical therapy for BPH is to improve quality of life by relieving the lower urinary tract symptoms and prevent complications.*

Objectives: *To compare efficacy and safety of double dose of tamsulosin monotherapy with combination of conventional dose of tamsulosin and finasteride in symptomatic BPH.*

Methods: *This was a prospective study carried out in the Department of Urology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh during the period of July 2005 to June 2006. Total 60 patients of 45-80 years of age were consequently selected according to inclusion criteria. After completion of baseline clinical evaluation and investigations, participants were divided into two groups, group A and group B. Group A were given tamsulosin 0.4 mg for 1 week. Then double dose of tamsulosin (0.8 mg) were given from 2nd week for 12 months. Group B were given tamsulosin 0.4 mg and finasteride 5 mg for the same duration. Efficacy was evaluated at 6 month and 12 month follow up visit and a comparison was made between them. During follow up each was observed for any adverse effect. The parameters monitored were International Prostate Symptom Score (IPSS), Maximum urine flow rate (Qmax), Post Voidal Residual Volume (PVR) and Prostate volume.*

Results : *Both double dose of tamsulosin 0.8 mg and combination of conventional dose of tamsulosin 0.4 mg and finasteride 5 mg are effective in relieving symptoms of BPH but combination dose is superior to double dose monotherapy. Outcome parameters at end point follow up after 12 months showed significant improvement of IPSS ($p<0.05$), PVR($p<0.001$), Q max ($p<0.001$) and prostate volume ($p<0.001$) in combination group than double dose group .The incidence of adverse events were also significantly less in combination group ($p<0.05$).*

Conclusion: *Combination of conventional dose of tamsulosin with finasteride appears to have more efficacy and safety than double dose of tamsulosin in symptomatic BPH.*

Key words*: Tamsulosin, Finasteride, IPSS, Q max, PVR, Prostate volume*

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Introduction

Benign prostatic hyperplasia (BPH) is defined histologically by proliferation of the stromal and epithelial elements of the prostate[1] and clinically it 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,

Correspondence to : Dr. Md. Zahid Hussain, Assistant Professor of Urology, Sheikh Abu Naser Specialized Hospital, Khulna, Mobile:01711397280. e mail :

including acute urinary retention[2]. BPH is common among older men, with approximately 25% of men over 40[3]. Histological evidence of the disease is noted in 8% of men in their 30s, the prevalence of which rapidly increases to over 70% after age 60[4].

As the mean survival age is increasing, the number of patients with symptomatic BPH is also on the rise. As because surgical intervention is reserved for patients with more severe symptoms, medical therapy rather than surgery may be the most judicious approach for many of these individuals suffering from mild to moderate obstruction due to benign prostatic hyperplasia.

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 an α-blocker or a 5α-reductase inhibitor or combination of both. An α-blocker reduces smooth muscletone in the prostate or bladder neck and a 5α-reductase inhibitor reduces prostate volume by inducing epithelial atrophy and apoptosis[1]. Treatment with an α-blocker or a 5α-reductase inhibitor can ameliorate symptoms and improve urinary flow rate[1]. Finasteride, a 5α-reductase inhibitor is more effective on a large prostate (>40 gm) than on a small one (<40 gm)[7]. Finasteride also substantially reduces the risk of acute urinary retention and the need for surgery[8].

Over the last decade, the incidence of surgery has declined in almost all countries and the incidence of medical treatment rising .The goal of the study was to find out the safety and efficacy of maximum dose of tamsulosin and combination of conventional dose of tamsulosin with finasteride in symptomatic BPH.

Materials and Methods

This was a prospective study conducted in the department of Urology, Bangabandhu Sheikh Mujib Medical University (BSMMU) Hospital, Dhaka from July, 2005 to June, 2006 .Study population included the patients who attended the out- patient department of Urology complaining of lower urinary tract symptoms (LUTS) due to BPH .The method and purpose of the study were explained to the patients and only those who agreed were finally selected. Written consent was taken from each respondent. The Inclusion criteria were: male between 45- 80 years, IPSS 8-19, peak urine flow rate (Q max) 10—15ml/sec, PVR <150ml, prostate volume >40 gram. Patients with carcinoma of prostate, refractory urinary retention, recurrent gross hematuria, bladder stone, renal insufficiency (serum creatinine >2 mg/dl) and bladder diverticula were excluded. Ethical approval was taken from Ethical Committee of BSMMU. A data sheet containing history, physical findings and relevant investigation report were used for the purpose. IPSS determination sheet bengali version[9] was supplied to the patients to whom it was difficult to understand in English.

