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Original Article

Comparative efficacy and safety profile of 4 vs 8 mg of silodosin once daily usage in patients with benign prostatic hyperplasia–related lower urinary tract symptoms divided into subgroups according to International Prostate Symptom Score severity

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ABSTRACT

Background: The purpose of this study was to compare once daily (QD) usage of 4 and 8 mg of silodosin in patients divided as those with moderate and with severe lower urinary tract symptoms (LUTSs) according to International Prostate Symptom Score (IPSS) categories in terms of effectiveness and adverse events.

Methods: A total of 234 patients aged ≥ 40 years were evaluated prospectively. All participants were divided firstly into two groups according to their IPSS severity as moderate and severe. They were further allocated to receive 4 mg of silodosin and 8 mg of silodosin QD. Demographic features and laboratory tests were recorded. The patients were questioned with International Index of Erectile Function-5 and IPSS along with quality of life index. Uroflowmetric measurements were applied to the patients. All tests and measurements were repeated at the 3rd month, and changes from pretreatment to posttreatment were analyzed by SPSS 21.0 Program. The statistical significance level was set at $p < 0.05$.

Results: Both treatments provided benefit in patients with both moderate and severe LUTSs. While results did not differ among 4 mg and 8 mg of silodosin in patients with moderate LUTSs, 8 mg of silodosin was significantly better than 4mg in those with severe LUTSs in terms of improvement of the total IPSS, IPSS voiding subtotal score, and quality of life score ($p = 0.015$, 0.030, <0.001, respectively). Both treatments did not affect erectile functions. Adverse events were seen more frequently in patients receiving 8 mg of silodosin than those treated with 4 mg of silodosin ($p = 0.024$).

Conclusion: Our study revealed that 4 mg of silodosin QD was as effective as 8 mg of silodosin QD in patients with moderate LUTSs but not with severe LUTSs. It can be inferred from this study that prescription of 4 and 8 mg of silodosin may be chosen to treat the patients with moderate and severe LUTSs due to benign prostatic heperplasia, respectively.

1. Introduction

Lower urinary tract symptoms (LUTSs) due to benign prostatic hyperplasia (BPH) are mostly seen in aging men and result in impaired quality of life (QoL).[1,2] LUTSs consist of voiding (incomplete emptying, intermittency, weak stream, and straining to void), storage (frequency, urgency, and nocturia), and postmicturition symptoms.[3] The use of several symptom score questionnaires such as International Prostate Symptom Score (IPSS) is recommended at the duration of diagnosis, as well as during treatment and follow-up by guidelines for male LUTSs.[2,4,5] IPSS, which is an 8-item questionnaire with 35 points for evaluation of LUTSs and 6 points for assesment of QoL, is useful in quantifying and identifying voiding and storage symptoms, as well as evaluating the patients' mood.[6] LUTSs are categorized as mild (1-7 points), moderate (8-19 points), and severe (20-35 points) according to the IPSS. While

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watchful waiting is preferred in patients with mild symptoms, medical or surgical treatment is offered to men with moderate to severe LUTSs.[7]

Alpha-1 blockers are commonly prescribed as first-line therapy for BPH-related LUTSs. Compared with nonselective α1-blockers, α_{1A}-blockers are more prostate specific and cause less common orthostatic hypotension and cardiovascular adverse effects.[8] Effect of those on erectile function is still unclear and controversial.

Silodosin, one of the selective α_{1A}-blockers, is a highly uroselective agent.[9] After phase trails,[10,11] 8mg once daily (QD) usage of silodosin was approved by The US Food and Drug Administration (FDA) in October 2008.[12] Conversely, 4 mg of silodosin twice daily (BID) has widespread utilization, especially in Asian countries for the treatment of LUTSs/BPH.[13-15] Moreover, Seki et al. [14] demonstrated usability of 4 mg of silodosin QD in their study. To the best of our knowledge, there is no study comparing 4 mg of silodosin QD with 8 mg of silodosin QD in patients with LUTSs in the literature up to date. We aimed to compare these two treatment modalities in terms of efficacy and side effect by dividing subgroups based on IPSS categories as the patients with moderate LUTSs and those with severe LUTSs.

