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Original Article

Comparison of Silodosin with Tamsulosin in Patients with Symptomatic Benign Prostatic Hyperplasia: A Prospective, Randomized Double-blinded Crossover Drug Trial

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Abstract

Introduction: The treatment option for benign enlargement of prostate gland (benign prostatic hyperplasia) ranges from watchful waiting, medical therapies to various surgical interventions. While various *in vitro* studies have indicated that silodosin has the greatest selectivity for a1 receptors, there are other studies that mention that silodosin is just non inferior to tamsulosin and is an alternative a1-AR blocker.

Materials and Methods: This is a prospective, randomized double-blinded crossover drug trial over a period of 2½ years. 60 patients were enrolled in our study. 30 patients were assigned silodosin preceding group (SPG) and 30 others were assigned to tamsulosin preceding group (TPG). The total duration of the study was 2 months and 1 week (4 weeks initial treatment with 1 week of washout period and 4 weeks of crossover drug for each patient).

Results: International Prostate Symptom Score (IPSS) was the more objective assessment taken into consideration to assess the magnitude of symptomatology and the responses to treatment. Maximal urinary flow rate significantly improved from baseline with both groups in the first treatment period with SPG producing more significant change 9.1-11.3 (P = 0.0005). With silodosin, the quality of life (QOL) is significantly improved (mean of 3.1-2.4 with P = 0.0005) compared to tamsulosin. No patients had a bothersome adverse drug reaction which persuaded for withdrawal of the drug.

Conclusions: Silodosin has significantly improved both storage and voiding symptoms in both the initial period and in the crossover group. Silodosin has scored over tamsulosin in the subgroup analysis of IPSS in nocturia, urgency, max flow rate, and residual urine volume showing an objective improvement. In addition, it has significantly improved the QOL index suggesting that the drug is both objectively and subjectively effective.

Key words: Nocturia, Prostatomegaly, Silodosin, Tamsulosin, Uroflowmetry

INTRODUCTION

Lower urinary tract symptoms (LUTS) constitutes a complex of symptoms comprising either storage (frequency, urgency, and nocturia) or voiding (strain to void, weak stream, intermittency, incomplete emptying) problems. In aging males, even though benign prostatic hyperplasia (BPH) is the most common cause of LUTS, other conditions such as detrusor dysfunction (advanced aging), polyuria, disorders of sleep, and rarely systemic medical illness not related to prostate or bladder should also be considered.

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Patients with LUTS related to BPH should be on periodic monitoring, and at some point, in their lifetime, they may need some form of intervention which could be either medical, MIST (minimally invasive surgical therapy), or

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surgery. Each option is associated with their own balance of risks, benefits, and levels of uncertainty about the long-term outcome. Although surgery is the definitive management for symptomatic BPH, there are potential complications involved both intra- and post-operatively.

The indications for initiating medical treatment in patients with BPH are bothersome LUTS which could affect the patients quality of life (QOL) negatively. The drugs definitely improve the QOL by relieving of symptoms.[1] The features favoring medical treatment are a symptomatic improvement, with less serious and reversible adverse effects when compared to surgery with increased morbidity and sometimes redosurgery may be needed.

The commonly used drugs in the management of BPH are α-1 adrenergic blockers and androgen antagonist (dutasteride and finasteride). The non-selective and short acting α-blockers are not used now due to their requirement of multiple doses in a day and development of tolerance. The subtype selective drugs tamsulosin (1000:1, α1-A:α1-B/α1-D) and silodosin (162:1, α1-A:α1-B) are used now.[2] There are only limited direct comparisons between the two drugs to compare the efficacy. *In vitro* study have indicated Silodosin has the greatest selectivity for a1-AR among all clinically used a-blockers;[3] however, there are lot of controversial studies which says silodosin is just non-inferior to tamsulosin and is an alternative a1-AR blocker.

BPH is a disease that impairs the patient's QOL. There are a less number of guidelines suggesting the clinical profile of the drug. Our study will help to evaluate the clinical profile of the drug in patient perspective to discover which medication they want to continue after completion of the study.

MATERIALS AND METHODS

The study was conducted from August 2013 to January 2016. This is a "prospective randomized double-blinded crossover drug trial with washout period of 1 week." Approval was obtained from the Institutional Ethics Committee, and the study is registered by the Institutional Ethics Committee.