Total 60 cases were selected according to selection criteria from the patients attending urology out patient department of BSMMU Hospital with LUTS due to BPH .Patients were placed in 2 groups by simple random sampling. Base line evaluation was done by history, physical examination, digital rectal examination (DRE), International Prostate Symptoms Scoring (I-PSS), Urinalysis, Ultrasonogram of kidney, ureter and bladder region with MCC & PVR, Uroflowmetry and Serum prostatic specific antigen (PSA).

Initially in Group-A (n=30) Tamsulosin 0.4 mg/day and in Group-B (n=30) Tamsulosin 0.4 mg +Finasteride 5mg /day were started. Then all the patients belonging to only Group-A were asked to report 7 days after to check vital signs, measurement of pulse and blood pressure. Then each patient underwent orthostatic test. When apparently found okay, they were given Tamsulosin 0.8 mg/day onward. In Group-B combination drugs (Tamsulosin 0.4mg and Finasteride 5 mg)/day were started at the outset. However, unlike Group-A, they were exempted from orthostatic test. Each patient of either arm was then observed and followed up at 6 month (1st visit), and 12 month (end point visit) of treatment. On each follow-up visit, each patient was evaluated by history, IPSS, uroflowmetry to see peak urinary flow rate (Q_{max}), ultrasonogram of kidney, ureter and bladder with MCC and PVR as done on baseline evaluation. Any adverse effects of the drugs were also recorded.

Statistical analysis was carried out using Statistical Package for Social Science (SPSS) program version - 12. Measures of dispersion (mean, standard deviation) and the tests of significance (Student's paired "t" test and Student's unpaired "t" test) were employed to examine the statistical significance of the study. A 'p' value <0.05 was taken as minimum level of significance.

Results:

There was no significant difference in mean age, baseline peak urine flow rate (Q max), International prostate symptom score (IPSS), Post Void Residual Volume (PVR) and prostate volume between the two groups.

In follow up visit after 6 months, patients treated with double dose Tamsulosin (0.8 mg), mean value change of IPSS, Q_{max}, PVR and prostate volume were, 4.39± 0.63 points, 1.55± 0.78 ml/s, 11.87± 7.64 ml and 1.83 ± 5.6 gm respectively (Table I).

In the same follow up visit patients treated with combination drugs, mean value change of Q_{max}, IPSS, PVR and prostate volume were, 3.93± 0.73 points, 2.14± 0.67 ml/s, 20.67±10.55ml and 7.17 ± 5.6 gm respectively in combination group. In comparison to baseline mean values, IPSS, Q_{max} and PVR values were of significant changes (P < 0.05) in both the groups . Mean prostate volume change was also significant in group B (P <0.05) but not significant in group A (p>0.05) (Table -II).

More significant changes of parameters occurred in combination group than double dose tamsulosin group except IPSS . p <0.05 for Q max & PVR , p<0.001 for prostate volume. (Table-III)

Results at end point (12 month) study period:

At end point ie, after 12 months, treated with double dose Tamsulosin (0.8 mg), the mean value change of IPSS, Q_{max}, PVR and prostate volume were, 5.55± 0.95 points 2.65± 1.04 ml/s, 14.93± 6.64 ml and 5.02 ± 12.20 gm respectively . In comparison to baseline mean values, all the IPSS, Q_{max} and PVR values were of significant changes (P < 0.05). Mean prostate volume-change was not, however significant (P > 0.05). (Table IV).

Table I *Results at 6 months follow up visit (Group A)*

Parameters	Baseline values	Follow up at 6 months	Change from baseline	Mean % change	p value
IPSS	17.07±1.42	12.68±1.12	4.39±0.63	23.14±3.19	p<0.001
Q max	11.7±0.96	13.25±0.93	1.55±0.78	13.28±7.1	p<0.001
PVR	82.4±12.4	75.53±11.2	11.87±7.64	14.63±8.41	p<0.001
Prostate volume	52.93±1.69	51.11±5.8	1.83±5.6	3.45±16.12	p>0.05

Table II *Results at 6 months follow up visit in group B*

Parameters	Baseline values	Values at 6 month follow up visit	Change from baseline	Mean % change	p value
IPSS	17.47±1.38	13.53±1.28	3.93±0.73	22.95±3.18	p<0.001
Q max	1.70±0.92	12.84±0.73	2.14±0.67	20.32±7.44	p<0.001
PVR	84.8±17.5	64.18±13.8	20.67±10.55	23.20±.8	p<0.001
Prostate volume	51.81±1.53	44.74±3.7	7.17±5.6	13.55±0.37	p<0.05

Table III *Comparison of change of variables at 6 month Follow up visit in both groups*

Parameters	Mean % change in group A	Mean % change in group B	p value
IPSS	23.14±3.19	22.95±3.18	p>0.05
Q max	13.28±7.1	20.32±7.44	p<0.05
PVR	14.63±8.41	23.20±9.8	p<0.05
Prostate volume	3.45±16.12	13.55±0.37	p<0.001

