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Tadalafil vs. tamsulosin in the treatment of lower urinary tract symptoms secondary to benign prostatic hyperplasia: a prospective, randomized study

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Introduction To compare the efiicacy of tadalafil 5 mg with tamsulosin 0.4 mg in the treatment of Lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH).

Material and methods A randomized prospective study on patients diagnosed with LUTS secondary to BPH with 50 patients in each group. Duration of the study is 12 weeks. Drug was given 30 min after dinner. Patients were assessed at baseline 1, 4 and 12 weeks with efficacy measures being Maximum flow rate (Qmax), Postvoid residual urine (PVR), International Prostate Symptom Score (IPSS), International Prostate Symptom Score Quality of life (IPSS QoL) and Sexual Health Inventory for Men (SHIM) scoring. Statistical analysis was done using paired sample t test and independent sample t test.

Results In tadalafil group, 12 (24%) patients were having mild LUTS and 38 (76%) were having moderate LUTS. In tamsulosin group, 9 (18%) patients were having mild LUTS and 41 (82%) patients were having moderate LUTS. Seventeen patients in tadalafil group had associated ED (erectile dysfunction) and 13 patients had associated ED in tamsulosin group.

Conclusions When both groups were compared, tamsulosin showed better efficacy than tadalafil in treating LUTS secondary to BPH.

Key Words: benign prostatic hyperplasia ‹› lower urinary tract symptoms ‹› tadalafil ‹› tamsulosin

INTRODUCTION

Benign prostatic hyperplasia (BPH) is highly prevalent in elderly men and often results in lower urinary tract symptoms (LUTS). LUTS secondary to BPH increases with age and negatively impacts patients' quality of life. The current standard of care in men with moderate to severe LUTS secondary to BPH is treatment with alpha-blockers or in men with enlarged prostates with5-alpha-reductase inhibitors either alone or in combination and transurethral surgery in those who have failed medical therapy [1–4]. Erectile dysfunction (ED) is a highly prevalent comorbidity in men with LUTS secondary to BPH. The observation that men with ED in general have greater LUTS suggests a common etiology [5]. The negative impact of LUTS and ED on the quality of life of aging men has been well acknowledged in the literature. The phosphodiesterase type-5 (PDE5-I) inhibitor tadalafil has recently received approval in the USA and European Union for the treatment of LUTS secondary to BPH, with or without erectile dysfunction (ED) [1,2]. The aim of this study is to compare the effect of tadalafil 5 mg with tamsulosin 0.4 mg on LUTS secondary to BPH.

MATERIAL AND METHODS

This is a prospective, randomized study included 100 patients with LUTS secondary to BPH. The

study was approved by the Institutional Ethics Committee.

Inclusion criteria

All patients who presented with LUTS secondary to BPH.

Exclusion criteria

Patients presenting with acute urinary retention, neurogenic bladder dysfunction, bladder neck contracture, urethral stricture, bladder calculi, active urinary tract infection (UTI), prostate cancer, history of pelvic radiotherapy, prostatectomy, any disease affecting urinary function, clinically significant cardiac disease,chronic renal failure,severe hepatic illnesses, discontinuation of treatment.

