BANGLADESH JOURNAL OF
UROLOGY
Bangladesh J. Urol. 2021; 24(2): 205-213
www.banglajol.info/index.php/BJU
DOI: https://doi.org/10.3329/bju.v24i2.59496

Original Article
ISSN : 2304 - 8514 (Print)
ISSN : 2304 - 8522 (Online)

A Comparison of Safety and Efficacy between Silodosin Monotherapy Versus Silodosin with Tadalafil add on Therapy in Patients with Benign Prostatic Hyperplasia.

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Received: 01 - 08 - 2021
Accepted: 21 - 12 - 2021
Conflicts of interest: None

Abstract

Background: *For relieving symptoms of LUTS due to BPH treatment modalities are watchful waiting, medical treatment and surgery. Among medical treatment, options are alpha 1 adrenoreceptor blockers, 5 alpha reductase inhibitors and recently introduced phospodiesterase 5 inhibitors or combination therapy.*

Objective*: To compare the safety and efficacy of silodosin versus silodosin and tadalafil for treating patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia.*

Materials and Methods: *This prospective observational study was conducted in the Department of Urology, BSMMU, Dhaka from April 2020 to March 2021. A total of 66 patients with LUTS due to BPH were selected by purposive sampling on the basis of selection criteria from OPD of Urology, BSMMU. They were randomly divided into two groups: according to odd or even hospital number and label as A group (odd no) and B group (even no). Group-A were provided with silodosin 8.0 mg daily and group-B were provided with silodosin 8.0 mg and tadalafil 5.0 mg daily (B group). Two patients from each group were excluded due to adverse effect and one patients from each group was lost to follow-up. Final analysis was done on sixty patients (30 from each group). The patients were assessed by IPSS, Qmax and PVR. The results were expressed as frequency & percentage (categorical data) and mean ± SD (numerical data). Unpaired t-tests and paired t tests were performed as applicable using SPSS 22.0 and p <0.05 was considered as the level of significance.*

Results: *Out of sixty six patients, sixty patients completed the study. Two patients from group A was suffering from hypotension and headache and two patients from group B was suffering from ejaculatory dysfunction and dizziness, one patient from each group was lost after 1st follow up, so they were excluded from study. Maximum study subjects were within 51 to 70 years of age in both groups. Mean age of the study subjects was 57.13 ± 9.36 years in Group-A and 59.33 ± 7.09 years in Group-B. Mean prostate volume of the study subjects was 37.93 ± 13.19 ml in Group-A and 35.50 ± 10.57 ml in Group-B. IPSS was reduced to 21.90±3.68 after 6 weeks and 18.90 ± 3.79 after 12 weeks from 25.10 ±*

Keywords: Silodosin, Tadalafil, BPH

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3.96 prior to treatment in Group-A. Similarly, in Group-B, IPSS was reduced from 19.67 ± 3.45 after 6 weeks and 16.37 ± 2.03 after 12 weeks from 23.03 ± 4.16 prior to treatment. PVR decreased to 58.00 ± 20.41 after 6 weeks and 42.10 ± 17.40 after 12 weeks from 74.15 ± 26.40 prior to treatment in Group-A. Similarly, PVR in Group-B reduced to 52.70 ± 12.51 after 6 weeks and 33.57 ± 8.97 after 12 weeks from 66.17 ± 15.50 before treatment. After 6 weeks, Qmax increased to 15.67 ± 2.11 and at 12 weeks17.73 ± 2.66 from 13.39 ± 1.83 before treatment in Group-A. Similarly, after 6 weeks, Qmax in Group-B increased to 16.74 ± 1.14 and at 12 weeks18.94±1.31 from 14.17±1.28 before treatment.

Conclusion: *Improvements in both silodosin (alpha blocker) group and silodosin in combination with tadalafil (PDE 5 inhibitor) group were found to be effective, safe and satisfactory in treating patients with symptomatic BPH. Even though combination group showed better efficacy than silodosin monotherapy group but as per improvement rate it was not statistically significant.*

Introduction:

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) is a progressive disease (Roehrborn, C.G et al., 2010) Incidence of BPH is increases with age from middle aged man (Yoshida, M et al., 2017). LUTS due to BPH includes obstructive symptoms (hesitancy, poor stream, sense of incomplete emptying, straining) and irritative symptoms (frequency, urgency, nocturia) (Chen, P.C et al., 2020). LUTS are scored by international prostate symptoms score (IPSS).