Inclusion and Exclusion Criteria

Ambulatory BPH patients were recruited on the basis of the clinical evaluation with the following inclusion criteria Age: Patients who are aged 50 years and above, the International Prostate Symptom Score (IPSS): 8 and above, QOL index of IPSS: 3 and more and a maximum flow rate of less than 10 ml/s. Patients with neurogenic bladder, bladder neck contracture, stricture urethra, bladder calculi, active urinary tract infection, prostate cancer, long-standing diabetes mellitus, concomitant drug usage such as anticholinergic agents, anti-depressants, anti-anxiety agents, large intravesical extension >2 cm, and large post-void residual urine >100 ml were excluded from the study.

Sample Size

The target sample size was 25 evaluable patients in each group. This was calculated to detect a difference of 4 in total IPSS between groups with 80% power and 0.05 probability of type 1 error, assuming a standard deviation of 5 in total symptom score. Allowing for a 50% dropout rate, this translated to a recruitment target of 60 subjects per group or 120 subjects overall. However, due to various clinical and patient-related reasons, 37 patients were enrolled in each group or over all of 74 subjects. Of them, 11 of them did not come for proper follow-up, and 3 of them withdrew from the study due to personal reasons and are removed from the study. Finally, total of 60 subjects were randomized in a double-blinded 1:1 ratio. Randomization is done using a computer-generated random table designed for 60 patients with 1:1 ratio making 30 patients in each group. Duration of the study is 2 months and one week (4 weeks initial treatment +1 week of washout period +4 weeks of crossover drug for each patient).

All the patients participated in the study were properly explained about the trial. A copy of the participant/patient information sheet typed both in English and Tamil for respective patients is given to the participant for his and our record. They were made to sign the form after understanding the possible risk and benefits involved in the study. Every patient is provided with the primary investigators phone number and was given full rights to contact the primary investigator and to withdraw from the study at any time.

Randomization

The following drugs were used: Capsule tamsulosin 0.4 mg and capsule silodosin 8 mg, respectively. The capsules were removed from their commercial blister strip packaging and repackaged in an empty unicolor coded capsule with sterile precautions. It is kept in air-tight, screw cap containers, and suitably labeled and coded as A group and B group trial medication. To ensure double blinding, repackaging was done with the help of urology clinical instructor and the group identity (Silodosin preceding group [SPG], tamsulosin preceding group [TPG]) is only known to the urology clinical instructor who is involved in the study. Capsule identity was revealed neither to the patients who received the total medication in four installments nor to the primary investigator. Allocation concealment was achieved using the serially numbered, random table with queue basis. The randomization list and the code breaking authority

were retained by a urology clinical instructor not directly interacting with the subjects. Patients will receive either tamsulosin 0.4 mg controlled release or silodosin 8 mg once daily after dinner for 4 weeks followed by 1 week of washout period followed by the crossover drug for 4 weeks. Parameters such as IPSS total score, QOL Score, maximal urinary flow rate (ml/s) residual urine volume (ml) were recorded at the baseline, after 4 weeks and after 8 weeks.

Compliance

By measuring the number of capsules returned at the next study visit, It was deemed to be excellent if <10% of scheduled doses were missed, good if 10- 20% were missed, and fair if 20-30% were missed and poor for any situation worse than fair.

Statistical Analysis

All the data's were compared statistically. The comparison was performed within the groups and between the groups. A baseline value 4th week, 8th week, and 4-8th week was compared. Cure, total responders, and non-responders were analyzed in both the groups. The collected data were analyzed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean and standard deviation (SD) were used for continuous variables. To find the significant difference between the bivariate samples in independent groups, the unpaired sample *t*-test was used. For the multivariate analysis, the one-way ANOVA with Tukey's *post-hoc* test was used and for repeated measures the repeated measures of ANOVA with adjustment for multiple comparisons to control the Type I error, the Bonferroni test was used. To find the significance in categorical data, Chi-square test was used. In all the above statistical tools, the $P = 0.05$ is considered as statistically significant level.

RESULTS

A total of 60 patients were enrolled in our study, and of them, 30 patients were assigned to silodosin as SPG and 30 patients were assigned to tamsulosin as TPG. Baseline parameters of age, prostate volume, total IPSS score, and its subscores, QOL score; Table 1 describes the comparison of the maximal urinary flow rate and residual urinary volume of both the groups recorded at day zero. The results are not significant between both the groups. Following 4 weeks of the drug intake, both the groups were compared again. The response evaluation at 4th week and the comparison from baseline to 4th week of the drug administration are summarized in Table 2. In SPG, the total number of cured patients (IPSS score <8) at initial drug administration were 2 (6.7%; $N = 30$), total number of 28 patients out of 30 (n) responded (reduction of IPSS to less than 4 points) to initial drug administration which is 93.3% of total response. In TPG, total number of responders to the initial treatment with tamsulosin is 21 (70%; $N = 30$) and there were 9 (30%; $N = 30$) non-responders (IPSS score not reduced to less the 4 points). There are no cure rates observed in TPG. Figure 1 illustrates 4th-week comparison of both the groups from baseline.

