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Prospective Observational Study to Assess the Safety and Efficacy of Once-Daily Tamcontin® Tablet (Continus® Controlled Release Tablet of Tamsulosin Hydrochloride, 0.4 Mg) in the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia (BPH) in the Routine Clinical Practice- An Indian Experience.

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ABSTRACT

To investigate the safety and efficacy of once-daily Tamcontin® Tablet (Continus® controlled release tablet of tamsulosin hydrochloride, 0.4 mg) in the routine clinical treatment of Benign prostatic hyperplasia (BPH) in India. BPH is a prevalent disease, especially in old men and if left untreated can lead to serious complications such as acute urinary retention, renal insufficiency and failure, urinary tract infection and bladder stones. The impact of BPH on quality of life (QOL) can be significant and cannot be underestimated. A total of 100 newly diagnosed, treatment naive BPH patients were included in the study from 6 urology centres. Patients were assigned to once-daily nighttime treatment with Tamcontin® tablet for a period of 6 weeks. Following the baseline visit, patients were examined at week 3 and 6. The efficacy variables of the study were International Prostate Symptom Score (IPSS), quality of life (QOL), maximal urinary flow rate (Qmax), post void residual urine volume and hours of undisturbed sleep (HUS). Safety was assessed via monitoring of adverse events at every visit. The mean age of the patients was 59.6±10.5 years. There was significant improvement in IPSS, QOL, post void residual urine volume and hours of undisturbed sleep (nocturia) at week 3 and 6. The study drug was well tolerated and no grade 3/4 toxicities were observed. The present study indicates the therapeutic advantage of Continus® controlled release tablet of tamsulosin hydrochloride (0.4 mg) in the treatment of BPH in the routine clinical practice.

Keywords: Benign prostrate hyperplasia; Tamsulosin hydrochloride; Nocturia; International Prostate Symptom Score; Quality of life

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone.[1] It is characterized by the non-malignant overgrowth of prostatic tissue surrounding the urethra thereby constricting the urethral opening and giving rise to associated lower urinary tract symptoms (LUTS) such as urgency, frequency, nocturia, incomplete bladder emptying, weak urine stream, decreased and intermittent force of stream and the sensation of incomplete bladder emptying. [2] BPH is a prevalent disease, especially in old men and about 80% of men in their 70's suffer from BPH related LUTS. With the rise of average life expectancy, the number of males suffering from voiding difficulty secondary to BPH is also increasing. [3] Data from epidemiological community based survey indicates that approximately 25% of men aged 40 years and over usually suffer from LUTS. [4-7]

The progression of disease has been associated with several factors such as age and prostate volume (PV). However, in routine clinical practice, LUTS are commonly the only determinant for a BPH diagnosis. BPH is not often a life threatening condition; however, its impact on quality of life (QOL) can be significant and it cannot be underestimated. [1] The prevalence and the severity of LUTS in the aging male can be progressive and if left untreated can lead to serious complications such as acute urinary retention, renal insufficiency and failure, urinary tract infection, and bladder stones. [8] In India, BPH is considered as a common pathological condition with an incidence of 92.97% and 93.3%. [9]

Treatment options for BPH include watchful waiting with lifestyle modification, pharmacological treatment and surgical procedures. [1-2, 10-13] BPH-related LUTS can be treated by surgical and medical therapy; however the choice of treatment is generally based on the severity of disease, risk of progression and co-morbidity. Medical management of BPH is the first therapeutic option available for a patient with symptomatic BPH. [6,7] Currently, alpha-1-adrenergic receptor antagonists (alpha-blockers) and 5-alpha-reductase inhibitors (5ARIs) are the recommended medical treatment for BPH. [14,15] Alpha-blockers are the most common prescription medications and include tamsulosin, doxazosin, terazosin, prazosin and alfuzosin. [16, 17] Because of high alpha-1a-adrenergic receptor affinity, tamsulosin may improve urinary symptoms and flow with fewer adverse effects. [17] It is well absorbed orally with half-life of 5 to10 hours and extensively metabolized by the cytochrome P450 system. Several studies have demonstrated a significant improvement in urinary flow after single dose administration of tamsulosin at doses of 0.2 to 0.8 mg once daily. [18-20] With the aim of generating the relevant data in Indian patients, we undertook this prospective observational study to assess the safety and efficacy of once-daily Tamcontin® tablet (Continus® controlled release tablet of Tamsulosin Hydrochloride, 0.4 mg) in the treatment of lower urinary tract symptoms secondary to BPH in the routine clinical practice.

