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A Comparative Study of Efficacy of Silodosin with or Without Tadalafil in Treatment of Erectile Dysfunction Associated With BPH-LUTS

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Abstract

Background: Benign prostatic hyperplasia (BPH) is the most common cause of lower urinary tract symptom (LUTS) development in men. Erection as a complex phenomenon involves arterial dilatation, trabecular smooth muscle relaxation and corporal veno-occlusive mechanism activation.

Methods: A total of 120 patients who fulfill the inclusion criteria were recruited into the study, which is approved by the hospital ethical committee of our hospital and study was conducted from August 2016 to December 2017. Full informed written consent was obtained from each eligible patient before enrolment.

Results: The International index of erectile function (IIEF) questionnaire is validate, multidimensional and self administered investigation that has been found useful in the clinical assessment of erectile dysfunction and treatment outcome in clinical trials. The Mean IIEF at zero week in silodosin (S) group was 18.58±3.01 (Baseline value) and after six weeks it was 18.96±2.79 (End point value) with Mean IIEF Difference (IIEF Diff) of 0.38±0.92. The Mean IIEF at zero week in silodosin with tadalafil (S+T) group was 18.42±3.20 (Baseline value) and at after six weeks it was 22.00±2.27 (End point value) with Mean IIEF Difference (IIEF Diff) of 3.58±1.53. The difference between the means of IIEF Diff was statistically significant ($p<0.001$), concluding that IIEF significantly improved with combination therapy but not with monotherapy.

Conclusion: In our study, results showed that the combination of Silodosin and Tadalafil significantly improving (reducing) LUTS when compared with alpha blocker (silodosin) monotherapy. We found improvement in the erectile dysfunction in terms of increasing the IIEF score of patients using the combination drug trial.

Keywords: Benign prostatic hyperplasia (BPH), Erectile dysfunction (ED), Lower urinary tract symptoms (LUTS)

Introduction

Benign prostatic hyperplasia (BPH) is the most common cause of lower urinary tract symptom (LUTS) development in men. The intensity of the symptoms may vary from mild to severe, significantly affecting the quality of life (QoL). Approximately 40% of men older than 50 years and 80% older than 80 years are known to have BPH . They report various LUTS, such as weak urine stream, stuttering urination, need to strain during urination, urinary spillage, feeling of incomplete bladder

emptying, frequent urination, urination at night (nocturia) and urgency.[1]

Erectile dysfunction (ED) is one of the most challenging issues in modern urology that significantly influences the QoL in men worldwide. Erection as a complex phenomenon involves arterial dilatation, trabecular smooth muscle relaxation and corporal veno-occlusive mechanism activation[2]. ED is a persistent inability to attain and maintain penile erection sufficient to permit sexual performance [3] The results of the study conducted in 1948 by Kinsey et al. [4] showed that approximately 10 million American men (1 in 10) have ED. Another large-scale epidemiological study was completed in 1994 (Massachusetts Male Aging Study). The authors reported the presence of ED in 52% of men aged 40 to 70 years In 2012, an epidemiological study was conducted to assess the prevalence of ED in the population of 20- to 75-year-old men in the Russian Federation [5] The results of the survey showed that 10.1% of responding men had no ED signs, whereas 71.3% had mild, 6.6% had moderate and 12% had severe ED. Therefore, 1101 of 1225 respondents had ED symptoms [6] A series of studies determined the main predisposing factors of ED development, including hypertensive disease, cardiovascular diseases and diabetes mellitus [7]

Material And Methods

Study Site: The study was conducted in the Department of General Surgery, Mata Chanan Devi Hospital, New Delhi. Patients was recruited from O.P.D. /I.P.D. including emergency patients.

Study Population: A total of 120 patients who fulfill the inclusion criteria were recruited into the study, which is approved by the hospital ethical committee of our hospital and study was conducted from August 2016 to December 2017. Full informed written consent was obtained from each eligible patient before enrolment.

Study Design: The present study is a prospective, randomized, controlled study.

Sample Size: Urodynamic effects of the combination of tamsulosin and daily tadalafil in men with lower urinary tract symptoms secondary to benign prostatic hyperplasia were observed by Rommel Regadas, Reges et al[35].The study observed IPSS, showed a significant reduction in tamsulosin/tadalafil group (-9.75 ± 5.1) compared to tamsulosin/placebo (-6.0 ± 3.6) group (P = 0.01).

Taking these values as reference, the minimum required sample size with 90% power of study and 5% level of significance is 30 patients in each study group.

Study duration: The study was conducted from August 2016 to December 2017

Inclusion criteria: Subjects with following conditions were included:

Male Patients >50 years with BPH and lower urinary track symptoms.

