Prospective Comparative Study between Silodosin 8 mg Versus Combination of Tadalafil 5mg and Silodosin 4mg for treatment of Lower Urinary Tract Symptoms related to Benign Prostatic Hyperplasia

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Abstract

Background: In men, lower urinary tract symptoms (LUTS) are associated with benign prostatic hyperplasia (BPH). Therapeutic options aim to relax prostate smooth muscle and/or reduce prostate enlargement.

Objectives: To evaluate the efficacy of Silodosin 8 mg alone versus the combination of Tadalafil 5mg and Silodosin 4 mg for treatment of LUTS related to BPH.

Patients and methods: About 203 patients with LUTS of BPH who completed the study up protocol presented to our department classified into two groups group A (101 patients) received Silodosin 8 mg, group B (102 patients) received the combination of Tadalafil 5mg and Silodosin 4 mg. All results recorded and analyzed with Statistical Package for Social Science® (SPSS) and Microsoft Excel 2010.

Results: The IPSS, QOL, IIEF score, Q-max and PVR showed significantly greater improvement in the combination of Tadalafil 5mg with Silodosin 4mg than monotherapy of Silodosin 8mg.

Conclusions: Despite Silodosin 8mg is well-tolerated and effective treatment option in men with LUTS of BPH, but the combination of tadalafil 5m and Silodosin 4mg is more effective and feasible for these patients.

Keywords: LUTS of BPH; Tadalafil 5mg; Silodosin 4mg; Silodosin 8mg.

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Introduction

BPH is the most common benign tumor in men, no convincing evidence exists regarding a positive correlation for any factors other than age and the presence of testes. It has been classically stated that from 25 to 50 percent of individuals with microscopic and macroscopic evidence of BPH will progress to clinically manifested BPH. The prevalence of clinical BPH in an individual community in men ages 55 to 74 years may vary from 5 % to 30 %. Some studies have suggested a genetic predisposition, and some have noted racial differences **(McConnell et al., 2003).**

According to the European Association of Urology guidelines, both α1 adrenoceptor blockers (α1-blockers) and phosphodiesterase type 5 inhibitors (PDE5-Is) are recommended as the first-line medical treatment for LUTS/BPH **(Gratzke et al., 2015).**

Silodosin is a third generation α1blocker, and its effect on LUTS is more selective to that of other α1-blockers. However, some men with BPH result in inadequate improvement in LUTS after silodosin treatment. Therefore, we sought to identify further treatment strategies, including combination or add-on therapy with other drugs for LUTS, for such patients **(Matsukawa et al., 2013).**

Tadalafil is a phosphodiesterase (PDE) type 5 inhibitor (PDE5-I) widely used as treatment of ED & was recently approved for treatment of signs and symptoms of BPH (LUTS/BPH). Although the mechanisms for improvements in LUTS with PDE5 inhibition include inhibition of PDE5 isoenzymes present in the bladder, prostate, urethra, and supporting vasculature and consequent increases in intracellular nitric oxide–cyclic guanosine monophosphate concentration, relaxation of the muscle cells in these structures, improved blood perfusion, and reduced afferent signaling from the urogenital tract **(Roehrborn et al., 2014)**.

New medications such as silodosin and tadalafil improve short-term LUTS. Data were not available to assess long-term efficacy or prevention of disease progression. Trials with longer duration of treatment and follow-up are needed to assess the effect of these therapies on response rates using disease progression and long-term outcomes **(MacDonald et al., 2019).**

Patients and Methods

Study design: This study is a prospective randomized study for patients with LUTS/BPH in the Urology Department, Qena University Hospital in the duration between May 2019 and December 2020.

Patient grouping: We planned to have two groups each group with at least 100 cases using closed envelope method.

Group A: consists of 101 cases, patients with LUTS/BPH will receive Silodosin 8 mg once daily for 3 months.

Group B: consists of 102 cases, patients with LUTS/BPH will receive Tadalafil 5mg and Silodosin 4 mg once daily for 3 months.

Patient selection:

Inclusion criteria:

1-Patient aged > 50years.

