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Research Article

EFFICACY AND SAFETY OF TAMSULOSIN (0.4 mg) ONCE DAILY FOR TREATING SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Objective: To evaluate the efficacy and safety of tamsulosin 0.4mg once daily compared with placebo in men with symptomatic benign prostatic hyperplasia. Patients and method: In this randomised, placebo-controlled study 69 patients were enrolled. Of these 51 were receive tamsulosin 0.4 mg and 18 patients were receive placebo once daily for 12 weeks. Study was designed to compare the efficacy safety and of tamsulosin verses placebo group. The primary outcome measures were; mean changes in total and /or individual I-PSS score, prostate volume and life style questionnaire, from baseline to 12 weeks of study. Result: Tamsulosin significantly improved lower urinary tract symptoms compared to placebo, with a mean change in I-PSS scores from baseline to end of the study was 16.7 VS 9.0 for placebo (P ≤0.0002). Improvement in symptoms was 85.74%. Compare to placebo. The life style questionnaire was significantly improved in tamsulosin group. Adverse events were similar to placebo, most common observed adverse event was dizziness (4.34%) similar to placebo ((7.14 %). While sexual disorder ((2.1% delayed ejaculation) was prominent in tamsulosin group. Conclusion: Once daily dosing of tamsulosin at bed time at a fix dose level (0.4mg) offers an efficient improvement in total and individual I-PSS score but have no effect on prostate volume, adverse events other than ejaculatory disorder were similar to placebo. Tamsulosin is safe and well tolerated and most effective for treatment of symptomatic BPH at a short term basis.

Keywords: BPH (Benign prostatic hyperplasia); I-PSS (International-prostate symptom score); AUR (Acute urinary retention);Placebo; amsulosin.

INTRODUCTION

Benign prostatic hyperplasia is the most common cause of voiding dysfunction in men. The prevalence of benign prostatic hyperplasia increases with age; as the average age of population advances an increasing prevalence of benign prostatic hyperplasia is expected. Benign prostatic hyperplasia is a heterogeneous disease which may be asymptomatic but often becomes symptomatic from the 5th decade of life[1]. Benign prostatic hyperplasia is a progressive disorder in some patient's progress more rapidly than others[2]. Incidence of benign prostatic hyperplasia by the age 60 years 50% and by the 8th decade of life 85% of men are found to have histological evidence of benign prostatic hyperplasia at post mortem[3]. The enlargement of the prostate in an older man is due to hyperplasia of the prostatic tissue. If patient with these symptoms are left untreated serious complications such as acute urinary retention (AUR), bladder decompensation and upper urinary tract compromise can develop[4]. A dynamic component related to the tone of smooth muscle fibres in the bladder neck, surgical capsule and fibromuscular stroma[5] are α adrenergic receptors. There are 2 types of α adrenergic receptors in the prostatic capsule adenoma, and bladder neck, designated as α1 and α2. The action of the α2 receptors is same as α1 but the receptor which predominantly mediating the contractile properties of the human prostatic adenoma is the α1 types[6]. α-receptor blockers have been proven to decrease the tone of prostatic capsule and (adenoma), decreasing the pressure in the prostatic part of the urethra and bladder neck without affecting bladder pressure[7].

MATERIAL & METHOD

The present study was carried out in the department of pharmacology and department of surgery S.S.M.C. & S.G.M.H. Rewa MP. The patients were selected on the basis of following criteria.

Inclusion criteria: All patients who entered the study had fulfilled the inclusion criteria relating to study (LUST, Total 1-PSS; score and prostate volume) of the placebo–controlled trial. I-PSS score was based on 7 (seven) items commonly referred to as irritative symptoms, but better term "storage symptoms") and obstructive symptoms (but better termed "voiding symptoms") each rated on a scale from 0 to 5 with a maximum score of 35 points. All patients gave informed consent for participation.

