

Tadalafil vs Tamsulosin for the Management of Lower Urinary Tract Symptoms in Men with Benign Prostatic Hyperplasia: A Randomised Clinical Trial

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ABSTRACT

Introduction: Tadalafil and tamsulosin have both been approved for use in the management of Lower Urinary Tract Symptoms (LUTS). Limited studies have shown the efficacy of tadalafil in terms of maximum urinary output flow (Qmax) and post-void residual (PVR).

Aim: To compare the efficacy of tadalafil 5 mg and tamsulosin 0.4 mg in patients with Benign Prostatic Hyperplasia (BPH).

Materials and Methods: A prospective, open-label, Randomised clinical study was conducted in the Department of Urology at Kurnool Medical College, Kurnool, Andhra Pradesh, India. The study duration was one year and five months, from February 2015 to July 2016. A total of 83 patients clinically diagnosed with BPH were included, but 23 patients were excluded from the analysis due to lost follow-up. The remaining 60 patients were randomly assigned to two groups: one receiving tadalafil 5 mg (n=30) and the other receiving tamsulosin 0.4 mg (n=30) for 12 weeks. Demographic characteristics, total International

Prostate Symptom Score (IPSS), individual IPSS, Quality of Life (QoL) score, Qmax, PVR, and differences in symptoms were analysed. Data were analysed using the Wilcoxon signed-rank test and Mann-Whitney U test. A p-value < 0.05 was considered statistically significant.

Results: The mean age for group I (tadalafil 5 mg) and Group II (tamsulosin 0.4 mg) was 62.7 and 61.0 years, respectively (p=0.147). Patients who received tadalafil showed significantly higher efficacy in all measures from baseline to 12 weeks, including increased Qmax (12.0 mL/sec vs 15.1 mL/sec), reduced QoL scores (4.2 vs 3.7), and PVR (26.5 mL vs 15.8 mL), compared to tamsulosin where the increase in Qmax was 11.6 mL/sec vs 13.6 mL/sec, reduction in QoL scores was 4.1 vs 2.4, and PVR was 24.0 mL vs 16.2 mL, between baseline and 12 weeks.

Conclusion: Tadalafil 5 mg is a recent drug option available for the treatment of LUTS-BPH. The efficacy and safety of tadalafil 5 mg and tamsulosin 0.4 mg are comparable.

Keywords: International prostate symptom score, Phosphodiesterase-5 inhibitors, Quality of life, Uroselective alpha-blocker

INTRODUCTION

BPH is the most prevalent benign disease in males with diverse LUTS [1]. It is the fourth most prominent condition among men aged ≥ 50 years and accounts for 80% of men aged ≥ 70 years [2]. According to available data, the prevalence of BPH surged from 25% in the 40-49 age group to 80% in the 70-79 age group [3]. Clinically, BPH causes LUTS and its symptoms, such as storage (impaired bladder emptying, urinary frequency, nocturia, urinary urgency, and urge incontinence), voiding (urinary incontinence, a restricted urinary stream), and postmicturition, which can impair patients' quality of life [4]. There are different treatment modalities for BPH, including conventional methods and surgical intervention. However, surgical intervention is associated with complications such as bleeding, ureteral orifice injury, bladder neck injury, rectal injury, Transurethral Resection of the Prostate (TURP) syndrome, bladder neck contractures, and urethral stricture disease [5,6]. In males with moderate to severe LUTS, alpha-blockers and 5-Alpha-reductase Inhibitors (ARIs) are regarded as the first-line conventional medicine. The recent American Urological Association (AUA) guideline recommends tadalafil 5 mg in patients with LUTS/BPH, irrespective of comorbid erectile dysfunction [7]. Phosphodiesterase-5 (PDE5) inhibitors have been shown in several in-vitro studies to relax smooth muscles in the bladder neck and prostate, as well as to reduce the overstimulation of the detrusor muscles [8,9]. PDE-5 inhibitors reduce alpha-adrenergic-induced contractions [10].

