

**Original Research Article**

## Tadalafil therapy in symptomatic improvement of LUTS due to BPH and associated Erectile Dysfunction

Authors

**Dr Puneet Mahajan<sup>1</sup>, Dr Girish Kumar Sharma<sup>2</sup>, Dr Balraj<sup>3</sup>, Dr Rishi Nabh<sup>4</sup>  
Dr Pawan Kaundal<sup>5</sup>, Dr Saurav Sultania<sup>6</sup>, Dr Karandeep Guleria<sup>7</sup>**

<sup>1</sup>Prof., <sup>4,6,7</sup>Junior Resident, Dept of General Surgery, Indira Gandhi Medical College, Shimla, HP 171001

<sup>2</sup>Associate Prof., <sup>5</sup>Senior Resident, Dept of Urology, Indira Gandhi Medical College, Shimla, HP 171001

<sup>3</sup>Associate Prof., Dept of Community Medicine, Indira Gandhi Medical College, Shimla, HP – 171001

Corresponding Author

**Dr Rishi Nabh**Email: [nabhrishi@gmail.com](mailto:nabhrishi@gmail.com). Phone No. 7018614647**Abstract**

**Introduction:** Benign prostatic hyperplasia, one of the most common urological problem in aging man, is a complex disease and is often associated with bothersome LUTS.

**Objective:** The aim of present study was to assess the efficacy of Tadalafil 5mg once daily in symptomatic improvement of LUTS and erectile function in patient's with comorbid BPH and ED.

**Material and Methods:** 34 patients of bothersome LUTS with IPSS>8, Qmax <15 were treated with Tadalafil monotherapy 5mg once daily for a period of 12 weeks.

**Observations:** Tadalafil therapy (5mg- once daily) resulted in clinically meaningful and statistically significant improvement in LUTS secondary to BPH. Tadalafil improved IPSS, Qmax, PVRU and quality of life index. Statistically significant improvement of IIEF score (mean change; 3.735±1.082) at 12 weeks was observed (p<0.001).

**Conclusion:** Tadalafil seems to be promising treatment option for patient's with LUTS secondary to BPH and associated ED.

**Keywords/Abbreviations:** LUTS– Lower Urinary Tract Symptoms, PVRU–Post Void Residual Urine, ED–Erectile Dysfunction, IPSS – International Prostate Symptom Score, PDE5-Is – Phosphodiesterase 5 Inhibitors, PFR- Peak Flow Rate, IIEF – International index of Erectile Function.

**INTRODUCTION**

LUTS due to BPH are associated with a significant negative impact on patient's quality of life. The presence of lower urinary tract symptoms because of bladder outlet obstruction has been shown to increase linearly with age. LUTS which is often because of BPH, and sexual dysfunction

are common in older men, with an overall prevalence of >50% in men aged ≥50 yrs<sup>[1]</sup>.

Patients with lower urinary tract symptoms that are bothersome and negatively affecting their quality of life should be treated. For past several years surgery remained the gold standard treatment for LUTS associated with BPH,

however since the 1990's, there has been a substantial shift in BPH management from surgical to medical therapy, and studies have reported 55% reduction in TURP, despite rising number of BPH patients enrolled for treatment.

Medical therapy is currently considered to be preferred treatment modality for BPH patient who lack absolute indications for surgical intervention and it includes: Alpha-blockers, 5-alpha reductase inhibitors, or combination of these two in patient with large prostate size. Although these drugs are effective but can have side effects viz .dizziness, hypotension and sexual dysfunction.

Several studies reported that ED and BPH linked LUTS are associated epidemiologically and can have common patho-physiological pathway, since then PDE-5 inhibitors have received increased attention for treating LUTS secondary to BPH. Tadalafil is an emerging drug for treatment of LUTS /BPH and has no side effects on sexual function rather it improves sexual function in men with erectile dysfunction.

The aim of present study was to assess the efficacy of Tadalafil (5mg- OD) in symptomatic improvement of LUTS and erectile function in patients with comorbid BPH and ED.

## MATERIAL AND METHODS

Thirty four patients of LUTS due to BPH with or without ED diagnosed by qualified physician were enrolled for the study and received Tadalafil 5mg once daily for 12 weeks. Key inclusion criteria were IPSS of  $\geq 8$ , PFR  $<15$  ml/sec. and LUTS associated with BPH which were bothersome and negatively hampering quality of life. Patients with raised Serum.PSA level/ suspected prostatic malignancy and those with PVRU of  $>200$ ml were not included in the study. Other exclusion criteria for enrollment were patients who received recent 5 ARIs, and those with history of lower urinary tract malignancy, penile/pelvic surgery, radiotherapy, neurological conditions causing bladder dysfunction, hepato-renal insufficiency, diabetes mellitus, and other contraindications of Tadalafil use in patients.