IPSS score was the more objective assessment taken into consideration to assess the magnitude of symptomatology and the responses to treatment. The changes in the objective and subjective parameters in each group are illustrated in Table 3. The total score was significantly improved from the baseline after administration of the drug in both groups. Table 4 illustrates the overall mean reduction of IPSS in SPG is 8.73 (SD = 3.4) compared to 5.93 (SD = 3.5) IPSS reduction in the TPG. Figure 2 depicts the comparison from the baseline, of both groups at the end of 4 weeks of treatment.

Sub Group Symptoms

Comparison of initial treatment period in TPG shows significant changes in both voiding and storage symptoms,

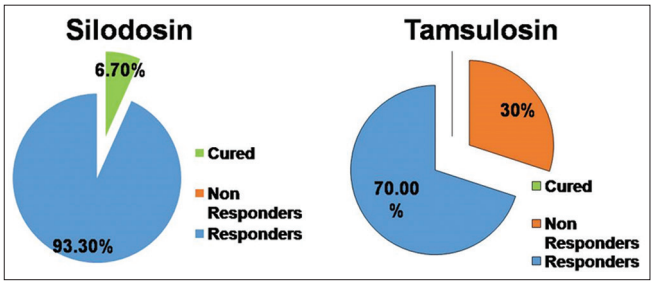

Figure 1: Overall comparison of both the groups from baseline at 4 weeks of drug administration

Table 1: Baseline parameters of all patients in both groups

Parameters	SPG	*N*	TPG	*N*	*P* value
Age (years)	60.5 (SD 6.4)	30	62.8 (SD 4.4)	30	NS
Prostate volume (ml)	39.9 (SD 8.5)	30	37.8 (SD 8.9)	30	NS
IPSS total score	20.6 (SD 2.6)	30	21.6 (SD 3.4)	30	NS
QOL score	3.9 (SD 1.0)	30	3.8 (SD 1.1)	30	NS
Maximal urinary flow rate (ml/s)	9.1 (SD 0.8)	30	9.1 (SD 0.6)	30	NS
Residual urine volume (ml)	89.2 (SD8.8)	30	90.7 (SD 7.8)	30	NS

SD: Standard deviation, SPG: Silodosin preceding group, TPG: Tamsulosin preceding group, QOL: Quality of life, IPSS: International Prostate Symptom Score, NS: Not significant

but of the subgroup parameters-incomplete emptying, nocturia does not show significant improvement. Subgroup analysis of SPG in initial treatment period shows significant changes in both storage and voiding symptoms and in all subgroup parameters (Figure 3).

Maximal Urinary Flow Rate

Maximal urinary flow rate was significantly improved from baseline with both groups in the first treatment period with SPG producing more significant change 9.1-11.3 ($P = 0.0005$) compared to 9.1-10.7 in TPG (0.0090) (Table 3).

Residual Urine Volume

Both the groups showed significant reduction in residual urine volume. The reduction in SPG was 44.3 ml (from 89.2-44.9), with $P = 0.0005$ and in TPG was 30.8 ml (from 90.7 to 59.9), with $P = 0.0005$. Figure 4 illustrates the change in residual urine at 4th week of drug administration.

Response Evaluation at 8th Week at the End of Crossover Period

IPSS

In TPG, silodosin produced a significant further reduction in the IPSS from 15.7 to 12.9 (difference of 2.8, mean with SD 2.4) which tamsulosin has not improved in the initial period of treatment. In SPG, tamsulosin also shows reduction in overall IPSS from 11.8 to 10.3 (difference of 1.5, mean with SD 2.59). The difference in the overall reduction of IPSS Score was high with crossover to SPG (difference −1.30) compared to TPG which is statistically significant ($P = 0.053$) with −2.616 versus 0.016 at 95% confidence interval goes in favor of silodosin (Table 5).

