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A Comparative Study Of Efficacy of Silodosin With Or Without Tadalafil In Treatment of Lower Urinary Tract Symptoms Associated With Bph (LUTS/BPH) In Men – A Single Centre Study

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Abstract

Background: Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells within the prostatic transition zone. Aim of this study was compare the efficacy of silodosin with or without tadalafil in treatment of lower urinary tract symptoms associated with BPH (LUTS/BPH) in men.

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: IPSS evaluated before initiation of treatment at 0 week, and re-evaluated after 4 week and after six week follow up in all cases. The means of IPSS in both groups were found comparable before initiation of treatment. The differences in means of IPSS were statistically not different in both groups after four weeks and six weeks follow up.

Conclusion: In our study, results showed that the combination of Silodosin and Tadalafil significantly improving (reducing) LUTS when compared with alpha blocker (silodosin) monotherapy.

Keywords: Benign prostatic hyperplasia (BPH), Lower urinary track symptoms (LUTS), Silodosin and Tadalafil.

Introduction

Lower urinary track symptoms include increased urinary frequency, urgency, nocturia, intermittency, straining, incomplete emptying and weak urinary stream.

Lower urinary track symptoms (LUTS) commonly classified as irritative or obstructive symptoms. The incidence of LUTS secondary to clinical BPH increases with aging and is often a comorbid condition in men. Lower urinary tract symptoms (LUTS), benign prostate hyperplasia (BPH), and erectile dysfunction (ED) are highly prevalent entities in aging men[1-3].

LUTS and BPH are usually treated with alpha blockers[4-5] and ED with phosphodiesterase 5 inhibitors (PDE5i) [6]. The negative impact of LUTS and ED on the

quality of life of aging men has been well acknowledged in the literature[7-8].

Blockade of the 1A-receptors has been shown to reduce prostatic tone and improve the dynamic aspects of voiding. Blockade of 1B receptors leads to venous and arterial dilation as smooth muscle cells in the vessel walls relax.8 Stimulation of 1D-receptors can lead to detrusor instability and blockade of these receptors has been shown in animal models to reduce irritative voiding symptoms.[9]

Silodosin is a highly sensitive alpha-1A receptor antagonist with little or no cardiovascular side-effects. It has been shown to have negligible effects on blood pressure and no effect on cardiac repolarization.8 Silodosin shows an affinity for the α 1A-AR that is 583 and 56-fold higher than its affinity for the α 1B- and α 1D-ARs, respectively.[10]

The aim of our study was to compare the safety and efficacy of silodosin 8mg/day vs. silodosin 8mg/day plus tadalafil 5mg/day in patients with LUTS/BPH in a randomized controlled study.

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.

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)

Consent and ethical clearance: Written and informed consent was taken from all the subjects participating in the study. Ethical clearance was taken from ethical committee before conducting the study.

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), 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. ultrasound KUB and IPSS score were performed at each follow up.

Efficacy Measures; Primary efficacy end points included subjective (IPSS) and objective (PVR) changes from baseline.

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. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. A p value of <0.05 was considered statistically significant.

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.

Male patients coming to outpatient department of General surgery, Mata Chanan Devi hospital and were diagnosed to have lower urinary tract symptoms with BPH and fulfilling the inclusion criteria were included in this study.

A total of 120 patients were included in the study and randomly divided into two groups; 60 in Silodosin group and 60 in Silodosin with Tadalafil group. In Silodosin group they were given Silodosin 8mg orally per day and patients of other group were given Silodosin 8mg with Tadalafil 5mg orally per day for 6 weeks.

Out of 60 patients in each group only 52 patients in silodosin group and 50 patients in silodosin with tadalafil group completed the study. The drop outs were due to either personal or family reasons.

Table 1: Comparison of different parameters in Silodosin and Silodosin+Tadalafil groups

Parameters	Silodosin+Tadalafil	Silodosin	P-value
N	60	60	
Age(years)	65.32±8.37	65.98±7.82	0.65
Duration of LUTS (Months)	5.96±2.85	5.91±2.38	0.92

History of	Hematuria	4(6.7%)	6(10%)	0.51
	Alcohol intake	6(10.0%)	8(13.3%)	0.57
	Constipation	22(36.7%)	23(38.3%)	0.85
	Hypertension	24(40.0%)	26(43.3%)	0.71
	Diabetes mallitus	8(13.3%)	7(11.7%)	0.78
	Coronary art disease	8(13.3%)	8(13.3%)	1.00
	COPD	6(10.0%)	7(11.7%)	0.77
	Anti diabetic medicines	8(13.3%)	7(11.7%)	0.78
	Anticoagulation drug intake	10(16.7%)	9(15.0%)	0.80
	Anti hypertensive Medicines	24(40.0%)	24(40.0%)	1.00
DRE		2.53±0.57	2.52±0.54	0.87
Serum urea(mg/dl)		28.88±7.21	31.67±6.26	0.03
Serum creatinine (mg/dl)		0.80±0.25	0.85±0.23	0.30
Prostate Specific Antigen(PSA) (ng/ml)		2.86±0.89	2.75±0.91	0.49
Prostate in gram		37.83±9.98	39.5±9.61	0.35
Median lobe protrusion		36(60.0%)	41(68.3%)	0.34
Sexually active		24(40.0%)	24(40.0%)	1.00

Rests of the demographic parameters were comparable in both groups.