IPSS which is validated self admitted questionnaire was used for assessment of symptom severity and patients were classified as : mildly symptomatic (score 0-7), moderately symptomatic (score 8-19) and severely symptomatic (score 20-35).Quality of life score was based on single question and patients were categorized, delighted to terrible (0 to 6).

Uroflowmetry was performed using standard calibrated uroflowmetry device and valid Qmax measurement required voided volume of  $\geq 150$ ml. PVRU volume was measured by trans abdominal ultrasonographic (logiq p6- machine).Patient with PVRU of  $> 100$ ml were reassessed with repeat ultrasound.

IIEF score was assigned based on IIEF-5 questionnaire and patient were classified as having severe ED (score of 5-7), moderate ED (score of 8-11), mild to moderate ED (score of 12-16), mild ED (score of 17-21) and no ED( score of 22-25).

The efficacy of Tadalafil in relieving symptoms of BPH and associated ED if any was assessed at completion of 12 weeks of therapy in term of:

- Improvement in IPSS and quality of life score from base line.
- Improvement in baseline ultrasonographic parameters in terms of PVRU.
- Improvement in IIEF scores from base line.

Patients were asked to remain in follow-up on 4weekly basis and all score / parameters were reevaluated at the endpoint of study i.e.12<sup>th</sup> week and we compared the mean of each of these scores/parameters at base line and at end of 12<sup>th</sup> week value by an unpaired/students 't' test. We also measured the hazard ratio along with its 95% confidence interval and p-value  $\leq 0.05$  was treated as statistically significant.

## OBSERVATIONS

### Change in Total IPSS Score from Base Line to 12 Weeks after Treatment

Once daily dose of Tadalafil 5mg resulted in statistically significant improvement in symptoms

as assessed by total IPSS. The baseline IPSS (Mean±SD) was 19.6±3.4 at entry point and Mean change of 16.9 was observed at end point of study (p value < 0.001) . (Table 1)

Table 1: Comparison of parameters at baseline and at 12 weeks of therapy

Variable	Baseline		12 weeks		Mean change	p-value
	Mean	S.D	Mean	S.D		
IPSScore	19.6	3.4	2.7	1.2	16.9	<0.001
QOL Score	4.0	0.4	0.7	0.7	3.3	<0.001
PVRU (ml.)	42.8	38.5	4.0	8.1	38.8	<0.001
IIEF-5 Score	14.24	3.095	17.97	2.918	3.73	<0.001

**Change in Post Void Residual Urine from Baseline to 12 Weeks after Treatment**

Baseline Mean ± SD of PVRU(ml) was 42.8±38.5 and after 12 weeks of tadalafil therapy it changed to 4.0±8.1 .The mean change of 38.8ml (95% confidence interval of mean change was 26.4 to 51.2 ) in PVRU at 12 weeks from the baseline was statistically significant (p value <0.001). (Table 2)

Table 2: Mean change in parameters at 12 weeks among patients treated with Tadalafil (n=34)

Variable	Paired differences				
	Mean	S.D	S.E of the mean	95% Confidence Interval of mean change	P value
IPSScore	16.9	2.9	0.5	15.873 to 17.951	<0.001
QOL	3.3	0.8	0.1	3.029 to 3.618	<0.001
PVRU (ml.)	38.8	35.6	6.1	26.422 to 51.284	<0.001

**EFFECT ON QUALITY OF LIFE**

Baseline Mean ± S.D of QOL score was 4.0±0.4 and after 12 weeks of tadalafil therapy it changed to 0.7±0.7 .The mean change of 3.3 (95% confidence interval of mean change was 3.0 to 3.6) in QOL score at 12 weeks from the baseline was statistically significant (p value <0.001). (Table 2)

**IIEF-5 SCORE**

Independent't' test was used to compare the IIEF-5 score at baseline and at 12 weeks of Tadalafil treatment.