Table IV *Results of Group-A at end point (12 month) follow-up visit:*

Parameters	Baseline values	Follow-up at end point	Change from baseline	Mean % change	P value
IPSS	17.07± 1.42	11.55± 0.83	5.55± 0.95	32.86± 4.17	p<0.001
Q_{max}	11.7± 0.96	14.30± 11.32	2.65± 1.04	22.22± 8.92	p<0.001
PVR	82.4± 12.4	68.12± 11.30	14.93± 6.64	22.08± 8.77	p<0.001
Prostate volume	52.93± 1.69	50.21± 2.54	2.71± 1.70	5.02± 12.20	p>0.05

Table V *Results of Group-B at end point follow-up visit.*

Parameters	Baseline values	Follow-up at end point	Change from baseline	Mean % change	P value
IPSS	17.47± 1.38	8.59± 1.17	7.87± 0.82	45.46± 3.37	p<0.001
Q_{max}	10.70± 0.92	17.14± 0.63	6.43± 0.82	60.76± 1.29	p<0.001
PVR	84.8± 17.5	45.33± 13.38	39.48± 10.8	47.62± 7.47	p<0.001
Prostate volume	51.81± 1.53	40.50± 1.66	10.31± 1.57	19.98± 13.53	p<0.001

At the end point , after 12 month therapy of combination drugs mean value change of IPSS, Q_{max}, PVR and prostate volume were, 7.87±0.82 points, 6.43± 0.82 ml/s 39.48± 10.8 ml and 10.31±1.57 gm respectively in combination group. In comparison to baseline mean values, all mean values of variables were of significant changes (P<0.05) (Table V).

Table VI *Comparison of change of parameters from baseline at end point visit between both groups*

Parameters	Mean % change in group A	Mean % change in group B	p value
IPSS	32.86±4.17	45.46±3.37	p<0.05
Q max	47.34±8.92	60.76±1.29	p<0.001
PVR	22.08±8.77	47.62±4.47	p<0.001
Prostate volume	5.02±12.20	19.98±13.53	p<0.001

Considering the adverse effects, 6 patients complained of headache and dizziness (20%), 5 of rhinitis (16.66%) and 6 of abnormal ejaculation (20%) in group A. In group B, abnormal ejaculation in 2(8.66%), decreased libido 2(6.66%) and impotence in 1 (3.33%) patients. No patient complained of postural hypotension in any group. Overall significantly more adverse effects observed in group A (56.66%) than group B (p <0.05) (Table VII)

Table VII *Adverse effects observed in two groups.*

Adverse effects	Group-A	Group-B
Postural Hypotension	0	0
Headache	6 (20%)	5 (16.66%)
Dizziness	6 (20%)	4 (13.33%)
Rhinitis	5 (16.66%)	3 (10.00%)
Decreased libido	0	2 (6.66%)
Abnormal Ejaculation	6 (20%)	2 (6.66%)
Impotence	0	1 (3.33%)

More significant improvement of parameters occurred in combination group than double dose group. p < 0.001 for Q max, IPSS & PVR and p<0.05 for prostate volume (Table VI).

Discussion

The α–blockers and 5 α–reductase inhibitors have gained widespread acceptance for the treatment of symptomatic BPH. IPSS , peak urine flow rate (Q max), PVR and prostate volume are the parameters used to determine the effectiveness of the medical treatment for BPH

In group-A, mean changes of IPSS was 4.09 ± 0.63 at 6 month and 5.55 ± 0.95 at end point .The values were 3.93 ± 0.73 at 6 month and 7.87± 0.82 at end point for the same variable in group B.

Hence a significant improvement of IPSS was found after 12 months of treatment with combination of Tamsulosin 0.4mg + Finasteride 5mg therapy (group-B) than double dose of tamsulosin group A (p<0.001). Similar improvement were observed in a separate study that IPSS was decreased significantly after 12 months of treatment with combination therapy[10].

Percentage improvement of Q max were 13.28 ± 7.1 and 22.22 ± 8.92 respectively in group A at 6 month and at end point .In group-B, mean Q_{max} improvement were 20.32 ± 7.44 and 60.76± 1.29 respectively. at 6 month and at end point . Combination (group-B) therapy was found to be superior to Tamsulosin monotherapy in terms of improving peak urine flow[11].

In group-A, percentage improvement of mean PVR was 14.63 ± 8.41 and 37.84 ± 8.77 respectively at 6 month and at end point .Whereas the values were 23.20 ± 9.8 and 47.62 ± 4.47 respectively. at 6 month and at end point in group B. Hence a significant decrease of post voidal urine volume in Group-B than Group-A at both follow up (p<0.001).Similar results were observed in another study showing reduction of PVR after using tamsulosin 0.4 mg [12] .

