

## Interchangeable alternative use of tadalafil and selective $\alpha$ 1-blocker versus their combined daily use

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### **ABSTRACT:**

**Background and Aims:** Lower urinary tract symptoms (LUTS) in association with benign prostatic hyperplasia (BPH) are frequent complaints among middle-aged men. Surgical intervention has represented the gold standard management for this condition for decades. Anyhow, there has been a significant turn towards medical therapy in BPH management. The currently accepted standard strategy for LUTS/BPH management includes  $\alpha$ -adrenergic blockers, 5 $\alpha$ -reductase inhibitors, phosphodiesterase inhibitor and phytotherapies. Combined use of Tadalafil & Selective  $\alpha$ 1-blocker are approved to improve LUTS. The tool used to screen Symptoms/Benign Prostatic Hyperplasia often The International Prostate Symptom Score (IPSS) which is a seven-question related to voiding symptoms written to assess disease severity and response to therapy. **The study aimed** to assess reduction in Lower urinary tract symptoms with interchangeable alternative use of Tadalafil & selective  $\alpha$ 1-blocker and to compare its therapeutic effect to combined daily use. **Patients and method:** 32 men age (50-70y), nondiabetic nor hypertensive, complaining of LUTS due to BPH was included. All patients received silodosin 8mg/day combined with tadalafil 10 mg/day for 3months, After 3 months the treatment program has been changed as all same patient group received silodosin 8mg & tadalafil 10mg day by day. **Results:** The mean LUTS before treatment was 13.88, the mean difference with use of combined treatment of Tadalafil & Selective  $\alpha$ 1-blocker was 11.53, while mean difference with using interchangeable alternative treatment was 11.47. Deference in both treatment modalities was statistically insignificant at *P* value (< 0.05). Complications of each treatment modality were compared and the results were better in interchangeable alternative treatment with statistically significant variation in retrograde ejaculation, flush and nasal congestion, and gastric upset. **Conclusion:** In patients with LUTS due to BPH, no statistically significant difference in therapeutic value between daily use of combination of Tadalafil 10mg & Selective  $\alpha$ 1-blocker and switch interchangeable use of both of the two drugs, while there is statistically significant less side effect observed with switch interchangeable use.

**Keywords:** *International Prostate Symptoms Score, Tadalafil & Selective  $\alpha$  1- blocker, benign prostatic hyperplasia, Lower urinary tract symptoms.*

### **INTRODUCTION:**

Lower urinary tract symptoms (LUTS) in association with benign prostatic hyperplasia (BPH) are frequent complaints among middle-aged men as well as elderly ones. These symptoms can range from mild to severe. They include frequency, urgency, intermittency, strangurea, nocturia, incomplete emptying, and poor stream of urine. They can significantly reduce the Quality Of Life (QoL). For many years, surgery has been the preferred treatment for this condition as it effectively reduces urinary symptoms and improves Quality Of Life (QoL).

In recent decades, there has been a significant change in managing BPH, with a shift from surgical to medical treatments. The typical approach for treating LUTS/BPH involves either the use of  $\alpha$ -adrenergic

receptors blockers, 5 $\alpha$ -reductase inhibitors, and phytotherapies individually or combined. While these treatments may cause sexual side effects, the occurrence and characteristics of these effects vary across medication classes, individual medications and drug combinations (1).

Phosphodiesterase inhibitors now widely used in treatment of lower urinary tract symptoms due to BPH, include; Vardenail, Sildenafil and Tadalafi. Tadalafil is considered preferred in treatment of LUTS/BPH as it has longest mean half-life of elimination (15-17.5h).

Tadalafil use in a once daily dose of 5 or 10 mg are also approved in treatment of men with LUTS with or without associated erectile dysfunction (ED). Tadalafil use in 5 mg once daily dose proved efficiency for treatment of LUTS as reported by several well-

designed studies (2). Tadalafil considerably improves the total IPSS and it is recognized as a new treatment alternative to other established medications for LUTS such as the  $\alpha$ -adrenergic blockers, 5 $\alpha$ -reductase inhibitors (3,4).