2. Materials and methods

This study was conducted prospectively after approval of ethics committee (IRB No. 2018/11) in accordance with Declaration of Helsinki. We evaluated the patients admitted to urology outpatient clinic due to LUTSs secondary to BPH. The inclusion criteria used in the present study were as follows: men aged 40 years and older, a total IPSS of ≥8, a QoL score of ≥2, a prostate volume estimated by transrectal ultrasonography of ≥20 mL, and a peak urinary flow rate (Q_{max}) less than 15 mL/s. Patients with a postvoid residual urine volume (PVR) higher than 200 mL, voiding volume (VV) less than 150 mL, history of medical or surgical prostate treatment, endourological intervention from the lower urinary tract, history of an indwelling urethral catheter, pelvic radiation therapy, prostate cancer or a prostate-specific antigen (PSA) level >4 ng/mL, neurogenic dysfunction or lithiasis or cancer of the bladder, urethral stricture, urinary tract infection, acute or chronic prostatitis, severe hepatic or renal or cardiovascular dysfunction, and inability to understand and answer the IPSS and International Index of Erectile Function (IIEF) questionnaires were excluded. Because there is no established PVR threshold for treatment decision yet in current European Association of Urology (EAU) guidelines, we chose exclusion criteria in terms of PVR volume according to the SILVER study.[13] In addition, the patients who left the follow-up and discontinued the treatment due to adverse effects were excluded from the study. We obtained written informed consent from the patients accepting to participate in our study. Then, we administered questionnaires of 5-item IIEF and 8-item IPSS along with QoL to those after taken a comprehensive patient's history. A detailed physical examination including digital rectal examination was