Methodology

A prospective randomized study on patients diagnosed with LUTS secondary to BPH with 50 patients in each group. Randomisation was done using a computer generated random table designed for 100 patients with 1:1 ratio making 50 patients in each group. The duration of the study was 12 weeks. A 4 week wash-out period (patients were withdrawn from all drugs for BPH, overactive bladder or ED) was conducted, when applicable. A standard investigation protocol which included general clinical examination with abdominal examination, examination of external genitalia and digital rectal examination, focused neurological examination was done to exclude any neurological deficit, uroflowmetry, abdominal ultrasound, blood tests including RFT (renal function tests), serum PSA (prostate specific antigen), urinalysis, urine culture was done. All patients were explained about the IPSS (International Prostate Symptom Score) and the IPSS scoring sheet was provided to quantify the severity of LUTS and Sexual Health Inventory for Men (SHIM) scoring in patients with erectile dysfunction. The drug was taken 30 min after dinner. Patients were assessed at baseline, 1 week, 4 weeks and 12 weeks with efficacy measures being Qmax, PVR (post void residual urine), IPSS, IPSS QoL (International Prostate Symptom Score Quality of Life). Sexual Health Inventory for Men (SHIM) scoring was evaluated at baseline, 4 weeks and 12 weeks [6]. All the patients participating in the study were properly informedabout the trial. Informed written consent was obtained from patients (properly explaining the aims, methods, anticipated benefits and potential drawbacks relevant for the decision to participate in the trial). Statistical analysis was done using paired sample t-test and independent sample t-test. Treatment group differences and changes from baseline to end of therapy in Qmax, PVR, IPSS, IPSS QoL and SHIM score were analysed [6].

RESULTS

In the present study, LUTS secondary to BPH was commonly seen in the age groups of 51–60 and 61–70 years. The mean age was (59.40 ±8.84) years in the tadalafil group and (63.66 ±9.05) years in the tamsulosin group. A total of 21 (42%) patients were hypertensive in the tadalafil group and 15 (30%) patients in the tamsulosin group. Diabetes mellitus patients totaled 16 (32%) in the tadalafilgroup and 17 (34%) in the tamsulsoin group. In the present study, in the tadalafil group, 23 (46%) patients had a prostate gland size less than 30 g and 27 (54%) patients had a prostate gland size more than 30 g. In the tamsulosin group, 28 (56%) patients had a prostate gland size less than 30 g and 22(44%) patients had a prostate gland size more than 30 g.

In the tadalafil group, 12 (24%) patients had mild LUTS and 38 (76%)had moderate LUTS. In the tamsulosin group, 9 (18%) patients had mild LUTS and 41 (82%) patients had moderate LUTS. Seventeen (34%) patients had associated ED in the tadalafil group and 13 (26%) patients had associated ED in the tamsulosin group. In this study, 4 patients received washout therapy in the tadalafil group and 6 patients in the tamsulsoin group.

Baseline (BS) characteristics of both the groups recorded at day 0 of the trial were compared and are presented inTable 1. Parameters such as age, prostate volume (g), total IPSS score, quality of life score, maximal urinary flow rate and residual urinary volume were not significantly different between both groups (Table 1).

In the present study, both the groups showed a response to the treatment after 1 week of initiation. The group receiving tadalafil showed a response in all the parameters with no statistical value. The group receiving tamsulsoin showed a significant change in Qmax and PVR but not in IPSS and IPSS-QoL after 1 week of treatment. After 4 weeks of initiation, both the groups showed response in all the efficacy measures. Patients receivingtamsulsoinhad statistically significant improvement in Qmax, reduction in PVR and IPSS, also in IPSS-QoL but this was not statistically significant. Patients who received tadalafilshowed a response in all parameters but with no statistical significance.

After 12 weeks of treatment, both groups showed a response in all the efficacy variables and these were

Table 1. *Baseline characteristics in both the groups*

	Tadalafil			Tamsulosin			P value
	Range	Mean	SD	Range	Mean	SD	
Age (years)	40–77	59.40	8.84	43–82	63.66	9.05	0.219
Prostate size (g)	16–50	32.32	9.09	14–48	30.20	9.76	0.264
Qmax (ml/sec)	2.9–23.2	13.44	4.89	3.9–23.1	12.41	4.74	0.288
PVR (ml)	0–180	51.76	40.84	0–220	83.5	58.02	0.122
IPSS	4–19	12.84	4.87	3–19	14.32	4.73	0.126
IPSS QoL	0–5	2.74	0.96	2–5	3.0	0.76	0.137

Qmax – maximum flow rate, PVR – postvoid residual urine, IPSS – International Prostate Symptom Score, IPSS QoL – International Prostate Symptom Score Quality of Life

Table 2. *Comparison of mean change from baseline in all the efficacy variables between both groups*