Table 3: Comparison of IIEF-5 score at baseline and 12 weeks of intervention

BASE LINE		12 WEEKS		MEAN CHANGE:	P VALUE
MEAN	S.D	MEAN	S.D		
14.24	3.095	17.97	2.918	3.73	P<0.001

Baseline Mean ± SD of IIEF score was 14.24±3.095 and at endpoint of study it changed to 17.97±2.918. Statistically significant improvement of IIEF score (Mean change of 3.73) at 12 weeks of Tadalafil therapy was observed (p value <0.001).( Table 3)

**Discussion**

Benign Prostatic Hyperplasia leading to prostatic enlargement has been shown to be associated with LUTS since long, however now it is widely recognized that BPH is not the sole cause. LUTS increases with age with overall prevalence of greater than 50 % in men 50 years or older and are associated with a significant negative impact on patient's QOL.

An association has been postulated between BPH and ED<sup>[2-3]</sup>. Although pathophysiology between both is not very well understood, and the precise mechanism by which PDE5-Is improves LUTS associated with BPH is incompletely understood, several theories have been postulated:

One theory focuses on PDE5 inhibition mediated accumulation of cGMP in prostate and bladder smooth muscle, which may decrease prostatic stroma tension and detrussor muscle over activity<sup>[4,5]</sup>. Another possible mechanism involves pelvic arterial insufficiency and various studies have suggested that increase vascular perfusion of lower urinary tract could result in beneficial therapeutic effect on LUTS associated with BPH<sup>[4,6]</sup>. Recently it has been hypothesized that PDE5-Is can reduce inflammation, thus leading to improvement in prostatic anatomy and physiological activity, because of improved tissue oxygenation<sup>[7]</sup>.

Approved medical treatments for LUTS associated with BPH include α<sub>1</sub> blockers, 5 ARIs or combination of these two, but can cause

bothersome sexual side effects. Several studies have demonstrated that Tadalafil provides clinically meaningful and statistically significant improvement in LUTS associated with BPH as well as positive effect on sexual function.

Lieu L, et al after meta-analysis of 5 studies (11 randomized control trials) assessing the use of PDE5-Is alone vs placebo in treating LUTS secondary to BPH, published a review article in 2011. They concluded that PDE5-Is are effective, safe and should be used as first line treatment for patient with co morbid BPH and ED<sup>[8]</sup>.

In a study by McVary KT, et al Tadalafil therapy showed significant improvement in IPSS, they reported mean change of -2.8 with 5mg tadalafil vs -1.2 with placebo at 6 weeks, -3.8 with 5/20mg tadalafil vs -1.7 with placebo at 12 weeks. Larger changes in IPSS was observed with inclusion of the placebo run-in at 12 weeks, and reported mean change of -7.1 with 5/20mg tadalafil vs -4.5 with placebo<sup>[9]</sup>.

Statistically significant improvement in IPSS from baseline were observed with Tadalafil doses of 2.5, 5, 10 and 20 mg at all post randomization visit (4, 8 and 12 weeks) compared to placebo in a study by Roehrborn C.G, et al. In this study, the Least squares mean  $\pm$  SE IPSS change from baseline in patients with mild – moderate symptoms was  $-4.3 \pm 4.94$ , whereas this change was  $-6.2 \pm 6.71$  in patients with severe symptom at baseline when treated with Tadalafil 5 mg. The Least squares mean  $\pm$  SE IPSS change from baseline for patients with severe symptoms was  $-7.3 \pm 6.71$  and  $-8.4 \pm 6.36$  with Tadalafil dose of 10 and 20 mg respectively<sup>[4]</sup>.

In a double blind, placebo control study by Egerdie et al significant improvement in IPSS (mean change of -6.1) was observed with 5 mg of Tadalafil<sup>[10]</sup>.

Benign prostatic hyperplasia is not a life threatening condition, but it can adversely affect quality of life. A study conducted by Hunter DJ, et al showed that increasing symptom severity was associated with worsening physical role, vitality, social functioning and mental health. As severity

of LUTS increases, general health status and quality of life worsens<sup>[11]</sup>.

In study of Oelke M, et al statistically significant change of  $-6.3 \pm 0.5$  and  $-5.7 \pm 0.5$  was seen in total IPSS (LS mean  $\pm$  SE) from baseline to 12 weeks was in Tadalafil and Tamsulosin group respectively. They reported significant improvement in IPSS, QOL index, compared with placebo at 12 week with Tadalafil (  $p= 0.022$  ) but not with Tamsulosin (  $p = 0.546$ )<sup>[12]</sup>.

In study of Roehrborn C.G, et al statistically significant improvement in QOL score (change of  $-0.86 \pm 0.11$  from base line) was observed with Tadalafil 5 mg in patients with LUTS and ED<sup>[4]</sup>.