Sub Score Analysis at Cross-over Period

In 4th versus 8th week, silodosin seems to show improvement over tamsulosin in voiding symptoms (mean 6.5-5.7 with $P = 0.01$) and storage symptoms (mean 6.0-1.6 with

Table 2: Comparison from baseline to 4th week of the drug administration

IPSS response	Groups		Total
	SPG	TPG	
Cured			
Count	2	0	2
% within groups	6.7	0.0	3.3
Non-responders			
Count	0	9	9
% within groups	0.0	30.0	15.0
Responders			
Count	28	21	49
% within groups	93.3	70.0	81.7
Total			
Count	30	30	60
% within groups	100.0	100.0	100.0

SPG: Silodosin preceding group, TPG: Tamsulosin preceding group, IPSS: International Prostate Symptom Score

Table 3: Changes observed in the objective and subjective parameters in each group

Parameters studies	Groups	Mean±SD			0 versus 4th week	0 versus 8th week	4th versus 8th week
		Baseline	4th week	8th week			
IPSS score	SPG	20.6±2.6	11.8±2.8	10.3±1.9	0.0005	0.0005	0.01
	TPG	21.6±3.4	15.7±2.1	12.9±2.6	0.0005	0.0005	0.0005
Voiding symptoms	SPG	10.1±2.1	5.6±2.3	4.8±1.8	0.0005	0.0005	0.02
	TPG	10.7±2.4	6.5±1.6	5.7±1.6	0.0005	0.0005	0.01
Storage symptoms	SPG	6.6±1.7	3.8±1.3	3.7±1.4	0.0005	0.0005	NS
	TPG	7.5±1.0	6.0±1.3	4.8±1.6	0.0005	0.0005	0.00
Incomplete emptying	SPG	2.4±1.2	1.3±0.6	1.2±0.6	0.0005	NS	NS
	TPG	2.6±1.3	1.7±0.7	1.5±0.6	NS	0.04	NS
Frequency	SPG	2.3±1.1	1.7±0.6	1.6±0.6	0.0100	0.0010	NS
	TPG	2.8±1.2	1.9±0.6	1.6±0.7	0.0040	0.0005	NS
Intermittency	SPG	2.2±1.2	1.3±0.7	1.2±0.6	0.0005	0.0005	NS
	TPG	2.5±1.4	1.8±0.8	1.6±0.9	0.0080	0.0120	NS
Urgency	SPG	1.9±0.9	0.9±0.6	0.9±0.6	0.0005	0.0005	NS
	TPG	2.2±0.9	1.5±0.9	1.2±0.8	0.0500	0.0010	0.05
Weak stream	SPG	3.3±1.4	2.2±1.4	2.0±1.4	0.0030	0.0010	NS
	TPG	3.4±1.2	2.0±0.9	1.8±0.8	0.0005	0.0005	NS
Straining	SPG	2.4±1.0	0.7±1.0	0.4±0.6	0.0005	0.0005	NS
	TPG	2.3±1.1	1.0±0.9	0.9±0.8	0.0005	0.0005	NS
Nocturia	SPG	2.2±1.4	1.2±1.0	1.2±0.9	0.0050	NS	NS
	TPG	2.4±1.4	2.1±0.7	1.9±0.7	NS	0.0040	0.04
QOL score	SPG	3.9±1.0	2.5±1.0	2.4±0.9	0.0005	0.0005	NS
	TPG	3.8±1.1	3.1±0.7	2.4±0.7	0.0090	0.0005	0.0005
Max.flow rate	SPG	9.1±0.8	11.3±2.8	10.2±2.3	0.0005	NS	NS
	TPG	9.1±0.6	10.7±2.2	11.4±2.2	0.0090	0.0005	0.0005
Residual urine volume	SPG	89.2±8.8	44.9±16.7	39.2±14.6	0.0005	0.0005	0.00
	TPG	90.7±7.8	59.9±14.9	42.8±14.3	0.0005	0.0005	0.0005

SD: Standard deviation, SPG: Silodosin preceding group, TPG: Tamsulosin preceding group, QOL: Quality of life, IPSS: International Prostate Symptom Score, NS: Not significant

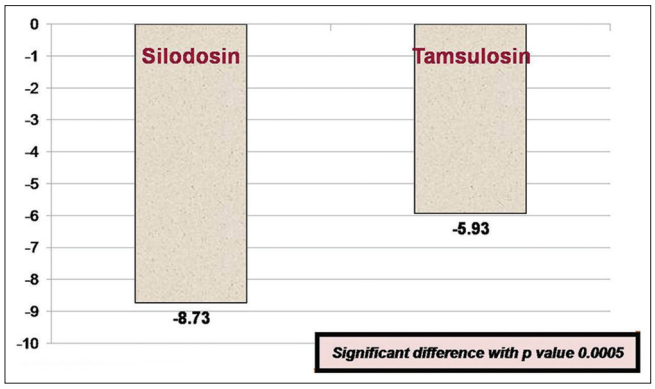

Figure 2: Comparison of International Prostate Symptom Score of both groups from base line at 4 weeks