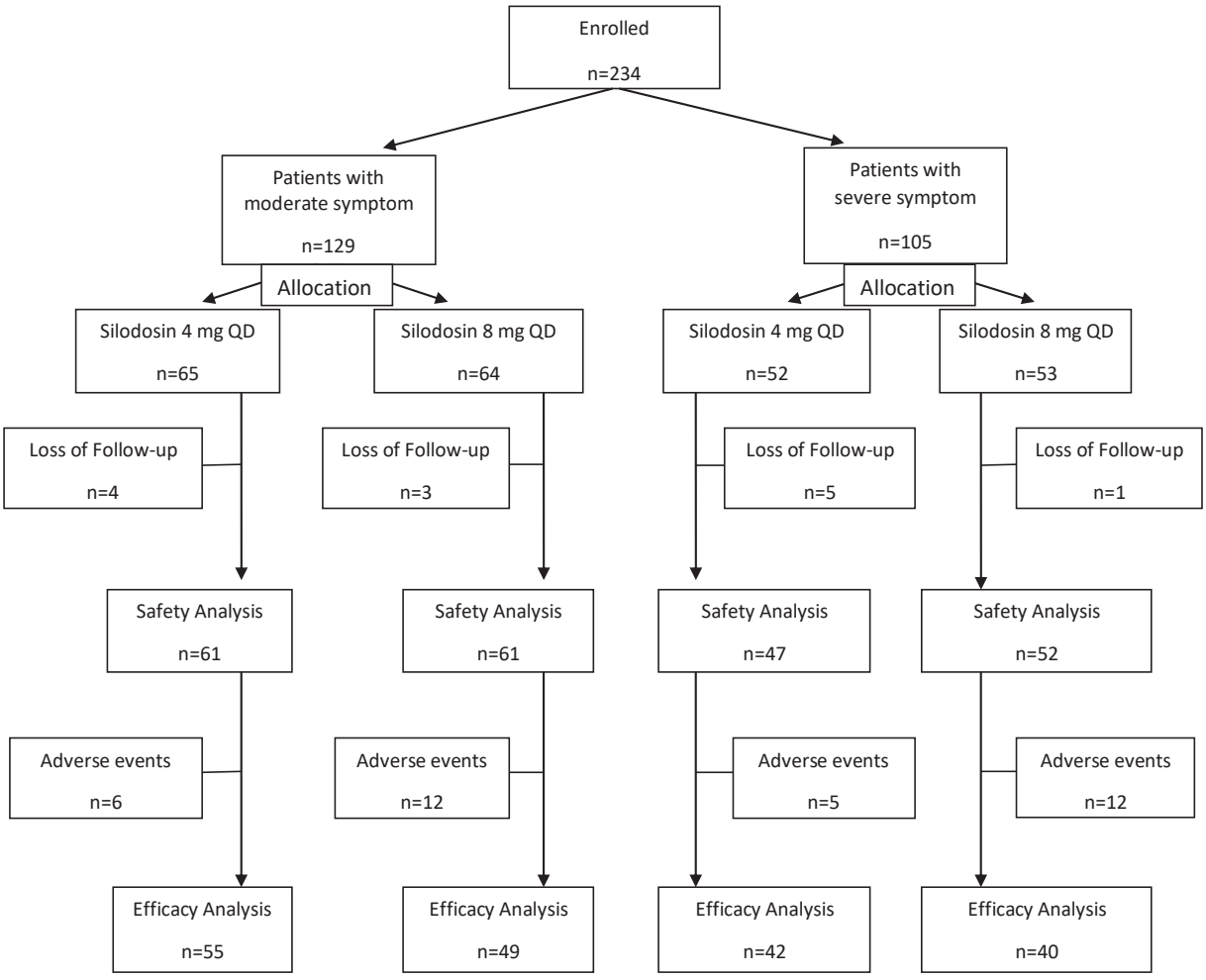

Fig. 1. Flow chart of the study.

performed, as well as evaluation of patients' urinalysis, serum creatinine, and total PSA levels.

Uroflowmetric measurements were applied to the patients with an uroflowmetry device (Dyno Urodynamic System, Aymed Medical Technologies, Turkey), and the Q_{max} and VV values were recorded. PVR was measured with the BladderScan BVI 9400 (Verathon, Bothell, WA) immediately after voiding.

All participants were divided firstly into two groups according to their IPSS severity as moderate and severe. Thereafter, two subgroups were created according to the treatment dosage as 4 mg of silodosin and 8 mg of silodosin (Fig. 1). After division based on symptom severity, intragroup allocation was made using a simple randomization method before starting treatment. The timing of both silodosin administrations was set as after dinner QD. Patients were followed up monthly and those who reached 3 months were evaluated for efficacy. The IIEF, IPSS, QoL score, Q_{max}, VV, and PVR measurements were repeated at final evaluation. Adverse reactions were recorded and not included for efficacy analysis. Safety analyses were carried out in all participants who received at least one dose of the study drug. According to the result of power analysis (using G*Power 3.1 program) with a 0.80 power value and a 0.05 error, at least 40 patients were needed for each group. Once reached necessity participants for all groups, we stopped new inclusions and follow-ups of the patients.

Descriptive statistics were performed as mean ± standard deviation. The intragroup comparison of the changes from pretreatment to posttreatment in the total IPSS, IPSS storage and voiding subtotal scores, QoL score, IIEF score, Q_{max}, VV, and PVR was estimated using the paired *t* test. The independent t test was used for numerical variables and for intergroup comparison. The Chi-square test, with Fisher exact test when appropriate, was applied to compare adverse events. The statistical significance level was set at $p < 0.05$. IBM SPSS 21 statistics, version 21.0, was used for data analyses.

3. Results

We enrolled 234 patients seeking treatment due to LUTSs/BPH into the present study. Of those, 129 (55.1%) had moderate LUTSs while 105 (44.9%) had severe. After allocation, 65, 64, 52, and 53 patients fell into the 4 mg of silodosin moderate group (SM4), 8 mg of silodosin moderate group (SM8), 4 mg of silodosin severe group (SS4), and 8 mg of silodosin severe group (SS8), respectively (Fig. 1). During the follow-up, 4(6.2%), 3(4.7%), 5(9.6%), and 1 (1.9%) patients in SM4, SM8, SS4, and SS8 groups, respectively, did not continue the program. Baseline features of the patients are demostrated in Table 1, and all the parameters were similar among the patients treated with 4 mg of silodosin and those receiving 8 mg of silodosin. Comparision of the changes in the total IPSS, IPSS storage and voiding subtotal scores, QoL score, IIEF score, Q_{max}, VV, and PVR as response to the both treatments are presented in Tables 2 and 3. Total IPSS, IPSS storage and voiding subtotal scores, QoL score, Q_{max}, and PVR in patients with both moderate and severe LUTSs were significantly improved by 4 mg of silodosin (Tables 2 and 3). Similarly, 8 mg of silodosin provided significant improvement on total IPSS, IPSS storage and voiding subtotal scores, QoL score, Q_{max}, and PVR in patients with both moderate and severe LUTSs (Tables 2 and 3). While improvements were similar among 4 mg and 8 mg of silodosin in patients with moderate LUTSs, 8 mg of silodosin was significantly better than 4mg in those with severe LUTSs in terms of improvement in the total IPSS, IPSS voiding symptom score, and QoL score ($p = 0.015$, 0.030, <0.001, respectively). Safety analyses of 221 patients revealed that the adverse events rate was 15.3% ($n = 35$) in total (Table 4). It was seen in 11 (10.2%) patients treated with 4 mg of silodosin QD, while in 24 (21.2%) patients who received 8 mg of silodosin QD ($p = 0.024$).