In this study, prostate volume was reduced significantly in group-B after 6 and 12 months of treatment ($p < 0.001$) but it was little decreased in group A ($P > 0.05$). Again in another study, treatment with combination of Finasteride + Doxazosin showed that reduction of prostate volume after 12 months[10].

In Group-A (Tamsulosin 0.8 mg) 06 patients complained of headache and dizziness (20%), 05 of rhinitis (16.66%) and abnormal ejaculation in 6 patients (20%). In a similar study, the numerical values were 21.1%, 17.1%, 17.9% and 18.1% respectively[13]. In Group- B, adverse events complained were abnormal ejaculation-02 (6.66%), decreased libido- 02 (6.66%), and impotence – 01(3.33%) patients. The most common adverse events reported after Tamsulosin were dizziness and headache in other studies[14]. Tamsulosin was shown as well tolerated drug for the long term treatment of lower urinary tract symptoms[15]. Similar results also observed with Tamsulosin 0.4 mg + Finasteride 5 mg combination therapy[16].

Conclusion

Finding of the study inferred that the best option of treatment for clinically BPH with mild to moderate symptoms is combination of 0.4mg Tamsulosin and 5 mg Finasteride once daily. Combination therapy is more effective in the treatment of lower urinary tract symptoms due to BPH leading to rapid improvement of symptoms by Tamsulosin moiety with optimal dose and decrease disease progression and sustained improvement by Finasteride. Incidence of adverse effects is also less in combination therapy.

Disclosure

All the authors declared no competing interest.

References :

1. Bartsch G, Muller,Oberholzer M et al: Light microscopic stereological analysis of the normal human prostate and benign prostatic hyperplasia . J Uro 1979; 122:487-489.
2. Berry SJ: The development of human prostatic hyperplasia with age . J Uro1984; 132:474.
3. Chule CG, Pander LA, Girman CJ, et al.The prevalence of prostatism: a population based survey of urinary symptoms . J Uro 1993; 150: 85-89.
4. Berry SJ, Coffey DS, Walash PC, et al. The development of human benign prostatic hyperplasia with age. J Uro, 1984; 132: 474-9.
5. Kaprianou N. Isacs JT:Experssion of transforming growth factor-beta in the rat Ventral prostate during castration induced programmed cell death. Motec Endocrinol 1989; 3:1515.
6. Gormley GJ, Stonner E,Bruskewitz RC et al. The effect of finasteride in men with benign prostatic hyperplasia. N Engl J Med. 1992 ; 327 : 1185=1191
7. Boyle P,Could AI, Roehrbom CG.Prostate volume predicts outcome of treatment benign prostatic hyperplasia with finasteride :a metaanalysis of randomized clinical trials. Urology,1996; 48 :398-405.
8. Michel MC, Grubbel, Taguchi K Veryurth Fet al.Drugs for treatment of benign prostatic hyperplasia: affinity comparison at cloned a1-adrenoceptor subtypes and inhuman prostate. J Auton Pharmacol, 1996; 16:21-8.
9. Salam MA,Zinnat H:International prostate symptom score –Bengali version.Prostate granthir nannan samaysha abong tar protikar, Unihealth publication, Dhaka,1999; p03.
10. Lepor H : Long term efficacy and safety of Tamsulosin in patients with benign prostatic hyperplasia.Tamsulosin Research Group. Urology 1995; 45:406-413.
11. Abrams P,Speakman M, Stott M. Arkell D, et al Adose ranging study of the efficacy and safety of tamsulosin , the first prostate selective a1A-adrenoceptor antagonist, in patients with benign prostatic obstruction(symptomatic benign prostatic hyperplasia). Br. J Urol, 1997,80:587-596.
12. Horiuchi K, Tsuboi N,Hatrori T, et al. The short arm effect of tamsulosin in Japanese men with benign prostatic hyperplasia. J Nipon Med Sch, 1999, 66(6):382386.
13. Oleary MP Tamsulosin :Current clinical experience. Urology. 2001;58(Suppl 6A);42-48.
14. Roehrborn CG,Oesterlong JE, Auerbach S et al :The Hytrim Community Assessment Trial Study: a one year of Tamsulosin versus placebo in the treatment of men with symptomatic benign prostatic hyperplasia. HYCAT Investigator group: Urology 1996;47(2):159-68.
15. Schulman CC, Cortvriend J, Jonas U, et al Tamsulosin, the first prostste selective a1a-adrenoceptor antagonist: an interim analysis of a multinational multicenter open label study assessing the long term efficacy and safety in patients with benign prostatic obstruction (symptomatic BPH). Eur Urol, 1996;29:145-54
16. Lepor H, Willford Wo, Barry MJ et al. The efficacy of Tamsulosin, finasteride or both in benign prostatic hyperplasia, Veteran Affairs Co-operative Studies Benign Prostatic Hyperplasia Study Group. New