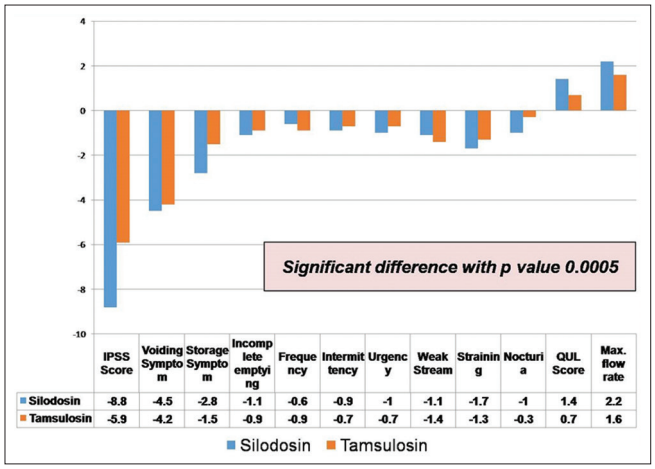

Figure 3: Change from baseline of International Prostate Symptom Score during the first treatment period

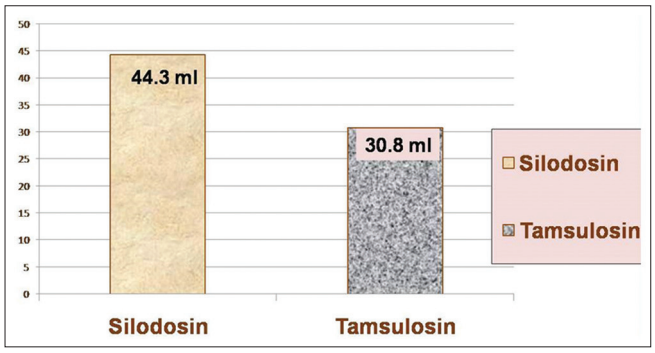

Figure 4: Changes in residual urine levels at 4 weeks

P = 0.001). The analysis shows a further improvement with sub-scores of silodosin in urgency (mean of 1.5-1.2 with P value of 0.05) and nocturia (2.1-1.9 with P value of 0.04). The changes from 4th week of international prostate symptom subscore to cross over treatment are depicted in Figure 5.

Maximal Urinary Flow Rate

It was showing significant improvement from baseline with both silodosin and tamsulosin in the first treatment period

Table 4: The overall mean reduction of IPSS in SPG is 8.73 (SD 3.4) compared to 5.93 (SD 3.5) IPSS reduction in the TPG

IPSS reduction	Mean±SD	*P* value	Mean difference	95% CI	
Diff. 4th versus baseline					
SPG	8.73±3.473	0.0005	2.800	0.979	4.621
TPG	5.93±3.571				

SPG: Silodosin preceding group, TPG: Tamsulosin preceding group, IPSS: International Prostate Symptom Score, CI: Confidence interval, SD: Standard deviation

Table 5: Change in IPSS at the end of 4th and crossover period

IPSS difference	Mean±SD	*P* value	Mean difference	95% CI	
Diff. 04					
SPG	8.73±3.473	0.0005	2.800	0.979	4.621
TPG	5.93±3.571				
Diff. at crossover					
SPG	1.50±2.596	0.053	−1.300	−2.616	0.016
TPG	2.80±2.497				

SPG: Silodosin preceding group, TPG: Tamsulosin preceding group, IPSS: International Prostate Symptom Score, CI: Confidence interval

with silodosin producing more significant change 9.1-11.3 compared to 9.1-10.7 in tamsulosin. However, similarly, this result was also evident in the crossover period with further improvement in the maximal urinary flow rate in silodosin group, TPG at 8th week which is 10.7-11.4 with P = 00005, whereas in SPG, tamsulosin does not produce any improvement in flow rate 11.3-10.2 (−1.1).

Residual Urine Volume

The change in the residual urine volume in SPG is 44.9 with SD of 16.7 compared to baseline of 89.2 with SD of 8.8 and with TPG it is 59.9 with SD of 14.9 compared to baseline of 90.7 (SD 7.8) in the initial treatment period. Both the drugs produced a significant response in the initial treatment period, but silodosin showed a statistical significant in the crossover group with a change of 42.8 (SD 14.3) from 59.9 (P = 0.0005). Figure 6 illustrates the changes in residual urine at the end of crossover group.

QOL

With silodosin, the QOL is significantly improved (mean of 3.9-2.5 with P = 0.0005) compared to tamsulosin (mean of 3.8-3.1 with P = 0.0090) in the initial treatment period, which is considered to be statistically significant. However, tamsulosin did not show any significant difference in the crossover group.