2-International Prostate Symptom Score (IPSS) of >8.

3-Max. Flow rate <10 ml/sec.

Exclusion criteria:

1- Suspicion of prostate cancer.

2- Complicated BPH.

3- Insufficient renal function (serum creatinine concentration of >2 mg/dl).

Diagnostic work up:

1. **History taking:** including IPSS scoring system, International Index of Erectile Function (IIEF).
2. **Complete physical examination**: including digital rectal examination (DRE).
3. **Laboratory investigations**: which include
   -Urine analysis.
   -Serum Creatinine.
   -Serum PSA.
4. **Abdominal Ultrasonography:** to assess post voiding residual Urine.

Uroflowmetry.

5. **Follow up schedule:**

Patients in the two comparative groups will be followed 1st, 2nd and 3rd month of treatment. By the 3rd moth of follow up, the following parameters will be assessed:

1- IPSS, IIEF score, QOL.
2- Uroflowmetry (Q-max).
3-Abdominal Ultrasonography to assess PVR.

Statistical analysis

SPSS version 21 was used. Data were presented as number and %, mean±SD. P value considered to be significant when <0.05.

Results

This study was designed to have two groups:

Group A: Which are patients with LUTS/BPH taking Silodosin 8 mg for 3 months, includes 101 cases. The age of patients in this group ranged from 52 to 75 years, (mean 61.7 ± 4.6 SD) **(Table 1).** PSA level ranged from 1-3.5 ng/ml, (mean 2.3 ± 1.4 SD) **(Table 1).**

Group B: Which are patients with LUTS/BPH taking Tadalafil 5mg and Silodosin 4 mg for 3 months, includes 102 cases. The age of patients in this group ranged from 54 to 72 years, (mean 62.9 ± 5.6 SD). PSA level ranged from 1.2-3.4 ng/ml, (mean 2.2 ± 1.4 SD)**.**

Before treatment Parameters: (Table 1, Fig.1)

- **Q-max:** The mean Q-max (7.1 ml/min.) in group (A), (7.2 ml/min.) in group (B) with no significant difference (P value 0.851).
- **IPSS Score:** The mean IPSS Score (21.2) in group (A), (20.8) in group (B) with no significant difference (P value 0.304).
- **IIEF Score:** The mean IIEF Score (15) in group (A), (14.5) in group (B) with no significant difference (P value 0.215).
- **QOL:** The mean QOL (4.8) in group (A), (5) in group (B) with no significant difference (P value 0.138).

Post 3 months of treatment Parameter: (Table 2, Fig.2)

- **Q-max:** The mean Q-max (14.4 ml/min.) in group (A), (15.2 ml/min.) in group (B) with highly statistically significant difference between studied groups**.**
- **IPSS Score:** The mean IPSS Score (17.6) in group (A), (16.7) in group (B) with highly statistically significant difference between studied groups**.**
- **IIEF Score:** The mean IIEF Score (20.8) in group (A), (21.5) in group (B) with highly statistically significant difference between studied groups.
- **PVR:** The mean PVR (39.8 ml) in group (A), (37.5 ml) in group (B) with highly statistically significant difference between studied groups**.**
- **QOL:** The mean QOL (3.1) in group (A), (2.7) in group (B) with highly statistically significant difference between studied groups.

Complications:

No statistically significant difference between studied groups regarding complications except retrograde ejaculation.

There is statistically significant difference between studied groups regarding retrograde ejaculation (In Add-on therapy only as 5.9 % of cases take tadalafil 5mg and Silodosin 4mg in comparison to 9.5 % of cases take Silodosin 8mg alone).

Table 1. Comparisons between the two groups regarding age, PSA, Pre-treatment (Q-max, IPSS, IIEF score, PVR, QOL).