A study by Angulo J et al. showed that tadalafil accelerated sodium nitroprusside-induced relaxation in muscle strips and improved cyclic Guanosine-Monophosphate (cGMP) accumulation in homogenized tissue [11]. In contrast, tamsulosin, a uroselective alpha-blocker, relieves bladder, neck, and prostate smooth muscle, promoting bladder emptying [12]. Several placebo-controlled trials have demonstrated the positive effect of tadalafil on LUTS [13,14]. However, limited studies have shown efficacy in Qmax and PVR [15-17]. In light of the above context, the present study was conducted to compare the efficacy of tadalafil 5 mg and tamsulosin 0.4 mg in terms of Qmax and PVR in patients with BPH.

MATERIALS AND METHODS

A prospective, open-label, Randomised clinical trial was conducted in the Department of Urology at Kurnool Medical College, Kurnool, Andhra Pradesh, India. The study duration was one year and five months, from February 2015 to July 2016. The study protocol was approved by the Institutional Ethics Committee (EC approval no: 143/2021), and written informed consent was obtained from all eligible patients.

Inclusion criteria: Patients aged ≥ 40 years with a confirmed diagnosis of BPH, a total IPSS score of ≥ 8 , and a prostate volume between 20 mL to 70 mL were included in the study.

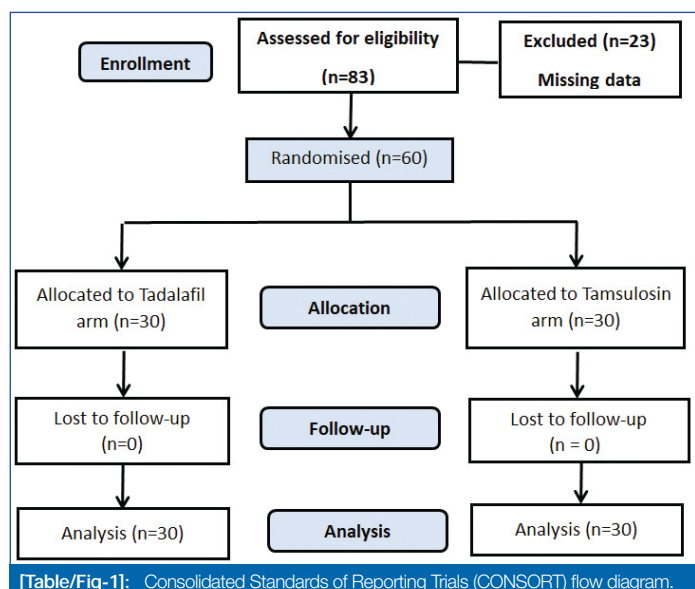
Exclusion criteria: Patients with bladder outlet obstruction and PVR > 200 mL and Qmax < 5 mL/s, patients with serum Prostate-Specific Antigen (PSA) > 10 ng/mL with a risk of prostate cancer,

and suspected or confirmed prostate cancer, a history of postural hypotension or syncope, hepatic or renal disease, acute urinary retention requiring catheterization, neurological conditions causing bladder outlet obstruction, any history of prostate surgery or other intervention, patients receiving alpha receptor antagonist within two weeks, 5-ARIs for LUTS, or nitrates for cardiovascular conditions were excluded from the study.

Sample size calculation: Based on a comparative study by Pawar DS et al., a standard deviation (SD) of 12.3 (1.2) and 10.5 (1.8) was considered for the tamsulosin and tadalafil groups, respectively [18]. The sample size was calculated using 80% power and a 5% significance level for peak flow rate. A sample size of 60 (30 in each arm) was calculated to detect improvement in IPSS, estimating a dropout of 10%.

Study Procedure

Single-blinded randomization was done using randomization software. The present study included 83 patients, out of which 23 patients were excluded due to missing data, and the remaining 60 patients were randomly assigned to two groups, with 30 in each group. One group received once daily oral doses of tadalafil 5 mg, and the other group received tamsulosin 0.4 mg for 12 weeks at night. The use of drugs that can affect the urinary function of the patients was restricted. The efficacy and safety of the treatment regimens were evaluated at baseline, four weeks, and 12 weeks after initiation of the treatment [Table/Fig-1].



The demographic characteristics of the patients, including age, prostatic volume, and other parameters such as the total IPSS and individual IPSS, QoL score [19,20], maximum urinary output flow (Qmax), PVR, and differences in symptoms were analysed. Uroflowmetric free urinary flow measurement (Urolyn 1000, Medtronic, UK) was performed to measure voided urine per unit of time and maximum flow rate (Qmax). Prostate size was measured by transrectal ultrasound (Siemens Sonoline SI-250 with a probe of 5-7.5 MHz), and PVR was measured by transabdominal ultrasound. All parameters were assessed at baseline, four weeks, and 12 weeks.