IPSS is most important tool to evaluate BPH patients before initiation of treatment and monitor treatment response (Homma, Y et al., 2003). BPH patient is diagnosed on the basis of history, digital rectal examination. IPSS scores, ultra sonogram of KUB, prostate with PVR and uroflowmetry. Ultra sonogram is used to detect prostate size and amount of urine left in the urinary bladder after voiding (PVR). Prostate size below 20 ml, and PVR below 50 ml is considered as normal (Yoshida, M et al., 2017). Uroflowmetry is a test method for observing urination. Maximum flow of urine (Qmax) is measured by uroflowmetry. Man with Qmax more than 15 ml/sec is considered as normal (Verhamme, K.M.C et al., 2002). Treatment options for BPH include watchful waiting, medical treatment, and surgery (Yokoyama, o et al., 2013).

Medical therapy for symptomatic BPH currently consist of alpha 1 blockers, 5 alpha reductase inhibitors, phosphodiesterase 5 inhibitors or combination therapy. For optimal management of symptomatic BPH patient medications should be chosen based on age, disease progression, need for long-term management, and other clinical parameters (Oelke, M et al., 2013). In 2011, the Japanese clinical guidelines for LUTS due to BPH proposed alpha 1 adrenoreceptor antagonists (á 1 blockers) as first-line drug therapy for LUTS due to BPH (The Japanese Urological Association, 2011). Tadalafil is a Phosphodiesterase type 5 inhibitor (PDE 5 inhibitors) was approved in Japan for treating LUTS due to BPH in 2014, which is routinely used for erectile dysfunction. The inhibition of PDE-5 leads to accumulation of cyclic guanosine monophosphate (cGMP) in the smooth muscles of the prostate and urethra resulting relaxation, and alleviation of the symptoms of LUTS due to BPH. Several placebo control studies show that men with BPH have demonstrated improvements in IPSS with tadalafil (Yoshida, M et al., 2017). Tadalafil is contraindicated for unstable angina, recent myocardial infarction, recent strokes, poorly controlled blood pressure, hepatic, renal insufficiency and ischemic optic neuropathy. It causes headache, dizziness (Brock, G et al., 2013).

There are several studies compared the effects of the alpha 1 blocker (tamsulosin) and tamsulosin with tadalafil in the treatment of BPH (Oelke, M et al., 2014). Silodosin is the most efficacious alpha 1 blocker with rapid onset of action. It significantly improves IPSS, maximum flow rate and quality of life than other alpha 1 blocker (Lee, J.Y et al., 2012). But a very few studies in the literature that compared the newer molecule silodosin (alpha 1 blocker) and silodosin with tadalafil (phosphodiesterase 5 inhibitor) in the treatment of BPH and also in Bangladesh there is no such study.

So this study was designed to compare the safety and efficacy of silodosin monotherapy and silodosin with tadalafil add on therapy in patient with symptomatic BPH.

Materials and methods

This prospective observational study was carried out from April 2020 to March 2021. All the patients presented in outpatient department of Urology, BSMMU with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) were evaluated by taking history, co-morbid conditions, drug history. LUTS severity was scored by international prostate symptom score (IPSS) questionnaire and documented by patient himself. IPSS questionnaire is a self-rated questionnaire, which is originally presented in English language. English version translated into Bangla language which is almost same as original English version. All the patients underwent general physical and genital examination and digital rectal examination (DRE). Prostate size and PVR was measured by ultra-sonogram of KUB, prostate and PVR in the Radiology and Imaging Department of BSMMU by a fixed Radiologist who also performed follow up USG. Uroflowmetry was done to detect Qmax, in the Urology Department, BSMMU. Serum PSA, serum creatinine, urine R/M/E with C/S was also done. Patients with BPH and raised PSA, urinary tract infection, hematuria were excluded from the study. Among these patients who was diagnosed to have LUTS due to BPH and met all the inclusion and exclusion criteria were invited to participate in the research. Written inform consent was taken from sixty-six patients who agreed to participate in the study.

They were randomly divided by odd and even hospital number. Odd number was named as group A and even number as group B. Total thirty-three patients from group A were provided with silodosin 8 mg once daily and thirty-three patients from group-B were provided with silodosin 8 mg and tadalafil 5 mg once daily. Weekly reminder was given to patients with message or phone call, so that they would not miss any medicines or follow up schedule.