IPSS and IIEF – erectile function domain scores, significantly improved in 56 % of the patients of LUTS associated with BPH who were sexually active in a study by McVary KT, et al<sup>[9]</sup>.

Gacci M, et al after meta-analysis of cross sectional data reported that PDE5- Is can significantly improve LUTS and Erectile function in patients with BPH. PDE5- Is monotherapy was associated with significant improvement of the IIEF score ( $+ 5.5$  :  $p$  value  $< 0.0001$ ) and IPSS ( $-2.8$  :  $p$  value  $< 0.0001$ ) at 12 weeks as compared with placebo<sup>[3]</sup>. Oelke M, et al reported that IIEF- Erectile function domain improvement was significant with Tadalafil 5 mg ( $4.0 \pm 1.0$  ;  $p < 0.001$ ) but not with Tamsulosin 0.4 mg ( $-0.4 \pm 1.0$  ;  $p = 0.699$ ) in comparison to placebo in the patients who had co existing ED and were sexually active (approximately 60 % of the subjects)<sup>[12]</sup>. In our series baseline IIEF score (Mean  $\pm$  SD) was  $14.24 \pm 3.095$  and statistically significant improvement of IIEF score (Mean Change of 3.73;  $p$  value  $< 0.001$ ) at 12 weeks of Tadalafil (5 mg- OD) therapy was observed.

There are many studies to suggest that symptomatic improvement in LUTS secondary to BPH after PDE5-Is therapy may not be solely because of prostatic smooth muscle relaxation, but direct effect of PDE5-Is on the bladder also play a role.

Dmochowski R, et al explored the impact of Tadalafil on uro-dynamic parameters in patients

of LUTS secondary to BPH in randomized, placebo control clinical trial. Treatment with Tadalafil resulted in significant improvement in IPSS (mean difference between treatments – 4.2,  $p < 0.001$ ), in their study. No negative impact on bladder function as measured by detrusor pressure at Vmax or any other assessed urodynamic parameter was seen in this study<sup>[13]</sup>.

The clinically significant change in total IPSS score with Tadalafil was seen in approximately 95 % patients in our study. This is a clinical response criteria as per AUA guidelines which suggest more than 3 point decrease in total IPSS score from baseline is indicative of a clinical meaningful improvement. This change is also consistent with that observed in other published studies.

In our study the magnitude of improvement in IPSS (Mean  $\pm$  SD) from baseline (  $19.6 \pm 3.4$ ) to the end point ( $2.7 \pm 1.2$ ) was statistically significant (Mean change 16.9;  $p$  value  $< 0.001$ ). The mean change in QOL score of 3.3 at 12 weeks from baseline (95% confidence interval of mean change was 3.0 to 3.6) was statistically significant (  $p$  value  $< 0.001$ ) in our study. The greater magnitude of IPSS improvement in our study might be because, the current study population differs from previous studies in term of higher baseline mean IPSS and most of the subjects had associated UTI at entry point of study, who were treated with antibiotics simultaneously based on culture report. This might have allowed more room for symptom improvement and greater magnitude of IPSS and QOL mean change improvement from baseline observed in current study.

Mean change in PVRU of 38.8 ml at 12 weeks from baseline was statistically significant ( $p$  value  $< 0.001$ ) in our study. In 1 year, open label extension study by Donatucci CF, et al mean post-void residual volume was  $61.1 \pm 60.4$  ml at study entry and  $42.2 \pm 64.1$  mL after the open-label extension period<sup>[14]</sup>. Bechara and colleagues in their study of comparison between combination of tadalafil (20 mg/day) plus tamsulosin (0.4

mg/day) vs tamsulosin alone in randomized, double-blind, crossover design, 12-week study found that PVRU improved significantly in both the groups<sup>[15]</sup>. Roehrborn G, C et al in their study found no significant change in PVRU with Tadalafil as compared to placebo<sup>[4]</sup>. Birch NC, et al reported wide variations in PVRU value, measured on the same day and found no strong correlation between PVRU and any cystoscopic or urodynamic findings. They concluded that it is of no clinical value to perform a single residual urine volume measurement in patients with prostatic hypertrophy<sup>[16]</sup>.

## CONCLUSION

Tadalafil (5 mg OD) demonstrated clinically meaningful and statistically significant improvement in LUTS secondary to BPH and there was a statistically significant improvement in the IIEF-5 score (Mean  $\pm$ SD) from  $14.24 \pm 3.095$  to  $17.97 \pm 2.918$  at 12 weeks of study ( $p$  value  $< 0.001$ ).