Exclusion criteria: Subjects with the following conditions were excluded:

1. Patients with postoperative retention following major abdominal or pelvic surgery.
2. Patients with large residual volume of more than 1 liter and clot retention from hematuria.
3. Patient who were not willing to give consent for participation in the study.
4. Patients with significant renal disease (serum creatinine 120 mmol/ml) and/or hepatic disease.
5. Patients with significant neurological disease such as multiple sclerosis.
6. Patients with confirmed or suspected urethral stricture.

7. Patients with history of prostatic or bladder neck surgery and confirmed cases of carcinoma prostate.
8. Patients with history of angina, unstable angina, and recent myocardial infarctions (on Nitroglycerin).
9. Patients with cerebro-vascular accidents with residual disease, transient ischemic attacks in the last 6 months.
10. Patients with background of orthostatic hypotension (decrease of > 20 mm Hg of systolic or diastolic BP).
11. Patients who were allergic to any ingredient in silodosin or tadalafil.
12. Patients who were taking ketoconazole, clarithromycin, itraconazole, nefazodone, ritonavir or non-selective alpha-blocker (e.g., prazosin)

Methodology

Demographic and patients data were recorded during recruitment. Clinical details including duration of lower urinary tract symptoms in the month prior to study (graded by International Prostatic Symptoms Score (IPSS) as given in annexure), past medical history, history of constipation within the last 2 weeks, digital rectal examination (DRE) findings, blood tests results including renal function, prostate specific antigen (PSA) were also noted. In addition, patients were investigated prior to study with a trans-abdominal ultrasound of their kidney, ureter and bladder to detect hydronephrosis, hydroureter, prostrate size, intravesical prostatic protrusion and post void residual urine volume would also be noted.

Subjects were randomized to receive one tablet of either silodosin (8 mg/day) or drug silodosin (8mg/day) and tadalafil (5mg/day) on the day of recruitment using Block Randomization and continued till four weeks. Uroflowmetry, ultrasound KUB,

Block Randomization with Sealed envelope system:- In this, I have prepare ten randomly generated treatment allocations within sealed opaque envelopes assigning A and B in 5 envelopes each, where A represents group receiving silodosin with tadalafil and B represents group receiving silodosin without tadalafil. Once a patient gave consent to enter a study an envelope was opened and the patient was then being offered the allocated group. In this technique, patients were randomized in a series of blocks of ten i.e., for every ten patients randomized five received silodosin with tadalafil and other five received silodosin without tadalafil.

Efficacy Measures; Primary efficacy end points included changes from baseline in their erectile function using the erectile function (EF) scores (sum of questions 1–5 and 15) from the International Index of Erectile Function (IIEF).

Follow up: Duration of the study was 6weeks with follow up at 4week, 6 weeks.

Data collection methods: The observations were recorded in a proforma for detailed analysis. (Annexure 1)

Statistical Methods

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean ± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality is rejected then non parametric test was used.

Observation and Results

The present study was conducted in Department of General Surgery, Mata Chanan Devi Hospital, Janakpuri, New Delhi. The study was conducted for a period of 16 months from August 2016 to December 2017, after the approval for study by institutional ethics committee, a written informed consent was taken from the patients after explaining the purpose of the study.

Table 1 : Comparison in change in IIEF score at 0 week, 4 week and after 6 week of initiation of treatment in Silodosin (S) group

S		N	Mean±SD	Mean Diff	P-Value
PAIR 1	IIEF 0 WK	24	18.58±3.01	0.17	0.295
	IIEF 4 WK	24	18.75±2.94		
PAIR 2	IIEF 4 WK	24	18.75±2.94	0.21	0.203
	IIEF 6 WK	24	18.96±2.79		
PAIR 3	IIEF 0 WK	24	18.58±3.01	0.38	0.059
	IIEF 6 WK	24	18.96±2.79		

The mean of IIEF in Silodosin group at 0 week was 18.58±3.01 and at 4 week after initiation of treatment was 18.75±2.94. The difference between the means of this pair (pair 1) was statistically not significant (p=0.295).

The mean of IIEF in Silodosin group at 4 week after initiation of treatment was 18.75±2.94 and after 6 week follow up was 18.96±2.79. The difference between the means of this pair (pair 2) was statistically not significant (p=0.203).

The mean of IIEF in Silodosin group at 0 week was 18.58±3.01 and at 6 week after initiation of treatment was 18.96±2.79. The difference between the means of this pair (pair 3) was statistically not significant (p=0.059).