Adverse Drug Reaction

The adverse drug reactions were noted in 22 patients of 60 in SPG and 25 patients of 60 in TPG. Table 6 illustrates the list of all adverse reactions observed during the study.

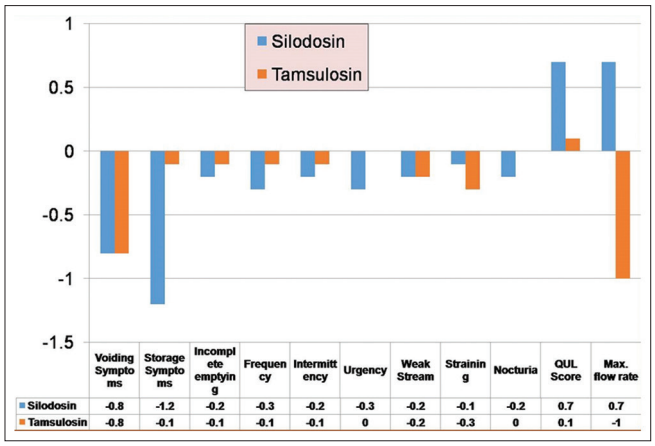

Figure 5: Change from 4th week of International Prostate Symptom Score subscore to cross over treatment

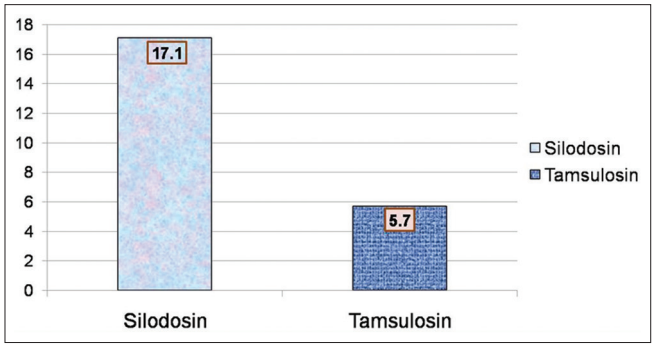

Figure 6: Changes in residual urine levels at the end of crossover group

Frequently observed adverse drug reaction to SPG was ejaculatory disorder in 17 of 60 patients. In TPG, adverse drug reaction was noted in 25 patients of 60; the most pronounced reaction was dizziness 16 of 60 patients. All of these adverse drug reactions were mild and resolved or were relieved in all patients with continued administration or dose reduction or withdrawal. No patients had a bothersome adverse drug reaction which persuaded for withdrawal of the drug.

DISCUSSION

The optimal initial treatment for patients with moderate or severe LUTS caused by BPH involves the use of a-blockers which acts mainly on dynamic component of obstruction (smooth muscle tone).[4] In men with large glands, 5a-reductase inhibitors such as finasteride and dutasteride may be beneficial that acts on the static component of obstruction.[4]

Various studies have confirmed that BPH is a progressive disease causing an average annual increase of the IPSS by 0.18 points, 2% annual reduction of the maximum flow rate (Q-max), and a median increase of prostate size by

Table 6: Adverse drug reaction: Adverse drug reaction was noted in 22 patients of 60 in SPG and 25 patients of 30 in TPG

Effects	SPG	TPG
Ejaculatory disorder	17	5
Dizziness	2	16
Nasal congestion	1	0
Diarrhea	2	0
Arthralgia	0	0
Orthostatic hypotension	0	4
Total	22/60	25/60

SPG: Silodosin preceding group, TPG: Tamsulosin preceding group

1.9% annually.[5] The uroselective a-blockers tamsulosin and silodosin are the preferred drugs for LUTS related to BPH due to their preferential action over α-1A receptor that is predominantly present in prostate and bladder base. Moreover, these drugs cause no significant change in blood pressure or heart rate at doses which are used for treating LUTS.[6]

There are very few head to head comparison studies, comparing the efficacy of these two a-blockers. A thorough PubMed search was carried out with keywords such as tamsulosin, silodosin, and their comparison in BPH that revealed various studies claiming mixed results. Yamanishi *et al.*, in his study on 194 male patients, compared the efficacy of silodosin and tamsulosin after 12 months of drug administration and concluded that both silodosin and tamsulosin improved LUTS and urinary flow rate significantly in patients with BPH.[7] Their efficacies were not significantly different. A randomized crossover study Watanabe *et al.* comparing patient preference for tamsulosin and silodosin in 84 (n = 42 per group) Japanese patients over 4 weeks for each drug concluded that patients preferred tamsulosin over silodosin.[8] A prospective randomized crossover comparative study of 46 patients by Yokahama *et al.* with 23 patients in each group of tamsulosin and silodosin found that both drugs have similar efficacy.[9]