STATISTICAL ANALYSIS

Data were analysed using the Statistical Package for the Social Sciences (SPSS) software, version 23.0. The quantitative data were presented as mean (standard deviation). The comparison within each group (baseline and post-treatment) was made using the Wilcoxon signed-rank test. A comparison of quantitative variables between the groups was performed using the Mann-Whitney U test. A p-value <0.05 was considered statistically significant.

RESULTS

The mean baseline age for the tadalafil and tamsulosin groups was 62.7 and 61.0 years, respectively (p-value=0.147). The prostatic volume at baseline was slightly higher in group I (tadalafil) compared to group II (tamsulosin) (36.7 cc vs 35.9 cc, respectively), with a p-value of 0.144 [Table/Fig-2].

Parameters	Group I (n=30) n (%)	Group II (n=30) n (%)	p-value
Age (in years)	62.7 (7.3)	61.0 (7.2)	0.147 ^c
Prostatic volume (cc)	36.7 (6.5)	35.9 (6.4)	0.144 ^c
Qmax (mL/sec)	14.8 (4.5)	14.7 (3.2)	0.992 ^c
PVR (mL)	26.0 (25.6)	23.6 (17.4)	0.944 ^c

[Table/Fig-2]: Demographic characteristics of the patients. Data given as mean (SD); c: Mann-Whitney U test; cc: Cubic centimeter; mL: Millilitre; mL/sec: Millilitre per second; PVR: Post-void residual; Qmax: Maximum flow rate

The intergroup comparison between the subjective symptoms at baseline and post-treatment showed improvements in IPSS in both groups. From baseline to 12 weeks, the mean IPSS changed from 19.4 to 16.0 in group I (p<0.001), and from 21.8 to 17.6 in group II (p<0.001). The average QoL at 12 weeks was comparable between group I and group II (3.7 and 2.4, respectively, p=0.631), while the Qmax was slightly higher in group I compared to group II (15.1 mL/sec vs 13.6 mL/sec, p=0.667). PVR was comparable between both groups (15.8 vs 16.2 mL, p=0.659) at 12 weeks [Table/Fig-3].

Duration	Group I n (%) (n=30)	Group II n (%) (n=30)	p-value
IPSS			
Baseline (a)	19.4 (4.9)	21.8 (4.9)	0.040 ^c
Four weeks (b)	17.8 (4.6)	19.4 (4.2)	0.128 ^c
12 weeks (c)	16.0 (5.9)	17.6 (4.9)	0.173 ^c
p-value	0.004 ^a , <0.001 ^b	0.020 ^a , <0.001 ^b	
QoL index			
Baseline (a)	4.2 (0.9)	4.1 (1.0)	0.928 ^c
Four weeks (b)	3.6 (0.9)	3.6 (0.8)	0.944 ^c
12 weeks (c)	3.7 (1.0)	2.4 (1.0)	0.631 ^c
p-value	<0.001 ^a , 0.009 ^b	0.021 ^a , 0.009 ^b	
Qmax (mL/sec)			
Baseline (a)	12.0 (4.1)	11.6 (2.6)	0.992 ^c
Four weeks (b)	12.8 (3.2)	12.5 (2.8)	0.771 ^c
After 12 weeks (c)	15.1 (3.5)	13.6 (2.5)	0.667 ^c
p-value	0.080 ^a , 0.182 ^b	0.258 ^a , 0.004 ^b	
PVR (mL)			
Baseline (a)	26.5 (24.5)	24.0 (15.2)	0.944 ^c
Four weeks (b)	18.6 (20.8)	18.3 (20.3)	0.976 ^c
After 12 weeks (c)	15.8 (19.7)	16.2 (16.1)	0.659 ^c
p-value	<0.001 ^a , <0.001 ^b	0.313 ^a , 0.062 ^b	

