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RESEARCH MANUSCRIPT

Tamsulosin sustained release preparation in patients of lower urinary tract symptoms due to benign prostatic hyperplasia

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Abstract

The efficacy and safety of tamsulosin sustained release preparation in patients of benign prostatic hyperplasia (BPH) with lower urinary tract symptoms (LUTS) was measured in this study. Thirty patients attending OPD were randomly selected from Government Medical College, Faridkot. Patients were subjected to tablet tamsulosin sustained release preparation (0.4 mg) once daily and the effect of the preparation of tamsulosin on international prostate symptom score (IPSS), quality of life (QOL) score, prostate size and residual urine volume was evaluated. At the end of the study, there was a significant decrease from 19.000 ± 4.594 at week 0 to 10.367 ± 3.429 at week 12 in IPSS as compared to the baseline ($p<0.05$). There was also a significant decrease at week 4 and 8 of the study. The percentage decrease was 45.43%. There was a statistically significant decrease of 1.967 at 12 weeks from the baseline ($p<0.05$) with regard to QOL score at the end of the study. There was also a significant decrease at week 4 and 8 of study in both the groups. The percentage decrease was 47.59%. There was a non-significant decrease in prostate size by 0.067 g from 43.200 ± 10.320 g at week 0 to 43.133 ± 10.352 g at week 12. Residual urine volume showed a significant decrease from 104.367 ± 29.005 mL at week 0 to 76.500 ± 24.370 mL at week 12 as compared to the baseline ($p<0.05$). The percentage decrease recorded 26.7%. Adverse effect was seen with in the treatment groups namely dizziness and headache. One patient had an attack of pharyngitis and one patient complained of abnormal ejaculation, incidence of 3.33%.The analysis clearly shows improvement in IPSS, quality of life score and residual urine volume without any improvement in prostate size.

Keywords: Tamsulosin, benign prostatic hyperplasia, lower urinary tract symptoms, quality of life, prostate size.

Introduction

Storage symptoms and voiding difficulties are two constituents of lower urinary tract symptoms (LUTS), former being more troublesome. Storage symptoms have their impact on quality of life (QOL). One of the common causes of male LUTS is benign prostatic hyperplasia (BPH) (Van Kerrebroeck *et al*., 2002). BPH is an age related phenomenon in nearly all men. Clinical hyperplasia of prostate gland starts at an early age of approximately 40 years. Several autopsy studies throughout the globe prove that histological BPH is prevalent in 10% of men in their thirties. This prevalence increases to 80% to 90% of men in their 70s and 80s. Histological prevalence is seen in most men as their age progresses (Roehrborn and McConnell, 2002).

BPH causes significant LUTS and most commonly presents as bladder outlet obstruction in males of age 70 years and above (Neal and Kelly, 2004). Clinical presentation of BPH is uniformly distributed around the world (Garraway *et al.,* 1991; Chute *et al.,* 1993; Tsukamoto *et al.,* 1995; Bosch *et al.,* 1995). International prostate symptom score (IPSS) is a standardized and validated tool for measuring the severity of BPH.

IPSS has been used by various researchers to categorize clinical BPH. According to IPSS score, clinical BPH is defined as score of $\geq$8, peak flow rate <15 mL/sec and prostate volume >20 cm^3 (Bosch *et al.,* 1995). In a study, 25% of men aged 50 years and above, about one third of men in 60s and 50% of all men aged 80 years and more were seen suffering from moderate to severe LUTS (McVary, 2006). Various types of oral controlled absorption system (OCAS) formulations are marketed for tamsulosin. Advantages of these tablets is the use of technology providing persistent continuous release, decreased peak plasma concentration, consistent and continuous plasma concentration over a period of 24 h and no effect of food on pharmacokinetics of the drug. A study carried out to prove continuous release of this formulation was carried out with the help of gamma scintigraphy and serum pharmacokinetic analysis proved the same for tamsulosin preparation throughout the entire gastrointestinal tract (Chapple and Chartier-Kastler, 2006). Against these backdrops, this study was conducted to measure the efficacy and safety of the tamsulosin sustained release preparation in patients of lower urinary tract symptoms due to benign prostatic hyperplasia.