Exclusion criteria: Patients with a consistent residual urine volume > 200 ml, or with history of previous bladder neck, prostate or pelvic region surgery, any other condition which would affect micturition, including neurological bladder disorder, bladder neck stenosis, urethral stricture, prostate cancer, bladder stone, severe diverticulum of the bladder and recurrent urinary tract infections; history of previous hypersensitivity to other α - adrenoceptor antagonists were excluded from study. Patients were also excluded if they had taken any other investigational drugs within the previous 3 months. Efficacy was evaluated in an intention-to-treat population. The evaluation of the efficacy was based on the I-PSS score scales 35 to 0 (0 = maximum improved, 35= worsened). The primary parameters for assessment of efficacy were changes in total I-PSS score. The patient's medical history, concomitant medication and the total I-PSS symptoms score and a life style questionnaire were completed. The life style questionnaire consists of urinary symptoms with activities of daily living, worries and concerns associated with the condition, the general well-being of the patients. Digital rectal palpation with optional ultrasound was used to estimate prostate size. An abdominal ultrasound was performed to determine residual urine volume. We maintain a diary card for each patients to record I-PSS score 1, 2, 4, 8, 12 week to facilitate to know the effect of different drugs on different I-PSS symptoms. Treatment responders were defined as having a ≥30% improvement over base line or 25% decrease in total I-PSS score.

Study design: The total duration of the study was 12 weeks. Patients were divided in to two groups. Group 1- Patients take tamsulosin (0.4 mg) as a modified release capsule, one capsule per day after dinner at night and group 2 Patients take placebo one cap per day after dinner at night.

Statistical method : Within-group changes in scores from baseline were assessed by using the paired student t- test. The significance level set at $p \leq 0.05$.

RESULTS

A total of 69 men were enrolled in the study. The men assigned to the tamsulosin and placebo was similar in term of age, baseline demographic characteristics and symptoms.

Table 1: Demographic parameters

S. No.	Age Group	Tamsulosin		Placebo		Grand Total	
		No.	%	No.	%	No.	%
1.	40-49	02	3.92	00	00	02	2.89
2.	50-59	08	15.68	02	11.11	10	14.49
3.	60-69	23	45.09	09	50.00	32	46.37
4.	70-79	14	27.45	06	33.33	20	28.98
5.	80-89	04	7.84	01	5.55	05	7.24
Total		**51**	**100**	**18**	**100**	**69**	**100**

Table 2: Efficacy of Drugs on Total I-PSS Symptom Scores in Between Baseline and after 1,2,4,8 and 12 Weeks of Interval with Statistical Calculation

S.No.	Regimen	Change in total I-PSS from Ist Visit to last visit					
		Ist Visit (Mean ± SD)	Last Visit (Mean ± SD)				
			Ist week	2nd Week	4th Week	8th Week	12th Week
1.	Tamsulosin (0.4 mg)	20.20 ± 8.95	16.5 ± 3.41	13.87 ±10.42	6.9 ± 3.54	4.62 ± 2.87	3.5 ± 1.08
2.	Placebo	19.78 ± 7.92	19.57 ± 4.35	17.44 ± 7.72	14.22 ± 6.68	12.89 ± 5.92	10.78 ± 4.76

Regimen	1 Week	2 Week	4 Week	8 Week	12 Week
Tamsulosin	P=0.44, T=0.786 df=12, Not Significant	P=0.185, T=1.38 df=16, Not Significant	P=0.0004, T=4.370 df=18, Significant	P=0.0002, T=4.704 df=16, Significant	P=<0.0001, T=5.858 df=18, Significant
Placebo	P=0.951, T=0.06 df=14, Not Significant	P=0.53, T=0.63 df=16, Not Significant	P=0.127, T=1.610 df=16, Not Significant	P=0053, T=2.090 df=16, Not Significant	P=0.060, T=2.922 df=16, Not Significant

During the 3 month of study, 5 (9.80%) men in tamsulosin and 4 (22.22%) in the placebo group were discontinued the treatment, the most common reason were; lost to follow-up, lack of efficacy, adverse drug effects. Acute urinary retention developed in 1 (2.4%) men in the tamsulosin and 3 (21.42%) men in the placebo group during the study. 10 (19.60 %) patients in the tamsulosin and 03 (n=18) in placebo group were enrolled in catheterized state (at 1st visit of study) and most of them remove their catheter within 15-25 days of treatment. Two men (4.3%) in the tamsulosin and 2 (11.11%) in placebo group underwent supra- pubic prostatectomy surgery.