[Table/Fig-3]: Intergroup comparison between subjective symptoms at baseline and post-treatment. Data given as mean (SD); aa vs b; ba vs c; A, b: Wilcoxon signed-rank test, c: Mann-Whitney U test; IPSS: International prostate symptom score; mL/sec: Millilitre per second; PVR: Post-void residual; Qmax: Maximum flow rate; QoL: Quality of life

There was a significant reduction in the symptom of weak stream of urination from baseline to 12 weeks in patients receiving both tadalafil (2.9 vs 1.9) and tamsulosin (3.1 vs 2.1) [Table/Fig-4]. Both drugs showed good treatment efficacy, with improvements seen in IPSS and QoL [Table/Fig-5]. Adverse effects such as dizziness were observed in three patients in group I and group

Duration	Group I n (%) (n=30)	Group II n (%) (n=30)	p-value
Incomplete emptying			
Baseline (a)	2.5 (1.1)	2.6 (0.8)	0.667 ^c
After four weeks (b)	2.5 (0.7)	2.8 (0.7)	0.197 ^c
After 12 weeks (c)	2.1 (1.0)	2.3 (0.9)	0.250 ^c
p-value	0.976 ^a , 0.047 ^b	0.289 ^a , 0.289 ^b	
Frequency			
Baseline (a)	3.8 (0.7)	4.2 (0.7)	0.057 ^c
After four weeks (b)	3.3 (0.7)	3.4 (0.7)	0.373 ^c
After 12 weeks (c)	3.1 (1.0)	3.3 (0.9)	0.378 ^c
p-value	0.004 ^a , <0.001 ^b	0.002 ^a , 0.001 ^b	
Intermittency			
Baseline (a)	2.7 (1.1)	3.0 (1.1)	0.246 ^c
After four weeks (b)	2.5 (0.8)	2.8 (0.8)	0.200 ^c
After 12 weeks (c)	2.0 (0.9)	2.3 (0.7)	0.147 ^c
p-value	0.254 ^a , 0.001 ^b	0.275 ^a , 0.004 ^b	
Urgency			
Baseline (a)	2.6 (0.8)	3.6 (1.0)	0.076 ^c
After four weeks (b)	2.7 (0.7)	3.2 (0.9)	0.490 ^c
After 12 weeks (c)	2.8 (1.0)	2.6 (0.9)	0.779 ^c
p-value	0.483 ^a , 0.548 ^b	0.267 ^a , 0.280 ^b	
Weak stream			
Baseline (a)	2.9 (1.3)	3.1 (1.1)	0.667 ^c
After four weeks (b)	2.2 (0.9)	2.5 (0.8)	0.204 ^c
After 12 weeks (c)	1.9 (0.9)	2.1 (0.8)	0.218 ^c
p-value	0.001 ^a , <0.001 ^b	0.014 ^a , 0.001 ^b	
Straining			
Baseline (a)	2.7 (1.4)	3.2 (1.3)	0.170 ^c
After four weeks (b)	2.1 (1.1)	2.4 (1.2)	0.322 ^c
After 12 weeks (c)	1.9 (1.0)	2.2 (1.0)	0.186 ^c
p-value	0.007 ^a , <0.001 ^b	0.001 ^a , 0.001 ^b	
Nocturia			
Baseline (a)	3.7 (0.7)	3.4 (0.9)	0.992 ^c
After four weeks (b)	2.8 (0.8)	3.0 (0.7)	0.373 ^c
After 12 weeks (c)	2.0 (0.9)	2.8 (0.8)	0.347 ^c
p-value	1.000 ^a , 0.575 ^b	0.342 ^a , 0.810 ^b	

[Table/Fig-4]: Intergroup comparison between IPSS symptoms at baseline and post-treatment.

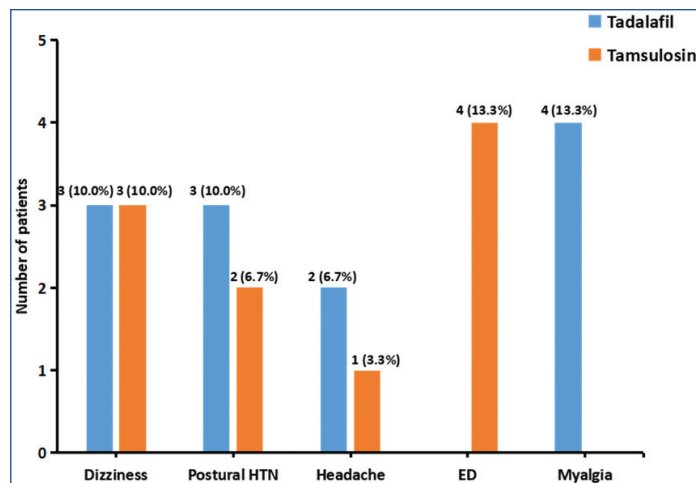
Data shown as mean (SD); ^aa vs b; ^ba vs C; A, b: Wilcoxon signed-rank test, c: Mann-Whitney U test

