

## **EVALUATION OF THE EFFICACY OF TADALAFIL IN IMPROVING LOWER URINARY TRACT SYMPTOMS IN PATIENTS WITH SYMPTOMATIC BENIGN PROSTATIC ENLARGEMENT**

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### **Abstract**

Lower urinary tract symptoms (LUTS) are common bothersome association with benign prostatic enlargement (BPE). The relationship between erectile dysfunction(ED) and LUTS/ BPE has been studied in the Multinational Survey of the Aging Male and in several epidemiologic studies, suggesting that the two diseases may share a common pathophysiology.

The aim of the present study is to evaluate the efficacy and safety of use of tadalafil monotherapy in improving LUTS in patients with symptomatic BPE.

Sixty patients aged more than 50 years with symptomatic BPE with LUTS more than 6 months were included from January 2013 to May 2015. These patients were assessed for their International Prostate Symptoms Score (IPSS) which was  $\geq 7$  and maximum urinary flow rate (Q max) which was  $>10$  and  $< 20$  ml/s. Patients were given tadalafil tablet 5 mg once daily without other therapy. The treatment was continued for three months and the patients were asked to come back for follow up each four weeks.

Among the 60 patients, 50 (83.3%) showed significant improvement in their IPSS by achieving  $\geq 3$ - points total IPSS improvement in symptoms. There was also significant improvement in the maximum urinary flow rate. The end point was at 12 weeks.

It is concluded that, Tadalafil 5 mg once daily can be considered as an option for relieving LUTS in patients with symptomatic BPE.

### **Introduction**

Lower urinary tract symptoms (LUTS) are common bothersome association with benign prostatic enlargement (BPE)<sup>1</sup>. There were large international placebo-controlled studies that confirmed the efficacy and safety of tadalafil in men with erectile dysfunction (ED), in men with BPE-LUTS, and in men with both ED and BPE-LUTS<sup>2-6</sup>. Beside surgical interventions, the current standard treatments for LUTS / BPE consist of  $\alpha 1$ -adrenergic blockers,  $5\alpha$ -reductase inhibitors and phytotherapies (used alone or in combination). Although efficacious, these therapies carry the potential for side effects related to sexual dysfunction<sup>7,8</sup>. The relationship between ED and LUTS /

BPE have been studied in the Multinational Survey of the Aging Male<sup>9</sup> and in several epidemiologic studies<sup>10</sup>, suggesting that the two diseases may share a common pathophysiology. The underlying mechanism for the relationship between LUTS and ED is still poorly understood. It is thought that common links such as RhoA/Rho-kinase signaling, over activity of the autonomic system, pelvic ischemia and the nitric oxide/ cyclic guanosinemonophosphate (NO/ cGMP) pathway to be potential targets for phosphodiesterase type 5inhibitors (PDE5-Is)<sup>11-14</sup>. A variety of (PDE5-Is), including sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis) and avanafil

(Stendra) is widely approved for treating ED. Tadalafil has a unique feature compared to other (PDE5-Is) which is its longest half-life reaching up to 17.5 h, with drug efficacy potentially lasting up to 36h. Tadalafil has also another unique feature which is its higher selectivity for Phosphodiesterase II (PDE II) as compared to sildenafil or vardenafil. PDE II is known to mainly present in the human prostate, testes and skeletal muscles<sup>15</sup>. Recently, significant improvements in LUTS / BPE have been showed by several clinical studies on (PDE5-Is). The precise mechanism for improving LUTS with (PDE5-Is) is unclear, but the proposed mechanisms include relaxing smooth muscle cells in the urogenital tract through the NO/cGMP / PDE5 pathway<sup>11,14</sup>. The aim of the present study is to evaluate the efficacy and safety of use of tadalafil monotherapy in improving LUTS in patients with symptomatic BPE.

### Patients and Methods

In this study, 60 patients aged more than 50 years with symptomatic BPE with LUTS more than 6 months were included from January 2013 to May 2015. These patients were assessed for their International Prostate Symptoms Score (IPSS) which was  $\geq 7$  and maximum urinary flow rate (Q max) which was  $>10$  and  $<20$  ml/s. During patients' evaluation, a digital rectal examination was performed initially and an ultrasound assessment of prostate volume was performed. Only patients with evident enlargement of the prostate gland on digital rectal examination and ultrasound examination were included in the study because patients with normal size of prostate gland were assumed to have other causes for their LUTS and thus were

excluded from the study. Patients also were assessed for their prostate specific antigen (PSA) and those with elevated PSA levels were evaluated to exclude prostate malignancy by prostatic biopsy and were excluded if the diagnosis was confirmed. Those patients with a post-void residual urine volume  $>150$  ml were excluded because they needed bladder catheterization or more invasive therapy. Patients with history of use of  $\alpha$ -adrenergic blockers, overactive bladder therapy, or ED therapy had to stop their treatment 2 weeks before commencing the use of tadalafil therapy in order to allow a wash out period for the effect of these medications. This was done with close observation so that patients would not develop worsening of their symptoms. Excluded from the study were men who received recent finasteride or dutasteride treatment and those with a history of pelvic surgery, lower urinary tract malignancy, radiotherapy, neurological conditions affecting bladder function, recent acute urinary retention, and those with severe medical conditions like hepatic or renal insufficiency. Patients with history of urinary tract infection (UTI) were treated appropriately with antibiotics before commencing the study. The selected patients were given tadalafil tablet 5 mg once daily without other therapy. The treatment was continued for three months and the patients were asked to come back for follow up each four weeks. During the follow up visit, the patients were assessed for their IPSS and Qmax. In addition to that, patients were asked to report bothersome adverse effects if they were found. The findings were compared with the baseline data. The IPSS Table (I) is a validated 1-month tool for assessing BPE symptoms severity and the response for treatment.