IIEF was re-evaluated after 4 week and after 6 week of initiation of treatment in all cases. As shown above the difference in means of IIEF at different level were compared (i.e. pair 1, pair 2 and pair 3) and no significant improvement in terms of increased IIEF score was noted in Silodosin group after six weeks follow up.

Table 2: Comparison of IIEF score in Silodosin with Tadalafil (S+T) and Silodosin (S) alone group at 0 week, 4 week and after 6 week of initiation of treatment

Parameter	Group	N	Mean±SD	Mean Diff	P-Value
IIEF 0 WK	S	24	18.58±3.01	0.16	0.853
	S+T	24	18.42±3.20		
IIEF 4 WK	S	24	18.75±2.94	1.75	0.037
	S+T	24	20.50±2.70		
IIEF 6 WK	S	24	18.96±2.79	3.04	<0.001
	S+T	24	22.00±2.27		

The mean IIEF in Silodosin with Tadalafil group before initiation of treatment was 18.42±3.20 and in Silodosin group was 18.58±3.01. The difference between means was statistically not different(p=0.853).

The mean IIEF in Silodosin with Tadalafil group at 4 week after initiation of treatment was 20.50±2.70 and in Silodosin group was 18.75±2.94. The difference between means was statistically significant (p=0.037).

The mean IIEF in Silodosin with Tadalafil group at 6 week after initiation of treatment was 22.00±2.27 and in Silodosin group was 18.96±2.79. The difference between means was statistically significant (p<0.001).

IIEF was evaluated before initiation of treatment at 0 week, and re-evaluated after 4 week and after six week follow up in all cases. As shown above the means of IIEF in both groups were found comparable before initiation of treatment. But the differences in means of IIEF were found significantly higher in Silodosin with Tadalafil group after four week and six weeks follow up.

Table 3: Comparison of Side Effects in Silodosin and Silodosin + Tadalafil group

Side Effect	S	S+T	P-Value
Total	12	16	0.375
Bodyache	1	1	
Dizziness	2	2	
Headache	4	9	
Hypotension	1	3	
Retrograde Ejaculation	4	1	

It has been observed that daily doses of Silodosin and Tadalafil were well tolerated during the study period. Total number of 28 patients experienced side effects of the drug trial during the study. A total of 12 patients received silodosin alone experienced the side effects while in case of silodosin with tadalafil group this number was 16 with p-value of 0.375 indicating that there was not significant difference in side effect profile of both the treatment trial. Nevertheless, we have found a high percentage of headache and hypotension as expected with combination therapy and the complaint of retrograde ejaculation was noted in higher number with silodosin group of patients.

Discussion

Out of 60 patients in silodosin with tadalafil group 50 patients had completed the study, and among the 60 of silodosin monotherapy group 52 patients had completed the study. All the drop outs were because of personal/unknown reason. However, the total number of patients who encountered the adverse event was 16 in silodosin with tadalafil group and was 12 in silodosin alone group among those who had completed the study.

The International index of erectile function (IIEF) questionnaire is validate, multidimensional and self administered investigation that has been found useful in the clinical assessment of erectile dysfunction and treatment outcome in clinical trials. The Mean IIEF at zero week in silodosin (S) group was 18.58±3.01 (Baseline value) and after six weeks it was 18.96±2.79 (End point value) with Mean IIEF Difference (IIEF Diff) of 0.38±0.92. The Mean IIEF at zero week in silodosin with tadalafil (S+T) group was 18.42±3.20 (Baseline value) and at after six weeks it was 22.00±2.27 (End point value) with Mean IIEF Difference (IIEF Diff) of 3.58±1.53. The difference between the means of IIEF Diff was statistically significant ($p<0.001$), concluding that IIEF significantly improved with combination therapy but not with monotherapy. These results were comparable with the results of study by Amado Bechara et al[8], their work was on tamsulosin as monotherapy versus tamsulosin plus tadalafil as combination therapy, in which improvements of IIEF score were 1.9 for monotherapy and 8.2 with the drug combination. So these results showed preferences for the combination treatment in all patients because during study period IIEF changes were better than monotherapy.

PARAMETER	S	S+T	P-VALUE
N	24	24	
BASELINE IIEF	18.58±3.01	18.42±3.20	
END POINT IIEF	18.96±2.79	22.00±2.27	
IIEF Diff	0.38±0.92	3.58±1.53	<0.001

Conclusion

In our study, results showed that the combination of Silodosin and Tadalafil significantly improving (reducing) LUTS when compared with alpha blocker (silodosin) monotherapy. We found improvement in the erectile dysfunction in terms of increasing the IIEF score of patients using the combination drug trial.

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