Patient safety measures was ensured by regular follow up, performing urine test, serum creatinine, ECG or symptomatic investigations. Pharmacological efficacy was ensured by NNT (number needed to treatment to achieve one additional study end point). It is calculated by absolute risk reduction = control event rate – experiment event. NNH (No need to harm when an experimental treatment is detrimental). All the patients was re-assessed after 6 weeks and 12 weeks with adverse events like headache, dizziness, vertigo, hypotension and ejaculatory dysfunction.

They were evaluated mean changes from base line to 6 and 12 weeks by IPSS, PVR and Qmax. All the data were collected and recorded in a data collection sheet. Results were expressed as frequency and percentage (categorical data) and mean± SD (numerical data). Student t test and Chi square test were performed as applicable using SPSS for windows version 22.0 and $p < 0.05$ will be considered as the level of significance.

Results

This prospective observational study was conducted from April 2020 to March 2021. Sixty-six patients with lower urinary tract symptoms due to Benign prostatic hyperplasia (BPH) who visited Out Patient Department of Urology, Bangabandhu Sheikh Mujib Medical University, Dhaka were included in this study to compare the safety and efficacy of silodosin (á1-adrenoceptor blocker) versus silodosin and tadalafil (phosphodiesterase type 5 inhibitor) for treating patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia. Two patients from Group A was suffering from hypotension and headache, and two patients from Group B was suffering from ejaculatory disorder (retrograde ejaculation) and dizziness so they were excluded from the study. One patient from each group was lost after 1st follow-up. Final analysis was done on sixty patients (thirty from each group). Results are as follows:

Table I: *Distribution of the study subjects according to age (N=60)*

Age (years)	Group		p-value
	Group-A	Group-B	
d"50	9 (30.0)	6 (20.0)	
51 – 60	11 (36.7)	9 (30.0)	
61 - 70	7 (23.3)	14 (46.7)	
>70	3 (10.0)	1 (3.3)	
Mean ± SD	57.13 ± 9.36	59.33 ± 7.09	0.405
Min - max	45 - 78	48 - 71	

Student t test was done to measure the level of significance.

Table I shows age distribution of the study subjects. In both groups, the majority of study subjects were between the ages of 51 and 70. The mean age of the study subjects in Group-A was 57.13 ± 9.36 years, ranging from 45 to 75 years, and 59.33 ± 7.09 years, ranging from 48 to 75 years in Group-B. The difference was not statistically significant.

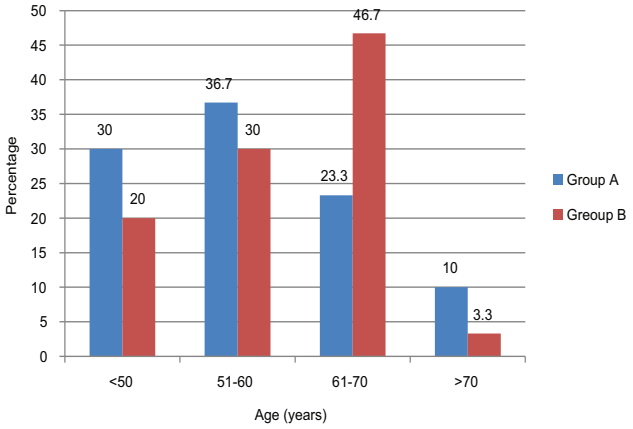

Figure 1: *Age distribution of the study subject*

Table II: *Prostate volume of the study subjects (N=60)*

Prostate volume	Group		p-value
(ml)	Group-A	Group-B	
Mean ± SD	37.93± 13.19	35.50 ± 10.57	0.226
Min - max	22 - 70	22 - 70	

Student t test was done to measure the level of significance

Table II shows prostate volume of the study subjects. In Group-A, the mean prostate volume was 37.93± 13.19 ml, ranging from 22 to 70 ml, and in Group-B, it was 35.50 ±10.57 ml, ranging from 22 to 70 ml.

Table IV: *Comparison of PVR between two groups following 6th and 12th Weeks after treatment (N=60)*

PVR (ml)	Group		p-value
	Group-A	Group-B	
1st visit	74.15 ± 26.40	66.17 ± 15.50	[a]0.159
After 6 weeks	58.00 ± 20.41	52.70 ± 12.51	[a]0.230
After 12 weeks	42.10 ± 17.40	33.57 ± 8.97	[a]0.020
% improvement	42.24 ± 19.42	48.57 ± 13.13	[a]0.144
p-value(1st visit vs after 12 weeks of treatment)	[b]<0.001	[b]<0.001	

PVR- Post voided residual urine.