Materials and methods

Ethics: The study was initiated after seeking approval of the protocol of the study from the ethics committee of the Government Medical College, Amritsar. Patients willing to participate in the study and gave informed consent, were recruited in the study.

Patients: Patients (*n=30*) of 45 years or more of age, diagnosed cases of BPH presenting with LUTS were selected randomly from the OPD of surgery, Guru Nanak Dev Hospital, Amritsar. At the time of recruitment, a proper history was taken from them. General physical examination was done along with required investigations to ensure that they met with the inclusion criteria i.e urine complete examination, urine culture and sensitivity test, serum prostate specific antigen, ultrasonographic for prostate size and residual urine volume. The investigations were done in Dept. of Radiodiagnosis, Government Medical College, Amritsar and Dept. of Microbiology, Government Medical College, Amritsar.

Inclusion criteria: (1) Males aged 45 years and more; (2) Patients with symptoms consistent with diagnosis of BPH but with no complications of BPH; (3) Patients with IPSS score of ≥8; (4) Patients with PSA ≤4 ng/mL; (5) Patients with ultrasonographic findings of residual urine less than 300 mL and prostate size more than 20 cm^3; (6) Patients with no evidence of prostatic malignancy and (7) Patients who sign the consent form were included in the study.

Exclusion criteria: (1) Patients with hypersensitivity to tamsulosin; (2) Patients with prostatitis, neurogenic bladder, bladder diverticulum and urethral stricture; (3) Patients with residual urine volume >300 mL on ultrasonography; (4) Patients with proven or suspected carcinoma; (5) Patients with definitive indication of invasive treatment such as history of urinary retention, previous history of catheterization to relieve retention, associated complications e.g. hydronephrosis, impaired kidney function, bladder stone, recurrent gross haematuria; (6) Patients with urinary tract infections within one month or recurrent urinary tract infections in the past; (7) Patients with severe cardiac, hepatic or renal dysfunction; (8) Patients taking drugs on a regular basis, which are documented to interact with tamsulosin; (9) Patients not signing consent form were excluded from the study.

Drug: Tablet tamsulosin sustained release preparation of about 0.4 mg daily once.

Experimental design: This study was a prospective, open labeled, randomized, intention to treat study. The duration of the study was 12 weeks. All patients were followed up in Dept. of Surgery even after the completion of the study. Baseline investigations of each patient were recorded.

About 30 patients were given tamsulosin controlled release preparation of 0.4 mg daily once. Patients were instructed not to chew or crunch the tablet. Compliance was checked by asking the patient to bring back the empty blister packets at every visit.

Parameters studied: IPSS score and QOL score at week 0 and then at regular interval of 4 weeks were recorded. Ultrasonography for prostate size and residual urine volume was evaluated at 0 weeks and at the end of study (12 weeks). The patients were scheduled to visit for regular checkups. History was taken, clinical examination done and adverse drug reaction monitoring performed at each scheduled visit. Patients were advised to report back immediately in case they develop symptoms of orthostatic hypotension.

International prostate symptom score: Two important standardized and validated symptom scoring instruments in initial assessment of each patient presenting with BPH are international prostate symptom score (IPSS) or American urological association (AUA) (Harada *et al.,* 1999). IPSS is a 7-item questionnaire which addresses the most common irritative and obstructive voiding symptoms (Table 1). This questionnaire is a self administered questionnaire with a response scoring ranging from 0 to 35 points. Scores from 0 to 7 points are considered as not or mildly symptomatic, scores between 8 and 18 points as moderately symptomatic and 19 or more as severely symptomatic (Roehrborn, 2005). These symptom score always keep on changing, thus degree of each patient's bother due to symptom should always be kept as the primary determinant of treatment response or disease progression in follow up period.

Ultrasonography: Trans-abdominal ultrasound performed with a GE RT 3200 advantage ultrasound machine using 3.5 MHz curvilinear abdominal transducer.