4. Discussion

LUTSs associated with BPH most commonly affect aging men and weaken their daily activities and QoL. While surgery for BPH was a single option until 1970, medical treatments took its place as first-line therapy with the help of detection of alpha receptors in the human prostate stromal muscle tissue and bladder neck in 1975 by Caine et al.[16] Studies showed that all α-1 blockers, whether selective or not, have similar effects on relief of LUTSs/BPH but not some adverse events with a similar rate. For instance, ejaculatory dysfunction is more frequently seen in usage of silodosin, while occurence of hypotension with that is less common and comparable with placebo.[17,18] Both the patients and doctors generally want to select optimal drug type and dosage in terms of efficacy, tolerability, and safety. In this manner, some studies were conducted for the treatment of LUTSs/BPH.[13-15,19] Among these studies,[13-15] 8 mg of silodosin QD vs 4 mg of silodosin BID was compared in 2 studies,[13-15] while 4 mg of silodosin QD vs 4 mg of silodosin BID was compared in one study.[14]

We compared QD administration of 4 and 8 mg of silodosin by dividing subgroups based on the IPSS as the patients with moderate LUTSs and those with severe LUTSs in this study. We found that 4 mg of silodosin QD improved the scores of both voiding and storage symptoms, total IPSS, QoL index, Q_{max}, PVR, and VV in patients with both moderate and severe LUTSs. Among these parameters, only VV did not change significantly from pretreatment to posttreatment in patients with moderate LUTSs. On the other hand, 8 mg of silodosin QD improved all those without exception in patients with both moderate and severe LUTSs. As for comparison of both treatment results, they were similar between moderate groups while 8 mg of silodosin QD was better than 4mg in patients

Table 1
Characteristics of the study population and comparison of their baseline features

Variables	Overall (n = 186)	4 mg/day (n = 97)	8 mg/day (n = 89)	4 mg vs 8 mg *p* value
Age (years)	64.32 ± 8.95	64.44 ± 8.79	64.18 ± 9.18	0.842
Prostate volume (ml)	44.87 ± 12.45	44.01 ± 11.78	45.82 ± 13.15	0.324
IIEF score	16.86 ± 5.29	16.73 ± 5.32	17.01 ± 5.28	0.720
IPSS voiding symptom score	11.56 ± 3.76	11.53 ± 3.69	11.61 ± 3.85	0.884
IPSS storage symptom score	7.62 ± 3.01	7.54 ± 3.05	7.72 ± 2.96	0.679
IPSS total score	19.18 ± 6.12	19.06 ± 6.09	19.33 ± 6.19	0.770
QoL index	4.67 ± 1.27	4.69 ± 1.28	4.66 ± 1.27	0.883
Q_{max} (mL/s)	9.00 ± 2.32	8.97 ± 2.32	9.03 ± 2.34	0.850
PVR (mL)	49.95 ± 20.09	51.68 ± 21.26	48.07 ± 18.67	0.221
VV (mL)	200.94 ± 50.72	198.78 ± 46.58	203.30 ± 55.06	0.545

VV, voiding volume; PVR, postvoid residual urine volume; IPSS, International Prostate Symptom Score; QoL, quality of life; IIEF, International Index of Erectile Function; Q_{max}, peak urinary flow rate.