Student t test was done to measure the level of significance

Table IV shows PVR of the study subjects. PVR decreased to 42.10±17.40 ml after 12 weeks from 74.15±26.40 ml prior to treatment in Group-A. Similarly, PVR in Group-B fell to 33.57±8.97 ml after 12 weeks from 66.17±15.50 ml before treatment. The percentage improvement in group B was higher than in group A, but the difference was not statistically significant.

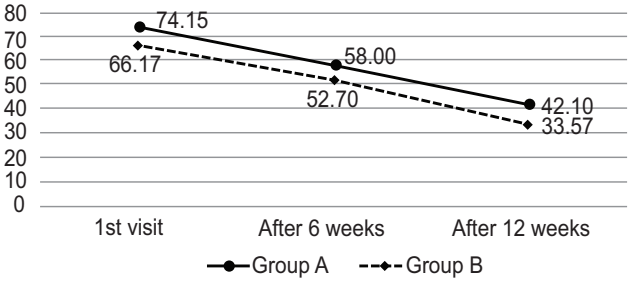

Figure-3: *Line diagram showing pre and post treatment PVR in ml*

Table V: *Comparison of Qmax between two groups following 6th and 12th weeks after treatment (N=60)*

Qmax (cc)	Group		p-value
	Group-A	Group-B	
1st visit	13.39 ± 1.83	14.17 ± 1.28	[a]0.061
After 6 weeks	15.67 ± 2.11	16.74 ± 1.14	[a]0.018
After 12 weeks	17.73 ± 2.66	18.94 ± 1.31	[a]0.029
% improvement	33.09 ± 14.69	34.48 ± 12.48	[a]0.698
p-value after (6 weeks and 12 weeks of treatment)	[b]<0.001	[b]<0.001	

Qmax- Maximum flow of urine per second.
Student t test was done to measure the level of significance

Table V shows Qmax of the study subjects. After 12 weeks, Qmax increased to 17.73±2.66, up from 13.39±1.83 before treatment in Group-A. Similarly, after 12 weeks, Qmax in Group-B increased to 18.94±1.31, up from 14.17±1.28 before treatment. The percent increase in group B was higher than in group A, but the difference was not statistically significant.

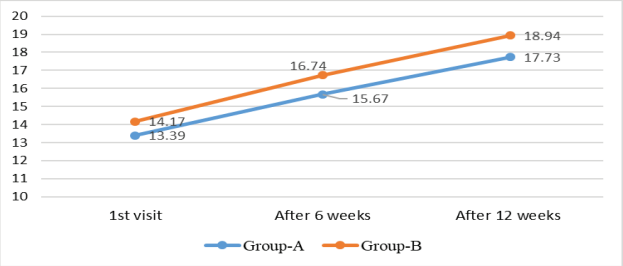

Figure 4: *Line diagram showing pre and post treatment of (Qmax) in ml*

Discussion

The treatment of lower urinary tract symptoms (LUTS) due to BPH has progressed from monotherapy with silodosin (alpha blocker) to combination therapy with tadalafil (Phosphodiesterase 5 inhibitor) and silodosin. The combination therapy came in the scenario because of inadequate response of monotherapy in the treatment of LUTS due to BPH. Marberger et al,(2006) and Roehrborn et al, (2010) in their study has been proven the superior efficacy of combination therapy over monotherapy in preventing disease progression. The Present study is carried out to compare the safety and efficacy of silodosin (alpha blocker) versus silodosin and tadalafil (Phosphodiesterase 5 inhibitor) for treating patients with lower urinary tract symptoms secondary to benign prostatic hyperplasia.

In this study, Group-A was given silodosin whereas Group-B was given silodosin and tadalafil. Baseline variables like age, IPSS score, prostate size with PVR, maximum urinary flow rate (Qmax) and adverse effects were compared between two groups during pre medication and post medication periods at 6th and 12th week.

Most of the patients with LUTS due to BPH are elderly. In the present study, subjects were within 51 to 70 years of age in both groups. Mean age of subjects was ranging from 45 to 78 years in Group-A and from 48 to 75 years in Group-B. The age difference between the groups is not statistically significant ($p< 0.05$) which is concordant with the study of Singh et al (2018). In another study by Oelke et al (2012) showed that the mean age was 64 years (10.2% of 75 years of age) which is similar to age of subject in present study.