Residual urine volume: The bladder was examined initially in the full state and then after voiding. The maximum full volume was taken when the patient reported fullness. Post voiding residual urine volume was measured by three linear orthogonal measurements of the bladder as a, b and c. Residual Urine Volume (RUV) was calculated by the following formula:

$RUV = a \times b \times c \times \pi/6 = a \times b \times c \times 0.52$

The normal bladder empties completely. In practice however post void residual urine volume <10 cm^3 is regarded as normal and in older men, <20 cm^3 may be regarded as clinically non-significant. The bladder should be reasonably full before asking the patient to void, to avoid chances of false high residual urine volume (Frankel *et al.,* 1998).

Prostate size: The volume calculation for the prostate was carried out in the same manner as for bladder volume.

Table 1. International Prostate Symptom Score (IPSS).

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
Incomplete emptying: Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5
Frequency: Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5
Intermittency: Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
Urgency: Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5
Weak stream: Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
Straining: Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5

	None	1 time	2 times	3 times	4 times	5 times
Nocturia: Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed-about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5

Total score: 0-7 mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

Assessment of prostate size by this method is approximate but is sufficiently accurate for clinical purposes and more accurate than digital rectal examination. However in obese men, adequate visualization of the prostate by this method is not possible (Frankel *et al.,* 1998).

Statistical analysis: Statistical analysis was performed using SPSS 17.0 software. Analysis of variance (ANOVA) was used to assess the change in the mean of efficacy parameters and adverse events and variations of each visit from the mean at baseline. For all comparisons $p<0.05$ was considered statistically significant.

Results

The effect of the preparation of tamsulosin on IPSS score, QOL score, prostate size and residual urine volume was evaluated. Incidence of adverse events was also noted. The baseline characteristics of subjects are listed in Table 2.

All the patients completed the study. The mean age of the patients was 57.267 ± 6.654 years. The IPSS score and QOL Score at 0, 4, 8, 12 weeks are listed in Table 3 and 5. The change in IPSS Score and QOL Score from 0 to 12 weeks is listed in Table 4 and 6. There was significant reduction of IPSS score and QOL from 0 to 12 weeks. The prostate size score at 0 and 12 weeks and change in prostate size score from 0 to 12 weeks are listed in Table 7 and 8. There was no significant change in prostate size from baseline to the end of the study. The residual urine volume score at 0 and 12 weeks and change in residual urine volume score from 0 to 12 weeks are listed in Table 9 and 10. There was significant reduction in residual urine volume score. The adverse effects amongst subjects in the study population are listed in Table 11. The most common adverse effect was dizziness. Headache and attack of rhinitis was noted in patient. No other side effect was shown in patients.

Table 2. Baseline characteristics of subjects in the study (*n=30*).

Parameters	Mean ± SD
Age (years)	57.267 ± 6.654
IPSS	19.000 ± 4.594
QOL score	4.133 ± 0.8190
Prostate size (g)	43.200 ± 10.320
Residual urine volume (mL)	104.367 ± 29.055

Table 3. IPSS (mean ± SD %) at 0, 4, 8 and 12 weeks.

0 week	4 weeks	8 weeks	12 weeks
19.000 ± 4.594	17.600 ± 3.820	11.733 ± 3.473	10.367 ± 3.429

Table 4. Change in IPSS from 0 to 12 weeks.

Percentage change	45.43%
Mean change	8.633

Table 5. QOL score (mean ± SD %) at 0, 4, 8 and 12 weeks.

0 week	4 weeks	8 weeks	12 weeks
4.133 ± 0.819	3.833 ± 0.834	2.367 ± 0.850	2.167 ± 0.950

Table 6. Change in QOL score from 0 to 12 weeks.

Percentage change	47.59%
Mean change	1.967

Table 7. Prostate size score (mean ± SD %) at 0 and 12 weeks.

Time period of study		P value
0 week	12 weeks	
43.200 ± 10.320	43.133 ± 10.352	>0.05 (ns)

Table 8. Change in QOL score from 0 to 12 weeks.

	Prostate size
Percentage change	47.59%
Mean change	1.967

Table 9. Residual urine volume score (mean ± SD %) at 0, 4, 8 and 12 weeks.

Time period of study		P value
0 week	12 weeks	
104.367 ± 29.005	76.500 ± 24.370	<0.0001 (s)

Table 10. Change in residual urine volume score from 0 to 12 weeks.

