Comparison of the Effect of Tamsulosin Versus Combination of Tamsulosin and Oxybutynin in the Medical Management of Patients with Benign Prostatic Hyperplasia: A Randomised Double Blind Placebo Controlled Study

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ABSTRACT

Introduction: Although alpha adrenergic antagonist have long been considered first line therapy for male lower urinary tract symptoms, many patients have persistent storage symptoms and do not reach their treatment goal. Study was done to compare the efficacy and tolerability of combination of Tamsulosin and Oxybutynin versus Tamsulosin alone in the patients with BPH-LUTS complex.

Material and methods: Between December 2008 and July 2010 at our institute 80 consenting patients of BPH –LUTS complex were selected for the trial. The trial was conducted on an OPD basis and patients were selected after meeting the inclusion criteria other than those coming under the exclusion criteria. Eligibility criteria were defined as International prostatic symptom score(IPSS) ≥13 ,IPSS storage symptoms≥ 8, Peak flow rate(Qmax) ≥4ml/s,4,PVR≤ 200ml, Voided volume ≥150 ml. Patients were randomized to receive tamsulosin (0.4 mg/d) with either oxybutynin (10 mg/d) or placebo for 12 weeks. Appropriate statistical tests like paired t test and analysis of covariance were used to analyze the data.

Results: Tamsulosin combined with extended-release Oxybutynin resulted in significantly greater improvement in total IPSS compared with Tamsulosin and placebo after 4(P=0.003), 8 (P=.001) and 12 (P=.001) weeks of treatment, and improved IPSS for storage and quality of life at all assessment points (P<0.001). The mean increase in post void residual urine volume was significantly higher in the combination therapy group (107.16 vs. 64.12ml)

Conclusion: In men with substantial storage symptoms, combination therapy with Tamsulosin and Oxybutynin demonstrated greater efficacy than and comparable safety and tolerability to Tamsulosin monotherapy.

Keywords: BPH, LUTS, combination therapy, Tamsulosin, Oxybutynin

INTRODUCTION

BenignProstatic Hyperplasia (BPH) is a common urological problem of the geriatric population and Lower urinary tract symptoms (LUTS) are commonly associated with benign prostatic hyperplasia (BPH). LUTS terminology was initially proposed by Abrams in 1994 and accepted by the 5th International consultation on Benign prostatic Hyperplasia (BPH) to replace the previous terms of "prostatism", "symptomatic BPH" and "clinical BPH". The same consultation recommended the use of the terms "benign prostatic hyperplasia" (BPH) only in the case of histological confirmation and "benign prostatic enlargement"(BPE) when such pathologic data were lacking. Bladder outlet obstruction (BOO) was proposed as an urodynamic concept of reduced flow rate with increased bladder pressure as the correlation between the urinary symptom and urodynamic observation is at best weak. The LUTS-BPH complex consists of both voiding and storage symptoms that may overlap with overactive bladder symptoms. The constellation of LUTS comprises storage (frequency, nocturia, urgency, urge incontinence) and voiding (slow stream, splitting or spraying, intermittent stream, hesitancy, straining) components[6]. The voiding symptoms are classically related to the BPE and more than 50% of the men have storage symptom also. The storage symptoms of BPH overlap with the symptom of another prevalent age related condition, overactive bladder (OAB). About 30% of men aged 50–80 years have either moderate or severe LUTS[1]. Half of the men with LUTS-BPH complex will have a pattern of spectrum which will overlap with the symptoms of over active bladder[2].The ICS defines OAB as a syndrome characterized by urgency with or without urge incontinence, usually with frequency and nocturia[3]. The prevalence of both OAB and LUTS increases with age. LUTS, BPH and OAB are all causally related but the underlying mechanism linking them and the extent of the association is poorly understood. OAB coexists with BOO in about 66% of cases[12] and about 30% of the men with OAB have failure to resolve their symptom even after the correction of the BOO[4].Bladder wall hypertrophy and progressive neuronal degeneration consequent upon functional overload due to BPH is thought to play the central role in the development of storage symptom and overactive bladder[9]. It has also been shown that alteration in cytoskeletal proteins, extracellular matrix, mitochondrial function, and development of denervation supersensitivity to the acetylcholine might explain the causes of bladder overactivity[10]. A straight forward association between BPH, LUTS and OAB however cannot always be established[7]. OAB has a significant adverse impact on the quality of life in the functional and social domains[5]. The American Urological Association Symptoms Index (AUASI) and the International Prostate Symptom Index Score (IPSS) are the most widely used instruments to capture severity of LUTS[11].