Total symptom score: In present study 1(n=46) patient in tamsulosin and 3 (n=14) in placebo group were increases their total symptom scores and 2 patients in placebo group have no changes in their total symptom scores from baseline. Treatment with tamsulosin resulted in a significant decrease in total I-PSS V/S placebo, the mean changes in total I-PSS from baseline to end of study was 16.7 points in tamsulosin and 9.0 points in placebo group as shown in table 2.

The mean change from baseline in the total I-PSS scores after 1 week of treatment with tamsulosin (p 0.44) better than that of placebo (p 0.95). After 4 weeks of treatment changes in tamsulosin group (P <0.0001) was statistically significant compare to placebo (p 0.12) and at the end (12 weeks) of study this change in total scores was more significant in tamsulosin (p <0.0001) V/S placebo (p 0.01) group.

Individual I-PSS Symptom: In individual symptom scores; the mean changes in *incomplete emptying symptom* scores from baseline to 1 weeks after of treatment with tamsulosin (p 0.67) is better than placebo (p 0.85); after 4 weeks this changes was statistically significant in tamsulosin group (p 0.032) V/S placebo (p 0.11) and at the end of study, this symptom score disappear in tamsulosin group as compare to placebo (p 0.105) in which improvement is not significant as shown in figure 1.

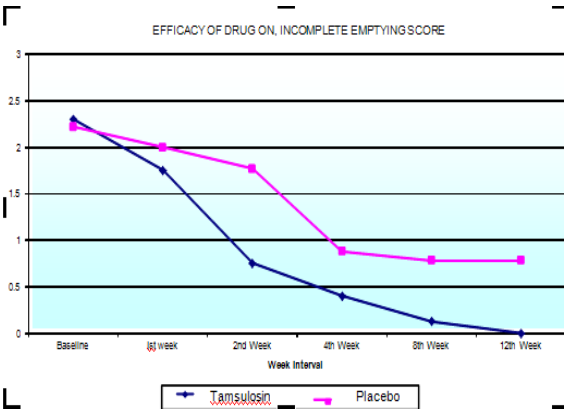

Figure 1: Efficacy of Drugs on Incomplete emptying Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

Frequency Score: Mean changes from baseline in frequency symptom scores first appear statistically significant (p 0.0009) after 4 weeks of treatment with tamsulosin and not significant (p 0.24) in Placebo treated patients at end of the study (12 weeks) this symptom was extremely significant (p <0.0001) in tamsulosin compare to placebo (p 0.10) as shown in figure 2.

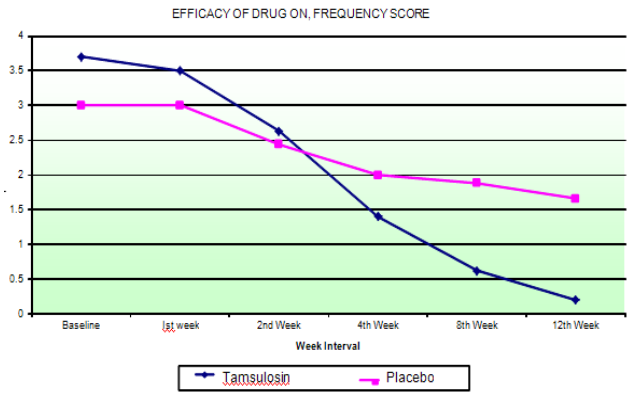

Figure 2: Efficacy of Drugs on Frequency Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

In intermittency Score: Changes in total intermittency scores from baseline was statistically significant after 2nd weeks in tamsulosin group, after 8 weeks in tamsulosin group symptom score disappear (p=nil) up to end of the study, however this is not quite significant with placebo (p 0.05) up-to the12 weeks as shown in figure 3.