	Residual urine volume
Percentage change	26.7%
Mean change	27.867

Table 11. Adverse effects amongst subjects in the study population.

Adverse effect	N (%)
Dizziness	1 (3.33%)
Headache	1 (3.33%)
Asthenia	-
Rhinitis	-
Pharyngitis	1 (3.33%)
Diarrhea	-
First dose hypotension	-
Orthostatic hypotension	-
Abnormal ejaculation	1 (3.33%)

Discussion

BPH is most commonly manifested as lower urinary tract symptoms. Two important presentations of LUTS are mechanical obstruction and irritative symptoms. Enlarged prostate gland can cause obstructive symptoms such as straining, hesitancy, prolonged micturition, poor and/or intermittent stream, dribbling and feeling of incomplete bladder emptying. Irritative symptoms are caused by increased tone of smooth muscles in bladder neck and prostatic stromal tissue causing increase in urinary outflow leading to urgency, urge incontinence, frequency and nocturia (Chute *et al.,* 1993). Surgical removal of prostatic stroma is a traditional method of treatment of patients of BPH presenting with LUTS. Due to discovery and isolation of α_1 adrenoceptor (AR) subtypes in the adenoma of prostatic tissue, a number of pharmacological treatment modalities with antagonists at these receptors became possible.

Currently many α_1 AR antagonists such as alfuzosin, doxazosin, terazosin and tamsulosin are used for pharmacological management of LUTS in BPH (Lee 2003). Use of these agents has resulted in significant improvement in symptoms and urinary flow rates in a number of patients of LUTS. Tamsulosin is an uroselective α_1 AR antagonist used for pharmacological management of LUTS. α_1 AR subtypes α_{1a} and α_{1d} are the targets for tamsulosin activity. But plain tablet preparations of tamsulosin resulted in many cases of orthostatic hypotension and many other adverse effects leading to decreased quality of life and low compliance rates (Bosch *et al.,* 1995). Advent of modified release preparation helped in decreasing the incidence of adverse effects and further enhanced the uroselectivity of tamsulosin to α_{1a} AR subtype (Han *et al.,* 1995; Rabasseda and Fitzpatrick, 1996; Mc Vary, 2006).

In this study, the effect of one of the preparations of tamsulosin available as tamsulosin sustained release preparation was evaluated on international prostate symptom score, quality of life score, prostate size and residual urine volume. Thirty patients were recruited in this study. At the end of the study, there was a significant decrease in IPSS as compared to the baseline ($p<0.05$). This significant decrease in IPSS score is supported by a study which also showed 6.8, decrease in IPSS for BPH. This significant decrease in IPSS was registered throughout the study period (Cervenakov and Fillo, 2001). Similar significant decrease in IPSS after administration of 0.4 mg of tamsulosin was also reported by Bechara *et al*. (2008). Similar findings were reported by Li *et al*. (2007) which also reported a significant improvement in IPSS with the treatment of tamsulosin (Li *et al.,* 2007). Rahardjo *et al*. (2006) found a significant decrease in total IPSS after treatment with tamsulosin as compared to baseline. Significant change of 6.8 in total IPSS was registered in comparison to baseline by Kawabe *et al*. (2006).

Another study by Pompeo *et al*. (2006) also found a similar significant decrease in IPSS in patients treated with tamsulosin as compared to baseline. Hutchison *et al.* (2007) also found a significant improvement of 6.3 in IPSS in patients on tamsulosin after comparing many drugs. Gotoh *et al*. (2005) also derived a statistically significant change in IPSS with tamsulosin. Significant mean change of 6.5 (adjusted $p= 0.014$) from baseline of IPSS with tamsulosin 0.4 mg was a reported fact in many studies. There was a statistically significant decrease as compared to the baseline ($p<0.05$) with regard to QOL score at the end of the study. There was also a significant decrease at week 4 and 8 of study in both the groups. In patients receiving tamsulosin sustained release preparation, the score decreased from 4.133 ± 0.819 at week 0 to 2.167 ± 0.950 at week 12, which was a statistically significant decrease of 1.967 from the baseline showing a percentage decrease of 47.59%.