	Tadalafil			Tamsulosin			P value
	Baseline	12 weeks	Change from baseline	Baseline	12 weeks	Change from baseline	
Qmax (ml/sec)	13.44	15.7	+2.4	12.41	16.4	+4.0	0.002*
PVR (ml)	51.76	39.8	-12.0	83.50	24.4	-59.0	0.004*
IPSS	12.84	12.22	-0.62	14.32	11.56	-2.76	0.438
IPSS QoL	2.74	2.48	-0.26	3.0	2.24	-0.76	0.127

Qmax – maximum flow rate, PVR – postvoid residual urine, IPSS – International Prostate Symptom Score, IPSS QoL – International Prostate Symptom Score Quality of Life

Table 3. *Change from baseline to 12 weeks in SHIM score in men with associated erectile dysfunction in both groups*

	Number	Baseline		4 weeks	12 weeks	Change from baseline at 12 weeks	P value
		Range	Mean	Mean	Mean	Mean	
Tadalafil	17	3–20	12.65	15.24	15.53	2.88	0.001*
Tamsulosin	13	2–20	13.38	14.23	14.62	1.24	0.217

maintained. Patients who received tadalafil showed a statistically significant change from baseline with improvement in Qmax, reduction in IPSS and IPSS-QoL scores. PVR was reduced in the tadalafil group but showed no statistical significance. Patients who received tamsulosin showed further significant efficacy in all the measures, rise in Qmax, reduction in IPSS, IPSS QoL scores and PVR.

Maximal urinary flow rate was significantly improved from baseline with both tadalafil and tamsulosin during the treatment period. Tamsulosin treatment resulted in a more significant change from baseline in Qmax of +4 compared to +2.4 in the tadalafil group with statistical significance, p = 0.002. The mean decrease in the residual urine volume in the tadalafil group was 12 ml and in the tamsulosin group was 59 ml. tamsulosin treatment showed significant reduction in PVR compared to the tadalafil with a p value of 0.004 (Table 2).

IPSS score was improved from the baseline to 12 weeks after treatment in both groups; reduction in IPSS was greated in the tamsulsoin group when compared to the tadalafil group, but this was of no statistical significance. The overall mean reduction of IPSS score in the tadalafil group is 0.62 compared to 2.76 IPSS reduction in the tamsulosin group (Table 2). The mean change in quality of life was noted in both groups, but this was not statistically significant, with a mean change from baseline of 0.26 in the tadalafil group and 0.76 in the tamsulosin group.

In this study, 17 patients in the tadalafil group had associated ED and 13 patients had associated ED in the tamsulosin group. The change in the SHIM score in the tadalafil group was 15.53 compared to a baseline of 12.65 and with tamsulosin treatment it was 14.62 compared to a baseline of 13.38. The mean change form baseline SHIM to 12 weeks after initiating treatment was noted in both groups, with tadalafil it was 2.88 (p = 0.001) which is statistically significant and with tamsulosin it was 1.24 (p = 0.217) with no statistical significance (Table 3). The mean change from baseline SHIM to 12 weeks after initiating treatment in thetamsulsoin group was 1.24 with no statistical significance (Table 3).

According to our analysis, there was no difference in the mean change from baseline to 12 weeks ob-

Table 4. *Comparison of mean change in efficacy variables in patients with associated erectile dysfunction between both groups*

	Tadalafil (N = 17)			Tamsulosin (N = 13)			P value
	Baseline	12 weeks	Change from baseline	Baseline	12 weeks	Change from baseline	
Qmax (ml/sec)	12.38	14.55	+2.17	13.62	17.56	+3.94	0.0001*
PVR (ml)	46.1	35.2	-10.9	65.7	20.3	-45.4	0.0001*
IPSS	14.0	13.18	-0.82	14.77	11.62	-3.15	0.334
IPSS QoL	2.71	2.47	-0.24	3.0	2.38	-0.62	0.238
SHIM	12.65	15.53	+2.88	13.38	14.62	+1.24	0.028*

Qmax – maximum flow rate, PVR – postvoid residual urine, IPSS – International Prostate Symptom Score, IPSS QoL – International Prostate Symptom Score Quality of life, SHIM – Sexual Health Inventory for Men

served with tadalafil in all the efficacy variables in men associated with ED to that of overall population. The mean change observed with tamsulosin in all the efficacy variables from baseline to 12 weeks in men associated with ED was similar to that of the overall population.