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Even though there is a significant overlap in the symptom and prevalence of BPH and OAB but the treatment varies greatly. The current recommendation for the initial treatment of BPH-LUTS complex is an alpha antagonist alone or with 5α reductase inhibitors[13] and invasive measures reserved for patients who are not candidates for medical management or respond poorly to it[14]. Tamsulosin is a third generation α_{1A}- adrenoreceptor blocker which is a safe and efficacious drug for the treatment of BPH with fewer documented side effects than the other available alpha blocking medications[15].The efficacy of OAB on the other hand treated with anticholinergics in the women and non obstructed men is established. Historically there were theoretical concerns in the use of anticholinergics in BPH primarily because of concerns of precipitations of acute urinary retention and increase in the post void residual urine. Consequent upon the concerns, current practice guidelines (AUA,BAUS and EAU) do not recommend the use of anticholinergics in men with LUTS due to BPH. Nevertheless as a significant percentage of patients on medical treatment with alpha blocker do not achieve their treatment goal, the clinicians have implemented the use of anticholinergics in their clinical practice even in the absence of any concrete data. However, recently several trials have been conducted to assess the utility of anticholinergics in BPH, either as a single agent or in combination with other medication classes. This study was also designed and aimed at assessing the role of commonly available anticholinergic "Oxybutynin" in combination with "Tamsulosin" in the medical management of BPH. The main objective of the study was to compare the decrease in severity of LUTS and individually the storage and voiding symptoms after use of Tamsulosin versus combination of Tamsulosin and oxybutynin.

MATERIAL AND METHODS

This double blind randomized placebo controlled trial enrolled 80 men diagnosed with BPH-LUTS complex between December 2008 and July 2010 at department of urology, JIPMER, puducherry. The trial was conducted on an OPD basis and patients were selected after meeting the inclusion criteria other than those coming under the exclusion criteria. Eligibility criteria were defined as men ≥ 45 years with International prostatic symptom score (table-1) (IPSS) ≥13, IPSS storage symptoms≥ 8, Peak flow rate (Qmax) ≥4ml/s, 4, PVR≤ 200ml, Voided volume ≥150 ml. Exclusion criteria was defined as history of urinary retention, symptomatic urinary tract infection, bladder or prostate cancer, PSA ≥4ng/dl, previous lower urinary tract infection, use of sympathomimetic drugs in the last 4 months, angle closure glaucoma, absolute indication for prostatectomy, serious medical comorbidities and allergy to tamsulosin or oxybutynin. This study was approved by Institutional review board and Ethics committee and all patients provided written informed consent. All patients were randomized into two groups using random number generator software (figure-1). All patient identification numbers and randomization numbers were assigned sequentially in ascending order beginning with the lowest number available. All study medication and placebo were similar looking and smelling and both patients and investigator was blinded to the results. All patients were screened one week before inclusion with complete history and physical examination, USG-KUB, Uroflowmetry, PVR assessment, serum PSA, urine analysis, urine culture, IPSS Questionnaire and given Tamsulosin0.4 mg OD. At randomization(Visit2) the patients were required to receive in addition to tamsulosin either extended release Oxybutynin 10mg/day or placebo. Treatment continued for 12 weeks with assessment of efficacy and safety by administration of IPSS questionnaire, SS questionnaire, GRA Questionnaire, SPI Questionnaire and QOL questionnaire at 4,8 and 12 weeks.