Pre-treatment	Groups		KW	P-value
	A	B		
Age (years)	61.7±4.6	62.9±5.6	3.76	0.152
PSA (ng/ml)	2.3±1.4	2.2±1.4	2.7	0.254
Q Max	7.1±1.2	7.2±1.2	0.32	0.851
IPSS	21.2±1.8	20.8±2.0	2.37	0.304

IIEF score	15.0±2.0	14.5±1.7	3.07	0.215
PVR	50.8±6.1	51.0±5.9	0.09	0.954
QOL	4.8±0.8	5.0±0.8	3.95	0.138

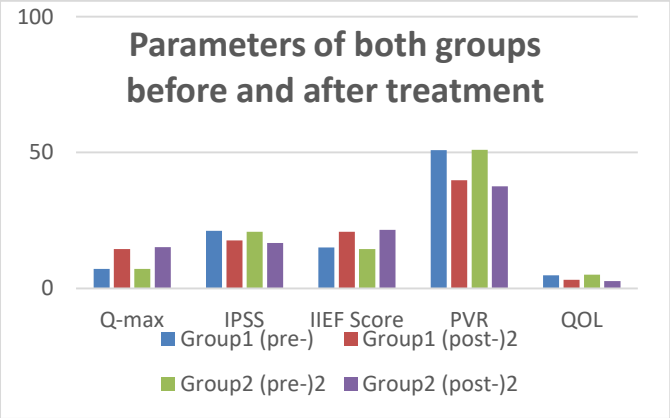

Fig.1. Comparisons between the two groups regarding Q Max, IPSS, IIEF score. QOL PVR (before and after treatment).

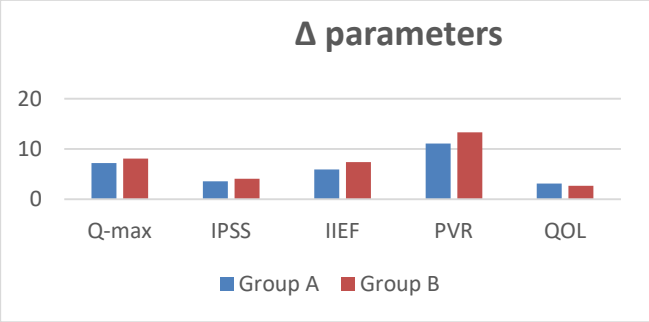

Fig2. Comparisons between the two groups regarding Δ Q Max, IPSS, IIEF score, PVR & QOL.

Table 2. Comparisons between the two groups regarding complications

Variables	**Groups**				**X^2**	**P-value**
	Group A (n = 101)		**Group B (n = 102)**			
Retrograde ejaculation	10	9.5%	6	5.9 %	**9.6**	**0.008**
Headache	5	4.8%	5	4.9 %	0.12	0.941
Nasal congestion	3	2.9%	3	2.9 %	0.22	0.892
Ocular hyperemia	3	2.9%	3	2.9 %	0.22	0.892
Myalgia	3	2.9%	2	2%	0.24	0.884
Dizziness	2	1.9%	2	2%	0.37	0.827
Palpitation	2	1.9%	1	1%	1.93	0.380
Dyspepsia	2	1.9%	2	2%	1.97	0.371
Peripheral edema	1	1%	1	1%	0.98	0.611
Flushing	2	1.9%	2	2%	0.32	0.847
Orthostatic hypotension	1	1%	1	1%	0.98	0.611
Treatment discontinuation due to AEs	4	3.8%	2	2%	3.9	0.141

Discussion

Both α1 adrenoceptor blockers (α1-blockers) and phosphodiesterase type 5 inhibitors (PDE5-Is) are recommended as the first-line medical treatment for LUTS/BPH **(Gratzke et al., 2015).**

New medications such as silodosin and tadalafil improved short-term LUTS. No data available to assess long-term efficacy or prevention of disease progression. Trials with longer duration of treatment and follow-up are needed to assess the effect of these therapies on response rates, disease progression, and long-term outcomes. **(MacDonald et al., 2019)**

In our study we compare between 2 groups of medications, group A take Silodosin 8 mg (101 cases) alone versus combination of Tadalafil 5mg and Silodosin 4mg (102 cases) group B for treatment of LUTS of BPH regarding Q-max, IPSS Score, QOL, IIEF Score, PVR, complications and cost.