In this study, significant change in Qmax and PVR was noted in tamsulosin when compared with tadalafil in men associated with ED which is similar to that of overall population. There was no difference in mean change in IPSS and IPSS QoL in men associated with ED to that of overall population. Significant response was seen in SHIM score with tadalafil when compared to tamsulosin (Table 4).

DISCUSSION

In the presence of moderate or severe LUTS due to BPH, medical management has become the standard of care in patients [7, 8]. Alpha1-adrenoreceptor antagonists (alpha-blockers) were the most widely prescribed drugs, while use of PDE5-Is has been recently gaining popularity for

LUTS secondary to BPH. The 2016 Guidelines on the Management of Male LUTS (including benign prostatic obstruction) published by the European Association of Urology (EAU) and guidelines compiled by the American Urological Association (AUA) recommend the use of several different pharmacotherapies for the treatment of LUTS, depending on the clinical situation. Alpha-blockers and 5-ARIs are considered the first-line medical treatment in men with moderate to severe LUTS. The newest drug class, PDE5-Is, are mentioned in the 2013 EAU guidelines [9, 10]. The aim of this study was to makea direct comparison of two medical treatment options for patients with LUTS secondary to BPH in daily clinical practice, that is, the alpha 1-adrenoreceptor antagonist (tamsulosin) and the PDE5-I (tadalafil) which had been less compared directly as monotherapy for LUTS secondary to BPH.

PDE5-Is act mainly to relieve the dynamic obstruction of the prostate with a direct relaxation of the bladder [11]. Several in-vitro studies have reported smooth muscle relaxation in the human bladder neck and prostate in the presence of PDE5-Is [12, 13] and relaxation of the bladder neck and decreases in detrusor muscle over activity.

In a dose-finding study, tadalafil 5 mg was approved to provide a positive risk benefit profile compared with other doses for 12 weeks [14]. The insignificant increase in Qmax for all doses suggested that tadalafil can exert its clinical activity differently compared to the traditional BPH treatment with alpha-blockers. tamsulosin, a uroselectivealpha-blocker, relaxes smooth muscle in the prostate and bladder neck, thereby enhancing bladder emptying. In randomized, controlled clinical trials using standardized instruments, tamsulosin improves lower urinary tract symptoms by at least 25% in 65–80% of patients with symptomatic benign prostatic hyperplasia [15]. Antagonism of alpha-1 adrenoreceptors by tamsulosin relaxes the smoothmuscles in the bladder neck and prostate to improve urine flow rate and symptoms of benign prostatic hyperplasia. Oelke et al. reported a significant outcome in Qmax (+2.4 ml/s, $p < 0.05$) in men with a lower baseline obstruction (Qmax at baseline: 9.9 ml/s) with tadalafil, which is similar to our study (+2.4 ml/s, $p = 0.001$) [2]. Chapple et al. reported the results of a meta-analysis of two multicenter randomized controlled trials, where tamsulosin treated patients had a greater increase in peak urinary flowrate and a more significant decrease in PVR when compared with patients in the placebo group [16].

In our study, when compared to tadalafil, tamsulosin showed more efficacy in raising Qmax. This was on par with Abrams etal. and Lepor et al. who stated that patients treated with tamsulosinexperienced a greater increase in peak urinary flow [17–20]. The lack of a significant peak flow improvement and reduction in PVR in men with LUTS secondary to BPH treated with tadalafil is consistent with pre-

vious reports of PDE5-I compounds [21, 22, 23]. Theoretically, the relaxation of the prostate and bladder neck after PDE5-I treatment could increase urinary flow, but the concomitant relaxation of the detrusor muscle counteracts this effect, thereby preventing the observation of a final improvement in Qmax [11]. In our analysis, IPSS score was improved from the baseline to 12 weeks after treatment in both groups, with a greater reduction in IPSS in the tamsulosin group when compared to the tadalafil group, but this was of no statistical significance.