A randomized crossover comparison of the short-term efficacy and safety of half dose of silodosin for 4 weeks and full dose of tamsulosin 4 weeks was done by Takeshita *et al.* in 34 Japanese men over 50 years and an IPSS of more than 8. He concluded that both half doses silodosin and tamsulosin are equally efficacious.[10] Since various studies had produced divergent results, we compared the efficacy and safety of 0.4 mg of tamsulosin and 8 mg silodosin. Our results have clearly shown that silodosin is safe and more efficacious in comparison to tamsulosin.

Primary Outcome Measure – IPSS

Various studies have compared the IPSS after the use of silodosin and tamsulosin and conflicting reports have

been arrived at. Multicentric randomized controlled trial (RCT) conducted by Chapple *et al.* found that responder rates according to total IPSS were significantly higher with silodosin (66.8%) when compared to tamsulosin (65.4%) than with placebo (50.8%) and concluded that the overall efficacy of silodosin is not inferior to tamsulosin.[11]

The trial conducted by Yu *et al.* found that, out of 170 (81.3%) study completed patients, 86.2% in the silodosin group versus 81.9% in the tamsulosin group achieved a ≥25% decrease in IPSS ($P = 0.53$). The mean difference in IPSS change from baseline was −0.60 (95% confidence interval −2.15 to −0.95) (silodosin minus tamsulosin) showed silodosin was non-inferior to tamsulosin.[12]

A phase III randomized, placebo-controlled, double-blind study Kawabe *et al.* in 457 patients who were randomized (silodosin 176, tamsulosin 192 and placebo 89) to receive silodosin 4 mg twice daily, tamsulosin 0.2 mg once daily, or placebo, for 12 weeks showed changes in the total IPSS from the baseline in the silodosin, tamsulosin, and placebo groups as −8.3, −6.8, and −5.3, respectively. A decrease in IPSS on patients with silodosin group started from 1 week compared with the placebo.[13] Marks *et al.* from a pooled analysis of two RCTs in the United States concluded the use of silodosin helps in rapid improvement in LUTS when compared to placebo and at 12-week IPSS, and subscores difference was increased.[14]

A randomized controlled trial done by Pande *et al.* with the evaluation of silodosin in comparison to tamsulosin in 53 subjects reported that the final IPSS scores at 12 weeks were significantly less than the baseline for both drugs and scores remained comparable concluding both are equally efficacious.[15] Another study comparing short-term effects of crossover treatment with silodosin and tamsulosin by Miyakita *et al.* showed that even though in the first-treatment period both drugs significantly improved the IPSS score, the improvement by silodosin was significantly superior to that by tamsulosin.[16]

In our study, out of 30 patients in SPG following 4 weeks of the drug intake, number of cured patients (IPSS score <8) were 2 (6.7%; $N = 30$)and 28 patients were responded (reduction of IPSS to <4 points) which is 93.3% of total response. In TPG, number of responders with tamsulosin were 21 (70%; $N = 30$) and 9 were (30%; $N = 30$) non-responders (IPSS score not reduced to less the 4 points). There are no cure rates observed in TPG.

Even though the total score significantly improved from the baseline after administration of the drug in both the groups. the overall mean reduction of IPSS in SPG was 8.73 compared to 5.93 in the TPG. At the end of crossover period in TPG, silodosin produced a significant further reduction in the IPSS from 15.7 to 12.9, whereas in SPG tamsulosin also shows reduction in overall IPSS from 11.8 to 10.3. The difference in the overall reduction of IPSS at both 4th week and at crossover period suggest silodosin to be more efficacious.

Secondary Outcome Measures

Sub group symptoms

Crossover treatment with silodosin and tamsulosin by Miyakita *et al.*[16] revealed that silodosin caused a significant improvement in nocturia and straining to void in the first and crossover period. In our study, at the end of 4th week, even though tamsulosin shows significant improvement in both voiding and storage symptoms, incomplete emptying, nocturia does not show any improvement, whereas silodosin shows significant changes in both storage and voiding symptoms and in all subgroup parameters also. At the end of crossover period, silodosin showed improvement in urgency and nocturia over tamsulosin, thus concluding that silodosin showed a better improvement in bothersome storage LUTS.