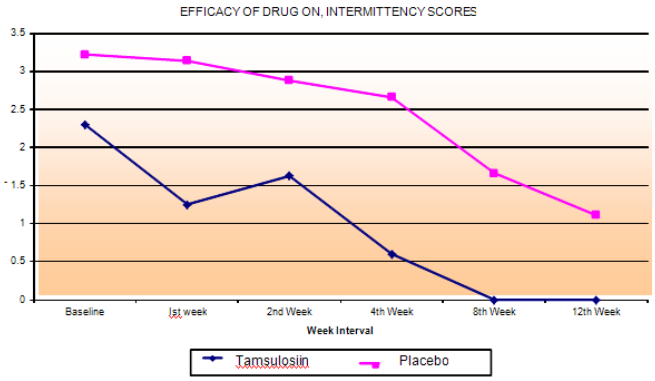

Figure 3: Efficacy of Drugs on Intermittency Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

Urgency Score: Mean changes from baseline in total urgency scores first significantly improved after 8 weeks of treatment with tamsulosin (p 0.039) while till end of study urgency Scores was not significant with placebo (p 0.26) as shown in figure 4.

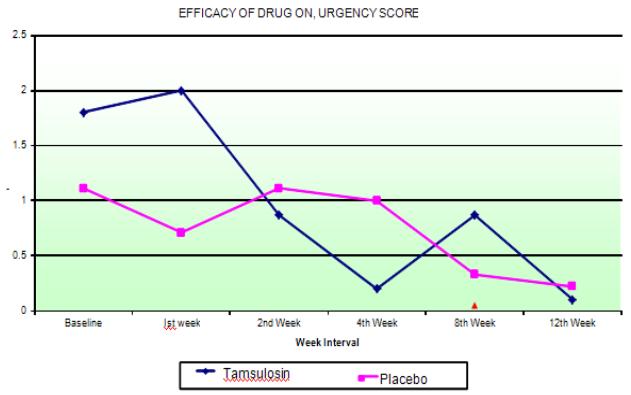

Figure 4: Efficacy of Drugs on Urgency Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

Weak Stream Score: significantly improved after second week of treatment with tamsulosin (p 0.0002) while it is not quite significant with placebo (p 0.05) up-to the end of study. Weak stream scores was extremely significant (p 0.0001) in tamsulosin at end of study compare to placebo (p 0.05) as shown in figure 5.

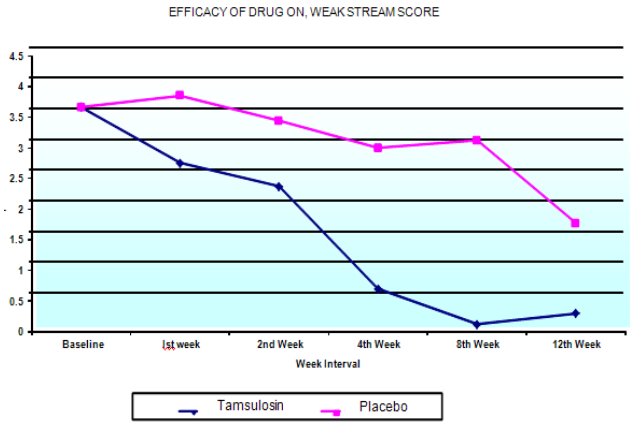

Figure 5: Efficacy of Drugs on Weak Stream Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

Straining Score: The mean change from baseline score in total straining score was significant (p 0.012) after 1 week with tamsulosin and not significant (p 0.28) with placebo up-to end of study as shown in figure 6.