Table 2 : Comparison of Post Void Residual Volume 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
PVR 0 WK	S	60	35.83±16.44	3.20	0.24
	S+T	60	39.03±13.13		
PVR 4 WK	S	54	31.17±9.94	6.40	<0.001
	S+T	53	37.57±8.52		
PVR 6 WK	S	52	29.48±8.12	4.16	0.003
	S+T	50	33.64±5.50		

The mean post void residual urine volume in Silodosin with Tadalafil group before initiation of treatment was 39.03±13.13 and in Silodosin group was 35.83±16.44. The difference between means was statistically not different (p=0.24).

The mean post void residual urine volume in Silodosin with Tadalafil group at 4 week after initiation of treatment was 37.57±8.52 and in Silodosin group was 31.17±9.94. The difference in between means was statistically significant (p<0.001).

The mean post void residual urine volume in Silodosin with Tadalafil group at 6 week after initiation of treatment was 33.64±5.50 and in Silodosin group was 29.48±8.12. The difference between means was statistically significant (p=0.003).

Post void residual urine volume evaluated before initiation of treatment at 0 week, and re-evalueted after 4 week and after six week follows up in all cases. As shown above the means of post void residual urine volume in both groups were found comparable before initiation of treatment. But the difference in means of PVR was found significantly higher in Silodosin with Tadalafil group after four week and six weeks follow up.

Table 3 : Comparison of Post Void Residual Volume 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
IPSS 0 WK	S	60	21.67 ±2.49	0.10	0.83
	S+T	60	21.77 ±2.60		
IPSS 4 WK	S	54	20.33 ±2.26	0.22	0.61
	S+T	53	20.11 ±2.18		
IPSS 6 WK	S	52	19.33 ±2.18	0.21	0.63
	S+T	50	19.12 ±2.12		

The mean IPSS in Silodosin with Tadalafil group before initiation of treatment was 21.77 ±2.60 and in Silodosin group was 21.67 ±2.49. The difference between means was statistically not different (p=0.83).

The mean IPSS in Silodosin with Tadalafil group at 4 week after initiation of treatment was 20.11 ±2.18 and in Silodosin group was 20.33 ±2.26. The difference between means was statistically not significant (p=0.61).

The mean IPSS in Silodosin with Tadalafil group at 6 week after initiation of treatment was 19.12 ±2.12 and in Silodosin group was 19.33 ±2.18. The difference between means was statistically not significant (p=0.63).

IPSS 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 IPSS in both groups were found comparable before initiation of treatment. The differences in means of IPSS were statistically not different in both groups after four weeks and six weeks follow up.

Discussion

Total 120 patients were enrolled for study (60 in each group). The baseline parameters were noted and found more or less statistically similar in both groups including age, duration of LUTS, past medical history, DRE findings, prostate size, and blood investigations except for serum urea level which was significantly higher in silodosin monotherapy group of patients. On the basis of these findings both groups were considered as comparable.

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.

Post voided residual (PVR) urine volume (ml) is a well known parameter for assessment of severity of LUTS. The Mean PVR at zero week in silodosin (S) group was 32.81±14.91 (Baseline value) and after six weeks it was 29.48±8.12 (End point value) with Mean PVR Difference (PVR Diff) of 3.33±10.87. The Mean PVR at zero week in silodosin with tadalafil (S+T) group was 40.94±12.67 (Baseline value) and after six weeks it was 33.64±5.50 (End point value) with Mean PVR Difference (PVR Diff) of 7.30±9.22. The difference between the means of PVR Diff was statistically significant (p=0.05), concluding that both monotherapy as well as combination therapy are helpful to decrease the amount of post voided residual volume but combination therapy was found to have greater impact on lowering the PVR volume. These results were comparable with Hoon Choi et al[11] who conducted a meta-analysis in 2016 of 616 men to find out the clinical

differences in long acting versus short acting PDE5-Is in the combination use with alpha-blockers and alpha-blocker monotherapy. Meta-analysis of the combination medication showed more effectiveness than alpha-blocker in improving symptoms, so Residual urine was decreased more in combination medication than α1- monotherapy with mean difference of -7.09, and the mean residual urine change in long acting versus short acting PDE5-I were -18.83 versus -5.93.

International prostate symptom score (IPSS) is an eight question written screening tool used to diagnose, track the symptoms of, and management of the symptoms of benign prostatic hyperplasia created by American Urological Association. IPSS at zero week in silodosin (S) group was 21.54±2.38 (Baseline value) and at after six weeks it was 19.33±2.18 (End point value) with Mean IPSS Difference (IPSS Diff) of 2.21±0.80. The Mean IPSS at zero week in silodosin with tadalafil (S+T) group was 21.88±2.34 (Baseline value) and at after six weeks it was 19.12±2.12 (End point value) with Mean IPSS Difference (IPSS Diff) of 2.76±0.80. The difference between the means of IPSS Diff was statistically significant (p=0.001), concluding that both monotherapy as well as combination therapy are helpful to improve IPSS but combination therapy found to have greater impact on improving the IPSS score As well as QoL score. These results were comparable with the result of meta-analysis conducted by Hoon Choi et al[11] in which the combination medication showed more effectiveness than alpha-blocker in improving symptoms, so mean IPSS change difference was 1.93 with monotherapy and was 2.12 with combination. Our results are also comparable the results of study by Amado Bechara et al[12],their work was on tamsulosin as monotherapy versus tamsulosin plus tadalafil as combination therapy, in which improvements of IPSS score were 6.7 for monotherapy and 9.2 with the drug combination.

Conclusion

In our study, results showed that the combination of Silodosin and Tadalafil significantly improving (reducing) LUTS when compared with alpha blocker (silodosin) monotherapy.

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