MATERIALS AND METHODS

Eligibility criteria

A total of 100 patients from the outpatient clinics of 6 centers in New Delhi, India were included in the study. Eligibility criteria included males aged ≥40 years and < 80 years with a confirmed clinical diagnosis of BPH. Patients were required to be treatment naïve and eligible for medical therapy with the single agent Tamsulosin, as per the clinical judgement of the treating physician. Further inclusion criteria were patient's willingness to participate in the study, signed and dated informed consent document and laboratory parameters suitable to start therapy with Tamsulosin as per the clinical judgement of the treating physician. Exclusion criteria included patients requiring combination therapy or surgery, suspicious hypersensitivity to α-AR antagonists and history of prostate cancer. The study was conducted according to the ethical principles stated in the latest version of Helsinki Declaration and the applicable guidelines for good clinical practice (GCP).

Treatment plan

Patients were assigned to treatment with Tamcontin® tablet (Continus® controlled release tablet of Tamsulosin hydrochloride, 0.4 mg) once daily at 9 pm for a period of 6 weeks. Following the baseline visit, patients were examined at week 3 (Day 21 ± 7d) and week 6 (Day 42 ± 7 d) as per the routine clinical practice.

Study objectives and assessment of response

The primary objective of the study was to assess the safety and efficacy of once-daily Tamcontin® tablet in the treatment of lower urinary tract symptoms secondary to Benign Prostatic Hyperplasia. The efficacy variables of the study were change in the baseline scores of International Prostate Symptom Score (IPSS), quality of life (QOL), maximal urinary flow rate (Qmax) and postvoid residual urine volume (PVR) at week 3 and 6. In addition, patients were evaluated for hours of undisturbed sleep (HUS) based on how long they can sleep at night before first awakening to pass urine using a scale ranging from <2 hours to > 6 hours. Patients were also questioned for Morning Activeness score on a 10 centimeter (cm) scale. This was to assess how active and fresh they felt after waking up in the morning. One end of this scale represented sleepy and tired (score 0) and the other end represented fresh and active (score 10). Safety assessments included monitoring of adverse events (AEs) and laboratory parameters.

Statistical Analysis

All statistical analyses were performed by using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Values of each parameter at every time point were summarized as mean ± SD and a p-value of < 0.05 was considered statistical significant.

RESULTS

Mean age of the patients was 59.6±10.5 years and their mean body mass index (BMI) and prostate volume were 26.4±4.1 kg/m^2 and 32.4±13.2 ml respectively. The baseline characteristics of the patients are shown in Table 1.

Table1: Demographics and other baseline characteristics (N=100)

Characteristics	Mean ± SD
Age (yr)	59.6 ± 10.5
BMI (kg/m^2)	26.4 ± 4.1
Prostate volume (ml)	32.4 ± 13.2

BMI: body mass index, SD: standard deviation

Table 2: Improvement in IPSS, QOL, Qmax, PVR and Morning Activeness score (N=77)

	Mean ± SD	Mean change from Baseline	p-value
IPSS			
Baseline	16.01 ± 6.5	---	
3 weeks	8.55 ± 4.6	-7.46 ± 5.27	<0.001*
6 weeks	6.07 ± 3.7	-9.94 ± 7.03	<0.001*
QOL			
Baseline	3.43 ± 1.0	---	
3 weeks	2.32 ± 1.1	-1.11 ± 0.78	<0.001*
6 weeks	2.12 ± 1.4	-1.31 ± 0.93	<0.001*
Q max (ml/sec)			
Baseline	13.66 ± 5.9	---	
3 weeks	15.93 ± 7.2	2.27 ± 1.60	0.034*
6 weeks	14.7 ± 5.9	1.04 ± 0.73	0.275
PVR (ml)			
Baseline	51.74 ± 61.8	---	
3 weeks	25.8 ± 29.5	-25.94 ± 18.34	0.001*
6 weeks	25.9 ± 46.2	-25.84 ± 18.27	0.003*
Morning Activeness Score			
Baseline			
3 weeks	6.6 ± 3.2	---	
6 weeks	8.2 ± 2.2	1.6 ± 1.13	<0.001*
	8.5 ± 2.2	1.9 ± 1.34	<0.001*