Combined use of tadalafil and  $\alpha$ -blocker are approved to improve LUTS/BPH better than using each one alone (5). Use of Tadalafil alone or with  $\alpha$ -1-blocker improve erectile function in men having LUTS/BPH and ED (6).

The IPSS standard include seven- question related to voiding symptoms written to assess disease severity and response to therapy. They include frequency, intermittency, strangurea, urgency, nocturia, incomplete emptying, and weak urine stream. The rating scale for the IPSS as: mild 0-7, moderate 8-19, sever 20-35.

### **AIM OF THE STUDY:**

To assess the reduction in LUTS with interchangeable alternative use of Tadalafil & selective  $\alpha$ 1-blocker and to compare its therapeutic effect to combined daily use of the same treatment.

### **MATERIALS AND METHODS:**

A comparative analytic prospective cross-over study between not independent two groups, conducted at urology department of National Cancer Institute NCI – Misurata – Libya, from 1<sup>st</sup> August 2023 to 31<sup>st</sup> March 2024. The study included 32 patients aged between 45 and 60 years not known to have any chronic disease that my cause LUTS other than BPH such as neurologic disease (stroke, multiple sclerosis, parkinsonism,) UTI, urethral stricture, stone, tumor. all of them had H/O LUTS due to BPH .all patients underwent important tests to prove this as follow: urine analysis and culture, urine for cytology, total and free PSA urinary flowmetry,ultrasound abdomen and pelvis with evaluation of post voiding residual, diagnostic urethrocystoscopy.

Only case with moderat rating scale for IPSS were included in this study. Patients with prostate median lobe bulging into urinary bladder were excluded. All patients received Silodosin 8 mg/day combined with Tadalafil 10 mg/day for 3 months; they were evaluated for IPSS. During this study we applied IPSS standards. Every one of these symptoms were evaluated accordingly. When symptoms occurred at rate of less than one in five (score 1), when occurred at a rate of less than half (score 2), when occur at a rate of half the time (score 3), when occurred at a rate of more than half the time (score 4), and when it occurred usually (score 5).

Regarding the side effect of the medications used in the study, we relied on asking patients about that.

After 3 months the treatment program were changed as all the same patients received Silodosin 8mg & Tadalafil 10 mg day by day for 3 months. Then evaluated in the same way as above.

After end of treatment period in both groups, maximum urinary flow rate (Qmax) used to ensure consistency of test result with the IPSS for each patient. post-voiding residual urine volume (PVR) by ultrasound also used to ensure no significant residual urine volume..

at 3 months of treatment, In both not independent two groups, we use both drugs in same way, i.e. silodosin taken 8 mg tab before bed time and Tadalafil 8 mg tab taken one hour before dinner meal.

**Statistical analysis:** McNemar test or related samples Wilcoxon signed rank test (when appropriate) were used to assess the association between qualitative variables. Quantitative variables were compared by paired t-student test. In all tests, *P* value was considered significant if less than 0.05. All statistical calculations were done using computer software SPSS (Statistical Package for the Social Science; SPSS inc., Chicago, IL, USA) version 26 for Microsoft Windows.

### **RESULTS:**

Number of patients included in the study were 32 patients; their mean age was 52 years, In addition, after applying the criteria that we mentioned during the study, we found the following: in the group that used two medication on a daily basis: 21 of them converted from moderate to mild (IPSS), While 11 no longer suffer from any symptoms.

As for side effect of this group 14 of them suffered from retrograde ejaculation (6 dry ejaculation , 8 weak ejaculatory function), 1 patient suffered from orthostatic hypotension ,flush and nasal congestion happened with 14 patient ,back pain happened with 12 patient ,gastric upset with 14 patient.

While the following in the group that used tow medication day by day in interchangeable basis: 21 of them converted from moderate to mild (IPSS), while 11 no longer suffer from any symptoms.

As for side effect of this group 2 of them suffered from retrograde ejaculation (both were weak ejaculatory function), no patient suffered from orthostatic hypotension, flush and nasal congestion happened with 6 patient ,back pain happened with 5 patient ,gastric upset with 6 patient.