	None	Less than 1 time in5	Less than half the time	About half the time	More than half the time	Almost always
Over the past month , how often you had the sensation of not emtying your bladder complete-ly after you finished urinating?	0	1	2	3	4	5
Over the past month ,how often have you had to urinate less than two after you finished urinating?	0	1	2	3	4	5
Over the past month ,how aften you you stopped and started again several times when yiu urinated ?	0	1	2	3	4	5
Over the past month ,how often you found it difficult to postpone urination?	0	1	2	3	4	5
Over the past month ,how often have you had a weak stream?	0	1	2	3	4	5
Over the past month ,how often you had to push or strain to begin the urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5 times or more
Over the past month ,how many times did you most typically get up to urinate from the time you went to bed at night untill the time you got up in the time you got up in the morning?	0	1	2	3	4	5
Total symptom score						
Score: 0-7=Mild, 8-19= Moderate, 20-35= severe						

Table-1: International Prostatic Symptom Score as adapted from J Urol[16]

End Points: The primary efficacy end point was the change in IPPS from the baseline to the final visit at 12 weeks or the last observation carried forward (LOCF). The secondary end points were assessment of subscore (comprising question 2, 4 and 7) and Quality of life assessment (QOL) component of the IPSS as well as assessment of symptom problem index(SPI)[17] to determine the degree of bother(from 0 ="no bother" to 4 = "a big problem") of the patient and Global response assessment (GRA) to determine the patients perception of the overall improvement (Markedly worse=0 to markedly better=7). IPSS subscore, SPI assessment were performed at visits 2 through 5 and GRA assessment administered at 3,4 and 5. Safety was assessed by history and physical examination at each visit and adverse effects were documented throughout the study. We hypothesized that patients receiving Oxybutynin with Tamsulosin could perceive greater treatment than men who received placebo.

STATISTICAL ANALYSIS

The sample size of the study was calculated using SPSS software keeping the power at 80%, two tailed α level of 0.05, true response rate to be 80% and an attrition rate of 10%. Intension to treat population (ITT) was defined as all randomized patients who received at least one dose of the study drug and had at least one post randomization safety evaluation and ITT population was used to assess primary and secondary end points. Treatment effects from primary and secondary end points were assessed using an analysis of covariance model with the baseline as a covariate and other values as qualitative factors. Missing observations were analyzed by last observations carried forward (LOCF).

RESULTS

A total of 80 patients received at least one dose of the study medication and had at least one post randomization evaluation and formed the intention to treat population. 40 of these patients received tamsulosin with placebo and the other 40 patients received tamsulosin with oxybutynin. 4 patients were lost to follow up and 3 patients discontinued of the study two of whom due to development of acute urinary retention and one due to lack of efficacy . Treatment groups were well matched in age, prostate size, PSA, PFR , PVR, and symptom severity at baseline (Table-2).

The addition of extended release Oxybutynin to the tamsulosin resulted in progressive improvement in the symptoms from the base line in comparison to the placebo group (Table-2). At 12 weeks the assessment of primary efficacy end point IPSS revealed mean± S.D of 7.24±4.27 (from the baseline of 18.4±5.13) for the Oxybutynin group and 13.27±4.16(from the baseline of 17.20±4.83) for the placebo group. There was a statistically significant decrease in the IPSS evident at 4 weeks in the Oxybutynin group which was sustained at 8 and 12 weeks. Significant improvement in the IPSS subscore, SPI score and QOL score were noted at all assessment points. The improvement as indexed by GRA was numerically greater at 4 weeks and became statistically significant at 8 weeks which was sustained at 12 weeks. There was no decrease in the PFR in the Oxybutynin group compared to the placebo group at all assessment points. At 12 weeks the mean± SD of PFR (ml/sec)in the oxybutynin group was 12.99±4.85 compared to 13.42±3.94 in the placebo group which was statistically not significant (P value=0.67). There was a statistically significant increase in the PVR at 4,8 and 12 weeks and the mean ±SD of the PVR at 12 weeks was 110.13±60.3ml from the baseline of 71.90±54.69ml in the Oxybutynin group(P value<0.01):the corresponding change for the placebo group was 60.34±9.92 from 42.99± 6.97ml.