**Table I: International Prostate Symptom Score (IPSS)**

In the past month:	Not at all	Less than 1 in 5 Times	Less than Half the Time	About Half the Time	More than Half the Time	Almost Always
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Urgency How often have you found it difficult to postpone urination	0	1	2	3	4	5
5. Weak Stream How often have you had a weak urinary stream	0	1	2	3	4	5
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5
	None	1 Time	2Times	3Times	4Times	5Times
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5
Total I-PSS Score						

Score: 1-7: Mild 8-19: Moderate 20-35: Severe

It consists of seven questions about urinary storage and voiding symptoms. It measures the severity of BPE related LUTS using a scoring range of 0-35 points; the higher the score, the more severe the symptoms (scores of 1-7= mild; 8-19=moderate; 20-35=severe)<sup>16</sup>. The responders were defined as patients having a total IPSS improvement of  $\geq 3$

points<sup>17</sup>. Data were expressed as mean $\pm$  standard deviation and percentage. Student's t-test was used to compare IPSS and Qmax after treatment with baseline data.

### Results

Patients' characteristics are shown in Table (II) & Table (III).

**Table II: Criteria of patients**

No. of patients	60
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Age	> 50yr.
IPSS	$\geq 7$
Q max	> 10 < 20 mL/s
Residual urine volume	< 150 mL

**Table III: Criteria of the severity of patients' symptoms.**

Patients with	No.	Percent
Mild-moderate IPSS	45	75%
Severe IPSS	15	25%
Qmax > 10 < 15 mL/s	10	16.7 %
Qmax $\geq 15$ < 20 mL/s	50	83.3 %
Residual Vol. < 100 mL	47	78.3 %
Residual Vol. 100 - 150 mL	13	21.7 %

The changes in the IPSS and Qmax, were assessed in each follow-up visit. The changes were compared with baseline data. The endpoint result was considered at 12 weeks. Among 60 patients, 50 (83.3%) showed significant improvement in their IPSS by achieving  $\geq 3$  - points total IPSS improvement in symptoms. The

maximum change was seen at the endpoint check (12 weeks). The improvement involved both the irritative and obstructive scores. There was also significant improvement in the maximum urinary flow rate as compared to baseline data. These results are shown in Tables (IV) & (V).

**Table IV: Changes in IPSS**

IPSS	12th week	P
No. & (%)	50 (83.3)	<0.0001
Mean (SD) change	- 4.8 (5.4)	<0.0001

**Table V: Changes in Qmax**

Qmax	12th week	P
No. & (%)	50 (83.3)	< 0.0001
Mean (SD) change	+4 (3.5)	< 0.0001

No adverse effects were reported by patients.

## Discussion

It is well known that men with BPE suffers from LUTS like urinary frequency, urgency, intermittency, nocturia, straining, incomplete emptying and a weak urinary stream. In addition to that, LUTS increase with age and incidence is about 55% in men of age 50 years or older. In fact, most of the drugs which are being used to treat BPE can cause side effects such as dizziness, low blood pressure, retrograde ejaculation and sexual dysfunction. Many studies of ED incidence, pathophysiology and treatment have shown a possible link

between BPE, LUTS and ED. How (PDE5-Is) work to relieve LUTS is still not clear, but there are many reasons to explain this. These drugs block the phosphodiesterase-5 (PDE-5) enzyme, which is present at high level in the bladder muscles and prostate. Thus these drugs relax the arteries and increase blood flow to the penis, prostate and bladder and this could improve urinary symptoms. Another possibility is that in older men with BPE-LUTS, the nerve signals to the brain, prostate, and bladder may not function properly. PDE5-Is may block

those abnormal signals and thus improve BPE symptoms. Many studies have shown the support for using tadalafil for BPE and these studies showed three observations that may explain the success for this use. First, with increasing age men usually have the combined occurrence of BPE with LUTS and ED; second, smooth muscle relaxation in the lower urinary tract area is affected by (PDE5-Is); and third, various clinical trials have demonstrated that (PDE5-Is) such as tadalafil is successful in treating LUTS and ED<sup>18</sup>. In addition to that, there are many pathophysiological changes that may explain the role of tadalafil in improving LUTS in BPE patients. PDE-5 inhibitors like tadalafil facilitate smooth muscle relaxation by inhibiting the breakdown of cyclic guanosine monophosphate which subsequently phosphorylates several other targets and results in smooth muscle relaxation. In addition to that tadalafil causes engorgement of cavernous sinuses and increases the length of the flaccid penis which helps in producing better stream of urine. Several studies in literature have shown that the use of tadalafil (5mg) once daily dose produces good results for patients suffering from BPE with LUTS<sup>19,20</sup>. Roehrborn et al. studied the

effectiveness of tadalafil in patients with LUTS secondary to BPE compared to placebo. They showed no significant change of peak urinary flow rate (Q<sub>max</sub>), but there was good improvement in the obstructive symptoms due to BPE<sup>21</sup>. Dmochowski et al., concluded that tadalafil is useful for both ED and for bladder outlet obstruction symptoms due to BPE<sup>22</sup>. The current study showed that the use of tadalafil as (5 mg) daily single dose is effective in improving LUTS in men with BPE as was seen in other studies. In addition to that the current study showed that tadalafil therapy was safe with no reported adverse effects. It was difficult to prescribe a placebo drug for the included patients in the study to compare the effect of tadalafil with placebo as is usually done in other studies. This is because of the ethical and social limitations for the patients in our community for whom it is very difficult to have a placebo run-in period.

### **Conclusion**

Tadalafil 5 mg once daily can be considered as an option for relieving LUTS in patients with symptomatic BPE. This is of importance in patients with erectile dysfunction because tadalafil improves both conditions.

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