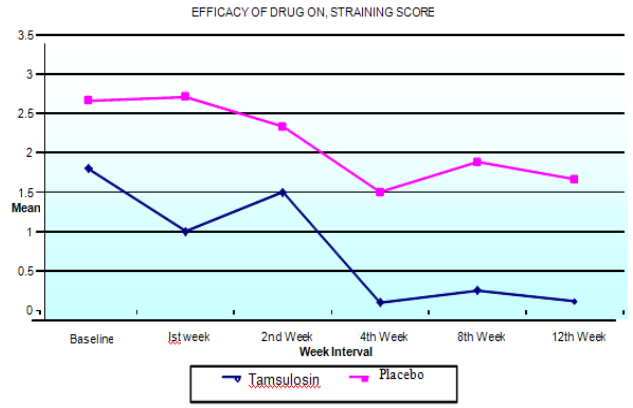

Figure 6: Efficacy of Drugs on Straining Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

Nocturia Score: Mean change from baseline in total nocturia symptom scores was first appear statistically significant (p 0.01) at 12 weeks of study with tamsulosin compare to placebo (p 0.28) in which symptom score was not statistically significant up-to end of study as shown in figure 7.

Notable adverse reaction of tamsulosin was similar to placebo shown in table 3. 14.28% of placebo and 13.04% of tamsulosin patients experienced treatment emergent adverse events. In tamsulosin group 2(4.34%) cases showed dizziness, 1(2.1%) headache, 1(2.1%) distended abdomen, 1(2.1%) decreased libido and 1(2.1%) somnolence. In placebo group, 1 (5.56%) cases showed distended abdomen and 1(5.56%) cases showed dizziness.

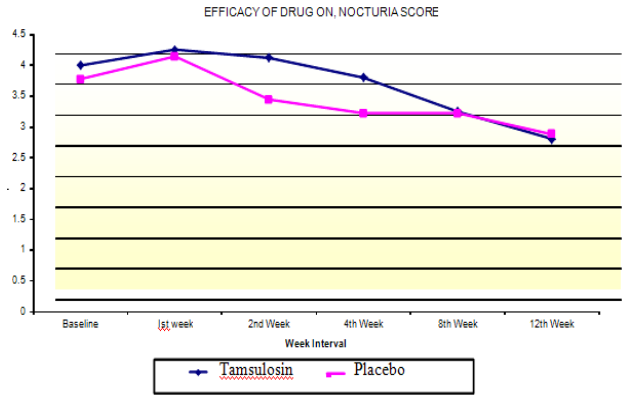

Figure 7: Efficacy of Drugs on Nocturia Score; and comparison of scores From Baseline to 1,2,4,8 and 12 weeks of Interval

Table 3: Commonly observed adverse effects

S.No.	Adverse effects	Tamsulosin (0.4 mg) (n=46)	Placebo (one cap) (n=14)
1	Dizziness	2 (4.34%)	1 (7.14 %)
2	Headache	1 (2.1%)	00
3	Tachycardia/ Palpitation	00	00
4	Syncope	00	00
5	Asthenia	00	00
6	Somnolence	1 (2.1%)	00
7	Abdominal distension	1 (2.1%)	1 (7.14 %)
8	Decreased Libido	00	00
9	Ejaculation Disorder	1 (2.1%)	00
10	Others (Hypersomnia)	00	00

Table 4: Comparison of Total I-PSS between treatment Groups from Baseline to 1,2,4,8 and 12 Weeks of trail

Duration of Treatment	Values of Tamsulosin V/S Placebo therapy Tamsulosin	Placebo	Tvalue	P value
Baseline	20.20 19.78±7.92	±8.95	0.10	0.91
1st Week	16.50 ± 3.41	19.57±4.35	1.20	0.25
2nd Week	13.87 ± 10.42	17.44±7.77	0.81	0.43
4th Week	6.69 ± 3.54	14.22±6.68	3.03	0.007
8th Week	4.62 ± 2.87	12.89±5.92	3.58	0.002
12th Week	3.50 ± 1.08	10.78±4.76	4.71	0.0002