The reasons that α-1A-receptor blockers improve both storage and voiding symptoms may be that bladder outlet obstruction is relieved, and this reduces detrusor overactivity (caused by obstruction). A reduction in the prostatic urethral tension may also cause reduction in detrusor overactivity.[17] Another possible mechanism of bladder outlet obstruction causing detrusor overactivity is that ischemia and reperfusion caused by obstruction leading to overactive bladder.[18] In the small arteries of the bladder, there is an abundance of α-1A-AR and α-1A-AR blockers may increase blood flow to the bladder causing reduced detrusor overactivity.[19,20]

Maximal urinary flow rate (Qmax)

Chapple *et al.* observed an increase in Qmax in all groups, where the adjusted mean change was 3.77 mL/s for silodosin, 3.53 mL/s for tamsulosin, and 2.93 mL/s for placebo. He concluded that the changes were not statistically significant between both drugs.[11] Yu *et al.* also reported that the changes in mean Qmax were comparable between both drugs and were not statistically different.[12] In the crossover study by Miyakita *et al.* even though Qmax increased in both groups initially after 4 weeks, at the end of crossover no significant improvement occurred in both groups.[16] In our study, Qmax showed a significant improvement in both groups with silodosin producing more significant change 9.1-11.3 ($P = 0.0005$).

Residual urine volume

Miyakita *et al.,* at the end of 4th week of the study, showed a reduction in residual urine noted only with silodosin, but

not with tamsulosin at 4th week or to both after crossover trial.[16] In our study, at the end of 4th week, both the groups showed a significant reduction in residual urine volume. However, silodosin showed a statistically significant improvement in the crossover group with a change of 42.8 ml from 59.9 ml ($P = 0.0005$) compared to tamsulosin of 39.2 from 44.9 ml.

QOL

The QOL as per Pande *et al.* was comparable between silodosin and tamsulosin groups at 12-week.[15] Miyakita *et al.* concluded that QOL score significantly improved in both at initial and crossover the period with silodosin.[16] Kawabe *et al.* also reported a significant improvement of the QOL score in patients with silodosin in relative to placebo.[13] In our study with silodosin, the QOL is significantly improved (mean of 3.9-2.5 with $P = 0.0005$) compared to tamsulosin in the initial treatment period and also at the crossover period. However, tamsulosin did not show any significant difference in the crossover group.

Adverse drug reaction

The most common adverse effects according to Pande *et al.* was retrograde ejaculation seen in 3 out of 26 subjects with silodosin. Dizziness or postural hypotension was found in 3 subjects out of 27 in patients who received tamsulosin.[15] In a phase III double-blind study, 28% of the patients on silodosin at 8 mg once-daily developed ejaculatory disorders (28.1% for silodosin versus 0.9% for placebo), followed by dizziness, diarrhea, orthostatic hypotension headache, nasopharyngitis, and nasal congestion in decreasing order of frequency.[14] About 2.8% of patients on silodosin discontinued it because of retrograde ejaculation. The reason for ejaculatory disorders could be attributed to either retrograde ejaculation due to a-receptor blockade on bladder neck contraction, or due to inhibition of the contraction of vas and seminal vesicle.[21] According to Kawabe *et al.* the rates of adverse events in the silodosin, tamsulosin, and placebo groups were 88.6%, 82.3%, and 71.6%, respectively, and the most common event in the silodosin group was abnormal ejaculation when compared to tamsulosin group (22.3% vs. 1.6%).[13] In our study, adverse drug reactions were noted in 22 patients of 60 in SPG and 25 patients of 60 in TPG. The frequently observed adverse drug reaction to SPG was ejaculatory disorder in 17 of 60 patients. In TPG, adverse drug reaction was noted in 25 out of 60, and the most pronounced reaction was dizziness in 16 patients. All the adverse drug reactions excluding ejaculatory disorder were minimal and were relieved with continued administration or dose reduction or after withdrawal of the drug. No patients had a bothersome adverse drug reaction which persuaded for withdrawal of the drug.

CONCLUSIONS

In this study, silodosin has significantly improved both storage and voiding symptoms in both the initial period and in the crossover group. Silodosin has scored over tamsulosin in the sub group analysis of IPSS in nocturia, urgency, max flow rate, and residual urine volume showing an objective improvement. In addition, it has significantly improved the QOL index suggesting that the drug is both objectively and subjectively effective. The incidence of ejaculatory disorder was higher in the silodosin than in the tamsulosin. All other adverse drug reactions were mild seems to be not much bothersome. These reactions were reversible when the drug is discontinued. Considering all the above, it is clearly evident that silodosin a highly selective α1-A-adrenoceptor antagonist exhibited excellent efficacy in improving subjective symptoms regardless of period of administration, and appears to improve QOL in patients with BPH/LUTS.

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