IPSS: International Prostate Symptom Score, QOL: Quality of life, Qmax: Maximal urinary flow rate, PVR: Postvoid residual urine volume
* Significant

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Of the 100 patients included in the study, 85 completed the 3 weeks and 77 completed the 6 weeks of treatment. Out of 23 subjects who did not complete the study, 21 (91%) did not turn-up for second visit and the drug treatment was changed for 2 (9%) by the study physician. All the efficacy analyses were run for 77 patients who completed the 6 weeks of treatment. The mean scores of IPSS, QOL, Qmax and PVR are shown in Table 2.

The mean IPSS score at baseline, 3 and 6 weeks was 16.01±6.5, 8.55±4.6 and 6.07±3.7 whereas the mean QOL score at these time points was 3.43±1.0, 2.32±1.1 and 2.12±1.4 respectively. There was significant difference in the IPSS and QOL scores at week 3 ($p < 0.001$) and week 6 ($p < 0.001$) as compared to baseline.

The mean Qmax value at baseline, 3 and 6 weeks was 13.66±5.9, 15.93±7.2 and 14.7±5.9 respectively. Although a significant difference was observed in Qmax value at week 3 ($p = 0.034$), the difference was found to be non-significant ($p = 0.275$) at week 6.

The mean PVR value at baseline, 3 and 6 weeks was 51.74±61.8, 25.8±29.5 and 25.9±46.2 respectively and there was a significant difference in the PVR value at week 3 ($p = 0.001$) and week 6 ($p = 0.003$) as compared to baseline.

The Morning Activeness score at baseline, 3 and 6 weeks was 6.6±3.2, 8.2±2.2 and 8.5±2.2 respectively and a significant difference was observed at week 3 ($p < 0.001$) and week 6 ($p < 0.001$) as compared to baseline.

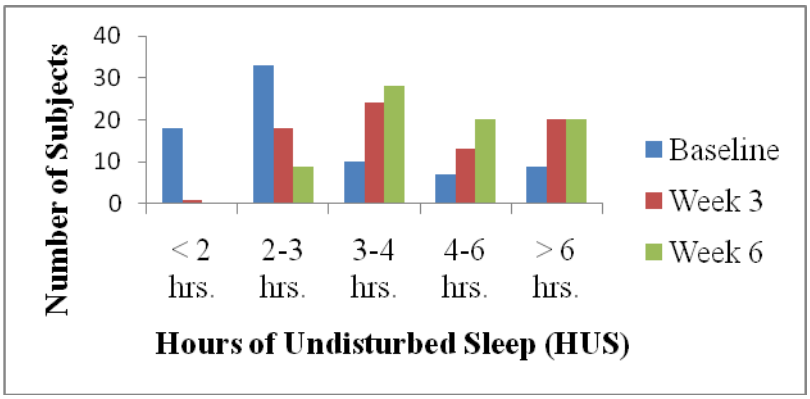
The results demonstrate a significant improvement in IPSS, QOL, post void residual urine volume (PVR) and Morning Activeness score at week 3 and 6. Further, a significant improvement in maximal urinary flow rate was also observed at week 3.

Table 3: Improvement in HUS at Week 3 and Week 6 (N=77)

No. of Hours of Undisturbed Sleep	Baseline	3 weeks‡	6 weeks
< 2 hours	18	1	-
2-3 hours	33	18	9
3-4 hours	10	24	28
4-6 hours	7	13	20
> 6 hours	9	20	20

‡ Data not available for 1 patient

Figure 1: Distribution of HUS at Baseline, Week 3 and Week 6



A significant reduction in nocturia was observed with 57 (74%) and 68 (88.3%) patients respectively experiencing more than 3 hours of undisturbed sleep at week 3 and 6 compared to 26 (33.7%) at baseline (Table 3). Figure 1 presents the distribution of hours of undisturbed sleep at baseline, week 3 and week 6.The study drug was well tolerated. Two patients reported vertigo and one each reported postural hypotension and headache. No grade 3/4 toxicities were observed.