DISCUSSION

Benign prostatic hyperplasia is the most common conditions associated with ageing in men, effecting 50% of those between the age of 50 and 60 years, and as many as 90% of those older than 80 years of age[8]. Symptoms such as urgency, dribbling and a weak urinary stream were present in the majority of men over 60 years of age[9]. In our study it was observed that maximum no. of cases belong to 60-69 year age groups. The possible deviation to general norms could be because of either Lack of time as well as awareness for older patients; Due to poverty or dependency of patients on other person at old age. In present study, the maximum sufferers (46.87%) were government which is supported by[10] study in which it is reported that physical activity was inversely related with total benign prostatic hyperplasia. Our study showed that tamsulosin 0.4 mg significantly improved total and individual symptoms score in men with benign prostatic hyperplasia, the improvements in total I-PSS was 82.6% as compare to placebo (45.51%). This improvement in total I-PSS with tamsulosin was similar to the previously reported study[11] in which the improvement in total I-PSS score was 34%. Previously 2 open-labels, observational study by[9] showed following results. In study 1, the change in total I-PSS score from baseline to 3rd visits (after 4 weeks treatment) was 8.5 point or 68% and in study 2, it was more than 10 point or 87% a from baseline to 4th visits (12 week). In the present study total symptom score first appear significant after 4 weeks similar to[12]. Variation in symptom score response to comparative study (82.6% v/s 34% or 35.1%) may be due to very less no. of cases or symptoms were due to mild urinary tract infection. In the present study, changes from baseline to end point; *incomplete emptying symptom* score were disappears at 12 weeks, similar condition was associated with another obstructive symptom; intermittency score, where it was disappear after 8 weeks of treatment. This may be due to, in maximum no. of patients this symptom was absent at 1st visit. The improvements from baseline to end point in two other obstructive (voiding) symptoms, (weak stream, and straining) were improved significantly first after 4 weeks and at end point, improvement was 91.82% with weak stream and 93.89% with straining. A European study[12] supported that like total scores, the obstructive and irritative symptom scores were improved significantly first after 4 weeks and improvement was continued up to end point. In our study, change of total frequency score was 94.59% and it appear statistically significant first after 4 weeks of treatment with tamsulosin while urgency score first appear significant after 12 weeks and total improvement from baseline to end point was 94.44%. Another symptom, nocturia, improved 30% from baseline and appears significant after 12 weeks. Tamsulosin was well tolerated during the 12 weeks of treatment; the incidence of adverse events in total population was 6 (13.1%). In which dizziness was maximum in 2 patients (4.34%), headache in 1 (2.1%), ejaculation disorder in 1 (2.1%) abdominal distention in 1 (2.1%), and somnolence in 1 (2.1%) patient, similar to our study showed that, the adverse events commonly associated with tamsulosin were dizziness (3.4%), headache (2.1%), digestive system disorder (7.6%), abnormal ejaculation (4.5%). and somnolence (0.3%). Another study[13] showed adverse events related to tamsulosin were dizziness 4.5%, abnormal ejaculation 5.3%, and others was following as asthenia 1.2%, somnolence 0.4%, postural hypotension 1.6%.

CONCLUSION

Tamsulosin was a highly efficacious and well tolerated during the short-term study. Tamsulosin significantly improved lower urinary tract symptom compared to placebo, with a mean change from baseline in the I-PSS to the end of study is 85.74%. Adverse events other than ejaculatory disorder were similar to placebo. 13.0 % ADR occurred in of patients treated with tamsulosin, more than half of which had occurred within the 1- 4 weeks of treatment however; in placebo group 14.28%. ADR is reported during study. The overall incidence of side effects was not significantly different from placebo.

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