According to AUA guidelines, a 3-point change from baseline IPSS is considered significant, which is nearer to the results seen with tamsulosin in our analysis. Consistent with the clinically meaningful improvement in total IPSS seen in this study for tamsulosin (-2.76), as well there is improvement in IPSS with tadalafil (-0.62) which was not statistically significant and similar to findings in the study by Dunn et al. [24].

Gacci et al. reported that the degree of improvement in IPSS after PDE5-I treatment depended on the baseline characteristics of the patients, such as age, body mass index (BMI) and the baseline IPSS, indicating that young men with a low BMI and severe urinary symptoms (as measured by IPSS) are the best candidates for PDE5-I therapy [11]. Aging and obesity appear to be associated with a testosterone decline, which can decrease the main target of PDE5-I in the bladder. Porst and colleagues in 2009 reported similarly on the efficacy of tadalafil, with changes in IPSS, Qmax and PVR which were small and statistically insignificant [25, 26]. The IPSS findings from the present study were consistent with those from other studies of tadalafil 5 mg and tamsulosin 0.4 mg in Asian and non-Asian men with LUTS secondary to BPH [27–32]. Oelke M et al., in a randomized control trial evaluating tadalafiland tamsulosin for LUTS secondary to BPH, suggested that monotherapy with tadalafilor tamsulosin resulted in a significant and numerically similar improvement in IPSS versus placebo, which is in contrast to our study [2]. The mean change in IPSS-QoLfrom baseline to 12 weeks with tadalafil (0.26) is comparable to tamsulosin (0.76) in our study, but not statistically significant, agreeing with other randomized, double-blind,placebo controlled study by Oelke M et al. and another study by McVary et al [2, 21]. Even though this study was not specially designed to demonstrate efficacy in treating ED, tadalafil showed significant mean change in SHIM when compared to tamsulosin ($p = .001$ and $p = 0.217$, respectively), which is consistent with study by Oelke et al. [2]. Notably, improvement in LUTS secondary to BPH after 12 weeks is similar in both groups in men with and without ED, as the p values for treatment by ED status interactions were not significant to that of the overall population. Broderick et al. [31] compared the efficacy of tadalafil in BPH patients with and without ED and reported that the relief in LUTS caused by tadalafil was not influenced by ED according to Alexander Govorov et al. [9], which is similar to our analysis.

Bechara and Kaplan reported on PDE5-Is vs. alpha-blockers monotherapy in treating both sexual dysfunction and LUTS, stating that the combination of alpha-blocker and PDE5-I is better in treating LUTS, significantly improved IPSS and IPSS-QoL and associated ED [32, 33]. Although not statistically significant for most sexual function-related items, there is a tendency for tamsulosin to have a better effect on sexual function.Both drugs were very well tolerated in our study. They have an almost negligible rate of adverse events, comparable to Oelke M et al. [2].

CONCLUSIONS

Tamsulosin 0.4 mg once daily for 12 weeks resulted in clinically meaningful improvements in Qmax, PVR, IPSS and IPSS-QoL in patients with LUTS secondary to BPH, which were statistically significant. tadalafil 5 mg also demonstrated better efficacy on the aforementioned outcomes, which were statistically significant in all the measures except PVR. Tadalafil also showed significant improvement in ED which was not seen with tamsulosin. When both groups were compared, tamsulosin showed better efficacy than tadalafil in treating LUTS secondary to BPH with significant difference in Qmax and PVR between both groups. Our study provides evidence supporting the above-mentioned conclusion and suggests that once daily tadalafil 5 mg is well tolerated and can be considered for the treatment of LUTS secondary to BPH when associated with ED.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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