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DISCUSSION

BPH is a common cause of lower urinary tract symptoms which are problematic in daily life and lower the quality of life in affected people. [2, 3] The exact aetiology is unknown, however, the similarity between BPH and the embryonic morphogenesis of prostate has led to the hypothesis that BPH may result from a reawakening of embryonic induction processes in adulthood. Complications such as acute urinary retention, renal insufficiency and failure, urinary tract infection, and bladder stones are the most common factors leading towards surgical management of BPH. [8, 21, 22] However, surgery also carries the risk of complications like bleeding, infections, retrograde-ejaculation, impotence and incontinence.

For quick and excellent results without significant adverse effects, alpha-adrenergic antagonists such as tamsulosin, alzusosin, doxazosin, terazosin and prazosin are considered as the first-line therapy of BPH-related LUTS. [1, 2, 23-25] Their efficacy in reducing LUTS is comparable although differences in adverse effects between these drugs have been clearly presented. The rationale for using α-adrenergic blockers is based on the fact that noradrenaline acts at α1-adrenergic receptors (α 1-AR) in the neck and sphincter of the urinary bladder to promote contraction and urinary retention. It also promotes contraction of smooth muscles in the prostate capsule and prostatic urethra. Therefore, α1-AR antagonists relieve the obstruction due to this dynamic component by relaxing the smooth muscle in and around the prostate and bladder neck.

Of the recently available alpha-blockers, tamsulosin has the most favorable efficacy, tolerability and safety, and is the most widely used medicine in clinical practice. [26] Tamsulosin, which is a uroselective third-generation α 1-AR antagonist, is the only agent able to discriminate between receptor subtypes. [27] It is a highly uroselective $\alpha1_A$ and $\alpha1_D$ blocker and causes minimal peripheral $\alpha1_B$ blockade. Therefore, tamsulosin tends to interfere less with blood pressure regulation and induces less vasodilatory side effects than other nonselective alpha-blockers. Compared to alfuzosin, it is well tolerated in patients with cardiovascular co-morbidity and with co-medications, especially in the elderly patients. [28, 29] Alfuzosin is often discontinued because of adverse vasodilatory events in elderly patients who are receiving therapy for concomitant cardiovascular diseases. This is because vasodilatory adverse effects might lead to potentially serious complications such as falls, fractures and institutionalization. Thus, a uroselective drug like tamsulosin represents a good therapeutic option for patients of BPH in the absence of absolute indications for surgical treatment.

The safety/efficacy profile of tamsulosin is further enhanced by administering it as a Continus® controlled release formulation which slows the drug release and prolongs the absorptive phase thereby extending the overall duration of action. In the Continus® formulation, the release of the drug is controlled in a very precise and predictable manner in order to provide smooth drug levels while minimizing the usual peak and trough fluctuations. [30] This helps in lowering the incidence of side effects associated with peak drug levels. The low incidence of side effects reported in our study corroborates with the improved tolerability of Continus® controlled release tamsulosin tablets.

Several studies have demonstrated a significant improvement in urinary flow after single dose administration of tamsulosin at doses of 0.2 to 0.8 mg once daily. [19-21] Our study also showed that Continus® controlled release tablet of tamsulosin hydrochloride at a dose of 0.4 mg once daily can lead to significant improvement in IPSS, QOL and post void residual urine volume (PVR) at week 3 and 6. Generally 4 weeks of treatment with tamsulosin is enough to improve symptoms, we designed a 6 week study to match the routine clinical practice of BPH treatment in India. Also the 9 PM recommended dosing time of the tablet achieves good control over nocturia, while maintaining effective control over LUTS for the rest of the 24 hours. This is clearly evident from our study results which show a good improvement in HUS and Morning Activeness score at 3 and 6 weeks of therapy.

CONCLUSION

Tamsulosin hydrochloride (0.4 mg) once daily is safe, well-tolerated and clinically effective in improving the symptoms and urinary flow rate in patients with symptomatic BPH. The present study indicates the therapeutic advantage of Continus® controlled release tablet of tamsulosin hydrochloride (0.4 mg) in the treatment of lower urinary tract symptoms secondary to BPH in the routine clinical practice. Nighttime once-

daily administration maintains effective control over nocturia and provides good symptom relief throughout the day. Minimal vasodilatory side effects support the safety of this formulation for use in BPH.

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Conflict of Interest

The Authors declares that no benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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