There was a significant decrease in QOL scores registered throughout the study period. Similar significant decrease in QOL after administration of 0.4 mg of tamsulosin was also reported by Cervenakov and Fillo (2001) and Bechara *et al.* (2008). Similar findings were recorded by Li *et al*. (2007) who also reported a significant improvement in QOL with the treatment of tamsulosin. Rahardjo *et al*. (2006) found a significant decrease in QOL score after treatment with tamsulosin as compared to baseline. A significant change of 1.4 in QOL score was registered in comparison to baseline by Kawabe *et al.* (2006). Pompeo *et al*. (2006) also found a similar significant decrease in QOL scores in patients treated with tamsulosin as compared to baseline. Gotoh *et al*. (2005) also derived a statistically significant change in QOL score with tamsulosin. Amongst the ultrasonographic parameters, prostate size decreased from 43.200 ± 10.320 g at week 0 to 43.133 ± 10.352 g at week 12, showing a statistically non-significant decrease of 0.067 g with a percentage decrease of 0.1% from the baseline. This non-significant decrease in prostate size was in correlation with study conducted on α_1 AR antagonists by Lepor *et al*. (1996). Patel and Chapple (2006) showed that unlike 5α reductase inhibitors, α AR antagonist have no alteration in disease process and no effect on prostate volume. Residual urine volume showed a significant decrease as compared to the baseline ($p<0.05$). In patients on tamsulosin sustained release preparation, the residual urine volume decreased from 104.367 ± 29.005 mL at week 0 to 76.500 ± 24.370 mL at week 12, showing statistically significant decrease of 27.867 from the baseline. The percentage decrease was 26.7%. The above findings were in correlation with the study conducted by Li *et al*. (2007) who compared drugs and observed significant decrease in residual urine volume in patients treated with tamsulosin at average follow-up of 6 months.

Narayan and tunuguntla (2005) also recorded significant reduction in residual urine volume in patients on tamsulosin. Lee (2000) in his review evaluated the efficacy and safety of tamsulosin compared with other adrenergic antagonists for treatment of symptomatic BPH also documented significant reduction in residual urine volume. Murayama *et al*. (1997) also evaluated efficacy and safety of tamsulosin in 54 patients and found that the residual urine volume decreased significantly. Bechara *et al*. (2008) also noted a significant decrease in residual urine volume in tamsulosin group from baseline ($p<0.001$). In his study, comparing tamsulosin with doxazosin, Rahardjo *et al*. (2006) also found significant reduction in residual urine volume only in tamsulosin group. However, the results of the present study were contrary to the study by Gotoh *et al*. (2005) who showed statistically significant improvement for the primary efficacy variables (total IPSS, maximum flow rate on free uroflowmetry) and the secondary efficacy variables (average flow rate, changes in the IPSS storage score, IPSS voiding score and QOL Index score) from baseline to endpoint except for residual urine in the tamsulosin group. Adverse effect seen within the treatment group was dizziness in one patient. One patient complained of headache and one had an attack of pharyngitis, incidence of 3.33% of total. One patient also reported of abnormal ejaculation, incidence of 3.33% of total. There was no case with history suggestive of orthostatic hypotension or first dose hypotension. None of the reported adverse effects was serious enough to hamper with daily activities of the patients or required discontinuation of therapy. These findings were supported by a review done on tamsulosin, stating headache asthenia, dizziness and pharyngitis, rhinitis like complaints as most common adverse effects. The review by Lee (2000) stated abnormal ejaculation in 4.4 to 14% of patients. Hypotension as an adverse effect was reported by this same review as nil with use of tamsulosin similar to this study report. This shows that the incidence of adverse effects was within range in accordance with the previous studies. The analysis clearly shows improvement in IPSS, QOL score and residual urine volume without any improvement in prostate size. This shows that the results of this study are promising and as such warrant further investigation with a larger number of patients.

Conclusion

LUTS in patients of BPH can cause many troublesome symptoms leading to lot of suffering and compromised QOL. This study showed that, before going for surgery for the relief, tamsulosin sustained release preparation can play a crucial role in decreasing the bother caused by various symptoms and improving the QOL of the patients. This preparation may immensely help those men with multiple comorbidities and on anti-hypertensive medications that might predispose them to symptomatic hypotensive episodes.

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