There is no statistically significant difference) between studied groups regarding age, PSA, Pre-treatment (Q-max, IPSS, IIEF score, PVR). In our study regarding Q-max, there is no significant difference in pre-treatment Q-max mean in all groups A, B, but there is high

significantly statistics difference of Q Max in each group before and after treatment& there is highly statistically significant difference between studied groups regarding Δ Q Max**.**

Although, we found high significantly statistics difference between studied groups 3 months after treatment regarding Q Max with high significantly statistics difference between group A & group B, so group B give the best improvement in comparison to the other group, these results match the results of these results match the results of (**Yoshida et al., 2017; Gacci et al., 2012; Sebastianelli et al., 2019).**

Regarding IPSS Score, there is no significant difference in pre-treatment IPSS mean in all groups A, B, but there is highly statistically significant difference of IPSS in each group before and after treatment & there is highly statistically significant difference between studied groups regarding Δ IPSS**.**

Although, we found highly statistically significant difference between studied groups 3 months after treatment regarding IPSS score with statistically significant difference between group A & group B, so group B give the best improvement in comparison to the other group, these results match the results of (**Yoshida et al., 2017**; **Kim et al., 2017; Fabiola et al., 2019**).

Regarding IIEF score there is no significant difference (P value 0.215) in pre-treatment IIEF mean in both groups A, B, but there is high significantly statistics difference of IIEF score in each group before and after treatment & there is high significantly statistics difference between studied groups regarding Δ IIEF score**.**

Although, we found high significantly statistics difference between studied groups 3 months after treatment regarding IIEF score with statistically significant difference between group A & group B, so the patients in group B showed the best improvement in comparison to the other group, these results match the results of (**Kim et al., 2017; Sebastianelli et al., 2019).**

Then we found regarding PVR in our study, there is no difference significantly in pre-treatment PVR mean in all groups A, B, but there is high significantly statistics difference of PVR score in each group before and after treatment & there is high significantly statistics difference between studied groups regarding Δ PVR score**.**

Although, we found highly statistically significant difference between studied groups 3 months after treatment regarding PVR score with statistically significant difference between group A & group B, so group B give the best improvement in comparison to the other group, these results match the results of **(Kim et al., 2017; Sebastianelli et al., 2019; Roehrborn et al., 2008).**

Regarding QOL, there is no significant difference in pre-treatment QOL mean in all groups A, B, but there is highly statistically significant difference of QOL in each group before and after treatment & there is highly statistically significant difference between studied groups regarding Δ QOL**.**

Although, we found highly statistically significant difference between studied groups 3 months after treatment regarding QOL score with highly statistically significant difference) between group A & group B, so group B give the best improvement in comparison to the other group, these results match the results of (**Yoshida et al., 2017; Fabiola et al., 2019).**

Limitations Of the study

1. The number of patients was not high enough to reduce the impact of statistical error during analysis. Also, short period of follow up (12 weeks) and patient co-morbidities should have been taken in consideration and these are the limitations of our study.
2. That clinical trials were not powered to assess superiority or non-inferiority of tadalafil in comparison with other therapies. In relation to this, more clinical trials comparing the association of tadalafil and other pharmacological agents used in LUTS-BPH as 5-alpha reductase inhibitors, β3- adrenoceptor agonists and muscarinic receptor antagonists are needed to personalize the therapeutic strategies for patients with LUTS-BPH.

Conclusion

Silodosin 8mg daily monotherapy improve

overall LUTS after 12 weeks. However, the addition of Silodosin 4 mg to tadalafil 5 mg can improve voiding symptoms and Q-max. Combination therapy is very effective. Even if the overall occurrence of side effects is slightly higher as compared with tadalafil alone, their low severity allows achieving good compliance and safety, so we recommend combination therapy especially Tadalafil 5mg with Silodosin 4 mg in patients with LUTS of BPH with or without ED.

Recommendations

1. Increase number of patients in each group.
2. Prolong period of follow up of patients.
3. Decrease cost of these medications especially combination therapy and offer one tablet contain both drugs.
4. Use of combination therapy in patients of LUTS of BPH especially with E.D.

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