characteristics	Test group (N=40)	control group(N=40)	P value
Age(y)	65.95±6.72	67.53±7.29	0.71
Prostate vol.(ml)	34.58±12.42	35.19±11.94	0.56
IPSS	26.78±6.76	23.03±6.54	0.70
IPSS-SS	14.03±2.17	13.18±2.28	0.06
PFR	9.40±5.29	11.40±4.22	0.32
PVR	71.77±48.14	62.23±46.86	0.72
PSA	2.32±1.17	2.10±1.17	0.73

ŧContinuous variables are expressed as mean ± SD. IPSS = International Prostate; Symptom Score; IPSS- SS= IPSS sub score; LUTS = lower urinary tract symptoms; PFR = peak flow rate; PVR = postvoid residual

Table-2: Baseline characteristics of enrolled patients[ŧ]

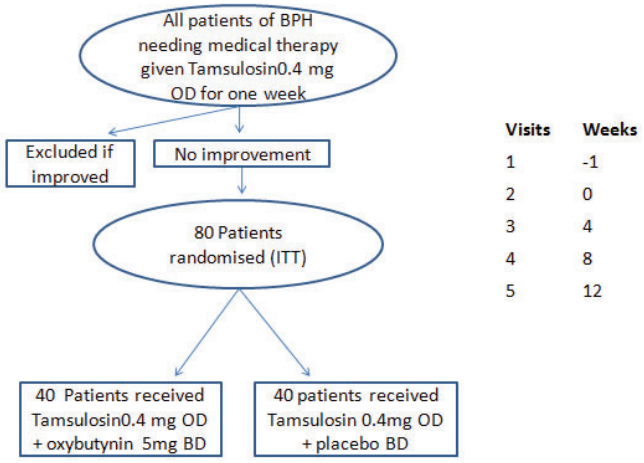

Figure-1: Study design and time line

Safety and tolerability: The patients taking Oxybutynin reported dry mouth in 35%(14/40), dry mouth with constipation in 2.5% (1/40) and dizziness in 5% (2/40). One patient in the Oxybutynin group discontinued the study due to precipitation of acute urinary retention (2.5%). He was catheterized for 7 days and later voided successfully on tamsulosin. The patients in placebo group reported tiredness and dizziness in 2.5% each (1/40) (table-3).

DISCUSSION

Though in recent times the importance of antimuscarinics have been realized by several studies but the three meta analysis[18-20] published till date identified only 5 RCT[21-26] concerning the role of combination therapy in the patients with BPH and only one RCT(MacDiarmid[18]) evaluating role of Oxybutynin and tamsulosin in BPH. One case series was reported by Lim[19] evaluating oxybutynin with terazosin in 89 cases of BPH. Though most of the RCT emphasize the safety and efficacy of the antimuscarinics in BPH but there is heterogeneity in the study methodology emphasizing the need for further studies. All the RCT on combination therapy with antimuscarinics

Patient visit	IPSS		IPSS-SS		IPSS-QOL		SPI- Total		GRA Total	
	Score	P value	Score	P value	score	P value	score	P value	score	P value
Baseline		NA		NA		NA		NA		
Oxybutynin group	18.4±5.13		10.93±3.30		5.70±0.64		3.78±0.48			
Placebo group	17.20±4.83		10.44±2.85		5.55±0.67		2.33±0.83			
Week 4		0.03		<0.01		<0.01		<0.01		0.63
Oxybutynin group	11.46±5.44		6.31±3.56		3.67±0.86		2.33±0.83		1.59±0.81	
Placebo group	14.90±4.54		9.40±2.64		4.58±0.67		2.98±0.53		1.68±0.76	
Week 8		<0.01		<0.01		<0.01		<0.01		0.002
Oxybutynin group	9.03±4.94		5.24±2.63		2.37±1.28		1.66±0.90		3.11±1.42	
Placebo group	14.18±4.43		8.95±2.52		4.30±0.68		2.73±0.64		2.28±0.78	
Week 12		<0.01		<0.01		<0.01		<0.01		<0.01
Oxybutynin group	7.24±4.27		4.41±2.82		1.84±1.28		1.24±0.83		4.49±1.40	
Placebo group	13.27±4.16		8.41±2.16		4.11±0.63		2.59±0.59		2.70±0.77	