Parameters	Group I n (%) (n=30)	Group II n (%) (n=30)
Total IPSS		
Excellent	10 (33.3)	11 (36.7)
Good	8 (26.7)	7 (23.3)
Fair	6 (20.0)	7 (23.3)
Poor/worse	6 (20.0)	5 (16.7)
QoL index		
Excellent	11 (36.7)	11 (36.7)
Good	8 (26.7)	7 (23.3)
Fair	7 (23.3)	9 (30.0)
Poor/worse	4 (13.3)	3 (10.0)

[Table/Fig-5]: Treatment efficacy of tadalafil and tamsulosin.

Data given as n (%); IPSS: International prostate symptom score; QoL: Quality of life

II. Myalgia was reported only in the tadalafil group, whereas erectile dysfunction was reported only in the tamsulosin group [Table/Fig-6].



[Table/Fig-6]: Adverse effects of tadalafil and tamsulosin.

DISCUSSION

The prevalence of LUTS increases as age increases [21], as demonstrated in a hospital-based study where nearly half of the population in the age group of <61-70 years suffers from LUTS [22]. Recently, tadalafil, a PDE5-I, has been authorized for the treatment of LUTS secondary to BPH in the United States and the European Union [23]. It is a well-tolerated and effective drug for patients with moderate to severe BPH-LUTS [24]. Previous placebo-controlled trials have also shown the positive effect of tadalafil on LUTS [17]. The findings of this integrated analysis support tadalafil and tamsulosin as effective and well-tolerated treatment options for Indian males with BPH-LUTS, and tadalafil 5 mg once daily can provide an alternative to currently established treatments for LUTS. The results of this study are similar to a study conducted by Guo B et al., which concluded that tadalafil and tamsulosin may have comparable effects on increasing patients' total IPSS, voiding and storage scores, as well as their QoL, PVR, and Qmax [16].

However, a study by Zhou Z et al. demonstrated that combination therapy of tadalafil and tamsulosin is more effective and safer in patients with LUTS-BPH compared to tadalafil monotherapy [25]. This contrasts with the results obtained in this study, which showed a significant improvement in Qmax with tadalafil. Alpha-adrenergic antagonists have the potential to cause adverse effects depending on dosage and selectivity, with dizziness being the most frequent adverse reaction, assumed to result from Central Nervous System (CNS) effects [26]. In this study, dizziness was observed in both groups (10.0% and 10.0%). Long-acting drugs alleviate hypotension, while alpha 1A adrenergic selective drugs are associated with a low risk of hypotension [27]. In patients using tamsulosin, intraoperative floppy iris syndrome complicates about 2% of cataract procedures [28].

The magnitude of improvement in Qmax with tadalafil 5 mg in this study was similar to the results observed in a study by Oelke M et al. (9.9 mL/sec to 12.3 mL/sec) [29]. Larger prospective Randomised studies in Indian men with LUTS due to BPH are required to evaluate patient-related parameters that may predict an improved response with one drug over the other.

Limitation(s)

The present study did not assess the Sexual Health Inventory for Men (SHIM) and International Index of Erectile Function (IIEF) scoring tools to assess Erectile Dysfunction (ED), which could have provided valuable data while interpreting the observations.

CONCLUSION(S)

Tadalafil 5 mg is a recent drug option available for the treatment of LUTS-BPH. It has shown significant efficacy and safety in patients with LUTS-BPH, along with tamsulosin. Both tadalafil and tamsulosin have significantly improved IPSS, Qmax, PVR, and QoL. Based on the present study, it can be concluded that the efficacy and safety of tadalafil 5 mg and tamsulosin 0.4 mg are comparable.

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