Mean prostate volume is within the range of 22-70 ml in Group-A and 22-70 ml in Group-B. All the baseline characteristics are generally balanced between the two treatment groups. Mean prostate size remains unchanged following pre and post treatment in both the groups, similar findings also noticed from Chen. P et al(2020) and Yoshida et al(2017). Chen. P et al (2020.

Changes in the IPSS is gradually improving from 6th week to 12th week of treatment with monotherapy (silodosin) and combination therapy (tadalafil and silodosin). This improvement in Group B (combination therapy group) is greater than Group A (monotherapy group). IPSS was reduced to 21.90 ± 3.68 at 6th weeks and 18.90 ± 3.79 at 12th week from 25.10 ± 3.96. The percentage (%) of improvement is higher in group B than group A, The magnitude of IPSS with Tadalafil (5mg) in this study was consistent and supported by Yoshida et al (2017), in their study a great improvement is observed due to add on therapy with tadalafil than monotherapy with silodosin in terms of the total IPSS. In another study by Chen et al (2012) showed that tadalafil (PDE 5inhibitors) could provide synergistic effects in reducing total IPSS with a pooled mean difference of 2.02 (95% CI : 1.53-2.52) when compared with placebo. A similar study by Singh et al 2018 revealed that in Alpha blockers group IPSS was 18.2 at the time of presentation which improved to 12.4 at 12th week (31.8% improvement). Where as IPSS in group treated with silodosin and tadalafil, improved from 17.9 to 10.4 at 12th week (41.9% improvement). In their study improvement was significant in combination group.

PVR reduced at 6th week and further reduced after 12 weeks in group A. Similar changes also documented in Group-B. The percentage reduction of PVR is higher in group B than group A, but the difference was not statistically significant. A significant reduction of PVR was also observed in both the groups in study conducted by Lee et al. (2014). Another study by Singh et al. (2018) revealed that PVR in group treated with silodosin reduced from from 64.33 ml (average) to 33.52 ml (47.89% improvement) while PVR in group treated with silodosin and tadalafil reduced significantly from 59.4 ml to 27.8 ml at 12th week (overall 53.40% improvement). In another study by Takashi et al., (2017) had shown improvement of PVR in both groups . Improvement is more in monotherapy group than combination therapy group. Combination therapy also improved Qmax from baseline to 6th week and improvement increased after 12th week. Similarly in monotherapy group Q max improvement at 6th week is less than 12th week but more than baseline, which is maintained at 12th week. Percentage (%) improvement

was higher in group B than group A but not statistically significan. Qmax was significantly improved in both groups which is not supported by Moon et al., (2014)and Singh et al., (2018).In Alpha Blockers group Qmax at the time of presentation was 13.45 and at 12th week was 17.44 (29.6% improvement).

In combination group Qmax at the time of presentation improved after12th week (44.06% improvement) (Singh et al., 2018). A meta-analysis conducted by Chen et al. (2020) revealed that combination therapy with an alpha blocker and PDE 5i (tadalafil) did not significantly increased Qmax than alpha blocker monotherapy. Weighted mean difference(WMD)=0.31ml/sec, 95%(CI: -0.24-0.85) which is similar to present study.

Definitive improvement in the total IPSS, Qmax and PVR from base line to 6 and 12 weeks in both groups individually. Improvements was more in combination group than monotherapy group and more after 12 weeks than 6 weeks and baseline, but the improvements is not statistically significant.

There was little adverse effects in both groups. In Group A hypotension (3.3%), headache (3.3%) were noted, In Group B common adverse events were ejaculatory dysfunction (3.3%) and dizziness (3.3%). Most of the adverse effects were self-limiting and resolved spontaneously but they were excluded from the study. The incidence of adverse effects wasconsistent with standard to those previously reported by Singh et al.(2018) and Cho and Yoo., (2014) for these drugs like dizziness, vertigo, ejaculatory dysfunction, headache which was also not significant.

Conclusion

Improvement in both silodosin (alpha blocker) and silodosin along with tadalafil (PDE 5 inhibitor) for treating patients with LUTS due to BPH was satisfactory. Even though combination group showed better improvement than silodosin monotherapy group but no significant difference was found between two groups as per improvement rate.

Acknowledgement

I would like to express my gratitude to all my respected teachers, my mentor and guide Prof. Tohid Md. Saiful Hossain sir for his guidance, supervision and knowledge sharing through out the study period. I am also thankful to all my patients, my colleagues, staffs and hospital authority for their support.

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