[#]Values expressed are mean ± SD; NA= Not applicable; QOL = quality of life; SPI = Symptom Problem Index, [§]P values were computed using analysis of covariance with baseline values as the variate, [₮]Based on Intention to treat analysis(ITT) and last observation carried forward(LOCF)

Table-3: Effects of Oxybutynin on primary and secondary efficacy outcome and comparison of changes from baseline at Weeks 4, 8, and 12 (LOCF)[₮]

have been conducted using tamsulosin except for Lee et al[23] who used Doxazosin and reported comparable results in 211 patients. AUA guidelines recommend any of the 4 drugs tamsulosin, alfuzosin, terazosin and prazosin as an option in medical management of BPH with equal efficacy. We selected tamsulosin for trial on the basis of widespread use and better safety profile. Even though only one RCT has used oxybutynin for the trial on BPH[18] we selected the drug as it is in common use and others have reported similar efficacy among non selective and M_3 selective antimuscarinic darifenacin [27] in OAB but the data as to the superiority of latter over former in BPH is lacking. Long acting Oxybutynin has been shown to have lesser adverse effects and equal efficacy justifying its selection for the trial. Lee et al[23] Asthanapoulos et al[24] and Abrams et al [25] used urodynamics both as a entry protocol and in follow-up after use of tolterodine to make the results objective but had no data on patient symptom. We chose not to use urodynamic studies with the belief that treatment of patients based on symptom end point would improve the generalizability of the results to the clinical practice as the symptoms represent the ultimate treatment goal. Moreover patient reported outcome are particularly important for evaluating the therapeutic benefit of pharmacotherapies that do not cure chronic condition. Though some studies have used tamsulosin for 4 weeks[21] before randomization but this study like that by Asthanapaoulas et al[24] required the patients to take tamsulosin only for 1 week before randomization assuming that any further change would occur in both the groups negating any impact on the result. SPI and GRA[29] was used in addition to the IPSS for efficacy end points as IPSS alone does not include an item for urgency urinary incontinence and does not allow for quantification of urinary frequency or degree of urgency. Steven AK et al[26] used perception of treatment benefit question[30,31] (similar to GRA) with 5 point urgency rating scale[31] as primary efficacy end point and IPSS as secondary efficacy end point along with bladder diaries for assessing response on the OAB component of BPH symptom complex. They reported benefit of 80% (P value<0.01) in the combination arm of Tamsulosin plus tolterodine. This study also brought out similar improvement in IPSS and IPSS-subscore(P value<0.01).Improvements in QOL, SPI and GRA Questionnaire(p value<0.01) corroborates with the other study by Macdiarmid et al[21] (P value<0.01). There was no significant change in PFR and a statistically significant but clinically non significant increase in the PVR as also noted in other studies[21,26].The incidence of acute urinary retention of 2.5%is acceptable as noted in the metaanalysis[18]. Dry mouth was the most common side effect in 35% which is acceptable[19,20].

CONCLUSIONS

Monotherapy with Tamsulosin or antimuscarinics do not help some men with BPH. Combination of Tamsulosin and extended release Oxybutynin at 10mg/d is a safe and efficacious option for the patients with BPH who have severe storage symptoms or who fail medical monotherapy. It would be prudent however to restrict the use to those who have severe storage symptoms with mild to moderate grade BOO. Those men with increased risk of urinary retention should be monitored particularly within 4 weeks of starting therapy. Well designed studies are needed to assess the long term effects of antimuscarinics in BPH-LUTS complex and to determine safe limits of PVR and PFR before starting therapy. Further studies are also needed to evaluate the additional benefit, if any, of uroselective antimuscarinics like Darifenacin and Solifenacin in combination with alpha blockers in the treatment spectrum of BPH-LUTS complex.

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