ED and BPH-associated LUTS are epidemiologically linked and share common pathophysiological pathways. Tadalafil 5 mg once daily is approved for the treatment of LUTS in men, in addition, it is an established treatment for ED and is the only drug available today which can treat two conditions simultaneously, that are highly prevalent in aging men. Moreover adverse events on sexual function commonly associated with  $\alpha$ -adrenergic antagonists or  $5\alpha$ -reductase inhibitors are avoided.

## BIBLIOGRAPHY

1. Rosen R, Altwein J, Boyle P, et al. Lower urinary tract symptoms and male sexual dysfunction, the multinational survey of aging male ( MSAM – 7 ). *Eur Urol* 2003; 44: 637-649.
2. Gacci M, Anderson K E, et al. Latest evidence on the use of phosphodiesterase type 5 inhibitors for the treatment of lower urinary tract symptoms secondary to

- benign prostatic hyperplasia, Eur Urol 2016; 70(1): 124-133.
3. Gacci M, Corona G, Salvi M, et al. A systemic review and meta- analysis on the use of Phosphodiesterase 5 inhibitors alone or in combination with Alpha blockers for lower urinary tract symptoms due to benign prostatic hyperplasia. Eur Urol 2012 ; 61 : 994 – 1003.
  4. Roehrborn CG, McVary KT, Elion-Mboussa A, Viktrup L: Tadalafil administered once daily for lower urinary tract symptoms secondary to Benign Prostatic Hyperplasia, a dose finding study. J Uro 2008;. 180(4):1228-1234.
  5. Uckert S , Kuthe A, Jonas U and Stief CG. Characterization and functional relevance of cyclic nucleotide Phosphodiesterase isoenzymes of the human prostate. J Urol 2001; 166: 2484.
  6. Berger AP, Deibl M, Leonhartsberger N, Bektic J, Horninger W, Fritsche G, et al. Vascular damage as a risk factor for benign prostatic hyperplasia and erectile dysfunction. BJU Int 2005; 96: 1073.
  7. Vignozzi L, Gacci M, Cellai I, et al. PDE 5 inhibitors blunt inflammation in human BPH: a potential mechanism of action for PDE 5 inhibitors in LUTS. Prostate 2013; 73: 1391 – 1402.
  8. Liu L, Zheng S, Han P, Wei Q. Phosphodiesterase 5 inhibitors for lower urinary symptoms secondary to benign prostatic hyperplasia: a systematic review and meta-analysis. Urology 2011; 77: 123-129.
  9. McVary KT, Roehrborn GG, Kaminetsky JC, et al. Tadalafil relieves Lower urinary Tract symptoms secondary to benign Prostatic Hyperplasia. J Urol 2007;177: 1401-1407.
  10. Egerdie RB, Aurbach S, Roehrborn CG, et al. Tadalafil 2.5 or 5 mg administered once daily for 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized placebo controlled, double blind study. J Sex med 2012;9(1):271-281.
  11. Hunter DJ, et al. Health status and quality of life of British men with lower urinary tract symptoms: results from the SF-36. Urology. 1995;45-(6):962-971.
  12. Oelke M, Giuliano F , Mirone V, et al. Monotherapy with Tadalafil or Tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo controlled clinical trial. Eur Urol 2012;61:917-925.
  13. Dmochowski R, Roehrborn C, Klise S, et al. Urodynamic effects of once daily Tadalafil in men with lower urinary tract symptoms secondary to clinical benign prostatic hyperplasia: a randomized placebo controlled 12 week clinical trial. J Urol 2010;183(3):1092-1097.
  14. Donatucci CF, Brock GB, Goldfischer ER et al. Tadalafil administered once daily for lower urinary tract symptoms secondary to benign prostatic hyperplasia: a 1-year, open label extension study. BJU Int 2011; 107:1110-1116.
  15. Bechara A, Romano S, Casabe A, Haime S, Debola P, Hernandez C and Rey H. Comparative efficacy assessment of Tamsulosin vs Tamsulosin plus Tadalafil in the treatment of LUTS/BPH. Pilot Study J. Sex Med. 2008: 5: 2170-2178.
  16. Birch NC, Hurst G, Doyle PT. Serial residual volumes in men with prostatic hypertrophy. Br J Urol 1988;62(6):571-575.