Initial pre-treatment IPSS ranging from 10 to 17 (mean 13.88), IPSS mean difference with use of combined treatment of tadalafil and alpha-blocker was 11.53, while mean difference of IPSS using switch interchangeable alternative treatment was 11.47. Difference in both treatment modalities was statistically insignificant at *P*-value < 0.05 (*P* = 0.751, 95% CI: - 0.34, 0.46) (Table 1).

**Table 1: mean minimum and maximum values for initial IPSS and post-treatment for both treatment modalities**

	Mean (SD)	Minimum	Maximum	P-value
Initial IPSS (pretreatment)	13.88 (2.03)	10	17	0.751
PC daily treatment change in IPSS	11.53 (1.16)	9	13	
PI treatment change in IPSS	11.47 (1.29)	8	13	

**SD= Standard Deviation, PC= post-combined, PI= post interchangeable**

Side effects of each treatment modality were compared, the results were better in the interchangeable alternative treatment with statistically significant variation in retrograde ejaculation, flush and nasal congestions, and gastric upset (Table 2).

**Table 2: comparison of side effects in each treatment modality**

Side effects		Combined treatment n (%)	Interchangeable treatment, n (%)	P
RE	weak ejaculatory function	7 (21.9)	2 (6.3)	0.01*
	Complete retrograde ejaculation	7 (21.9)	0 (0)	
Orthostatic hypotension		1 (3.1)	0 (0)	0.32
flush and nasal congestion		14 (43.8)	6 (18.8)	0.008*
gastric upset		14 (43.8)	6 (18.8)	0.008*
Back pain		12 (37.5)	6 (18.8)	0.07

(\* ) = statistically significant (P-value < 0.05)

## **DISCUSSION:**

This study is an extension of a series of studies conducted and dealt with combined therapy of selective  $\alpha$ -1 blocker & tadalafil, most of previous researches and studies centered around comparison between therapeutic value of combined use of selective  $\alpha$ 1 blocker & tadalafil versus therapeutic value of each one of these drugs.

In this study, we used same combination but interchangeably, so that one day patient took tadalafil and other day he took a selective  $\alpha$ 1 blocker (silodosin).

We would like to note that all cases in this study are not known to have any chronic disease that may cause LUTS except BPH such as Diabetes Miletus stroke Parkinson disease, peripheral neuropathy.

The statistical analysis in this current study has shown that it is important to switch interchangeably between using a selective  $\alpha$ 1 blocker and tadalafil in order to reduce the side effects of the two drugs when used together daily, without diminishing their therapeutic value. This approach aims to improve the quality of life for patients, which is the primary goal of our study. Quantitative data used to evaluate the change in IPSS among the two treatment modalities, qualitative data used to assess side effect of the drugs and statistical significance tests have evidently strengthened our conclusion.

Based on previous research, it appears that the side effects of using tadalafil and a selective  $\alpha$ 1 blocker may not be significant (7). However, our study has helped to reduce some of these side effects. Overall, the therapeutic value of the two drugs in our study

closely aligns with the therapeutic value found in previous studies on the same subject.

All primary and secondary researches and studies that we have reviewed, have proven the advantage of combined use of selective  $\alpha$ 1 blocker& tadalafil versus using each one of these drugs alone (6,8). Anyhow we recommend further studies related to this treatment method, as sample at this study was not large. In addition, this study did not address some aspect as quality of sexual life for example, considering that there is a relationship between BPH and erectile dysfunction proved in previous studies (9), certainly use of tadalafil is of great importance in this aspect.

## **CONCLUSIONS:**

In patients with LUTS due to BPH, there is no significant difference in therapeutic value between combination daily use of tadalafil 10mg & selective  $\alpha$ 1 blocker and switch interchangeable use of both two drugs. There are significantly fewer side effects (retrograde ejaculation, orthostatic hypotension, dizziness, low back pain, blocked nose, gastric upset) observed with switch interchangeable use.

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