Table 2
Response to the treatments in patients with moderate symptom and comparison of the results

Variables		Intragroup comparison		Intragroup comparison		Intergroup comparison
		4 mg/day (n = 55)	*p* value	8 mg/day (n = 49)	*p* value	*p* value
IIEF-5 score	Pretreatment	20.09 ± 3.56	0.637	20.59 ± 3.28	0.382	0.812
	Posttreatment	20.16 ± 3.55		20.71 ± 3.29		
IPSS voiding symptom score	Pretreatment	9.01 ± 2.07	<0.001	8.78 ± 2.01	<0.001	0.772
	Posttreatment	4.92 ± 1.98		4.81 ± 1.88		
IPSS storage symptom score	Pretreatment	5.62 ± 1.54	<0.001	5.80 ± 1.44	<0.001	0.557
	Posttreatment	2.72 ± 1.58		2.89 ± 1.34		
IPSS total score	Pretreatment	14.62 ± 2.95	<0.001	14.57 ± 2.73	<0.001	0.913
	Posttreatment	7.65 ± 2.96		7.71 ± 2.54		
QoL index	Pretreatment	3.93 ± 1.16	<0.001	3.88 ± 1.18	<0.001	0.478
	Posttreatment	2.92 ± 1.08		2.77 ± 1.08		
Q_{max} (mL/s)	Pretreatment	10.02 ± 2.22	<0.001	10.22 ± 2.28	<0.001	0.350
	Posttreatment	11.10 ± 2.27		11.53 ± 2.30		
PVR (mL)	Pretreatment	45.71 ± 14.45	<0.001	44.33 ± 11.69	<0.001	0.264
	Posttreatment	29.50 ± 11.27		27.49 ± 5.92		
VV (mL)	Pretreatment	192.49 ± 38.72	0.073	198.61 ± 44.94	<0.001	0.071
	Posttreatment	198.96 ± 31.23		211.71 ± 39.81		

VV, voiding volume; PVR, postvoid residual urine volume; IPSS, International Prostate Symptom Score; QoL, quality of life; IIEF, International Index of Erectile Function; Q_{max}, peak urinary flow rate.

Table 3
Response to the treatments in patients with severe symptoms and comparison of the results

Variables		Intragroup comparison		Intragroup comparison		Intergroup comparison
		4 mg/day (n = 42)	*p* value	8 mg/day (n = 40)	*p* value	*p* value
IIEF-5 score	Pretreatment	12.33 ± 3.83	0.173	12.62 ± 3.73	0.105	0.869
	Posttreatment	12.11 ± 3.73		12.37 ± 3.62		
IPSS voiding symptom score	Pretreatment	14.83 ± 2.55	<0.001	15.08 ± 2.49	<0.001	0.030
	Posttreatment	10.47 ± 2.37		9.37 ± 2.13		
IPSS storage symptom score	Pretreatment	10.05 ± 2.71	<0.001	10.08 ± 2.62	<0.001	0.076
	Posttreatment	6.47 ± 2.51		5.50 ± 2.39		
IPSS total score	Pretreatment	24.88 ± 3.76	<0.001	25.15 ± 3.77	<0.001	0.015
	Posttreatment	16.95 ± 3.79		14.87 ± 3.79		
QoL index	Pretreatment	5.69 ± 0.51	<0.001	5.63 ± 0.49	<0.001	<0.001
	Posttreatment	4.50 ± 0.77		3.67 ± 0.85		
Q_{max} (mL/s)	Pretreatment	7.60 ± 1.63	<0.001	7.58 ± 1.41	<0.001	0.129
	Posttreatment	8.88 ± 1.67		9.40 ± 1.37		
PVR (mL)	Pretreatment	59.50 ± 25.94	<0.001	52.65 ± 24.06	<0.001	0.052
	Posttreatment	45.40 ± 25.01		38.42 ± 10.79		
VV (mL)	Pretreatment	207.02 ± 54.62	0.008	209.05 ± 65.51	0.001	0.549
	Posttreatment	215.35 ± 45.15		222.10 ± 55.93		

VV, voiding volume; PVR, postvoid residual urine volume; IPSS, International Prostate Symptom Score; QoL, quality of life; IIEF, International Index of Erectile Function; Q_{max}, peak urinary flow rate.

Table 4
Adverse events in the patients treated with silodosin

Adverse events	Overall (n = 221)	4 mg/day (n = 108)	8 mg/day (n = 113)	*p* value
No participants with adverse events	35 (15.3%)	11 (10.2%)	24 (21.2%)	0.024
Ejaculatory disorder	18 (8.1%)	7 (6.5%)	11 (9.7%)	0.377
Dizziness	8 (3.6%)	3 (2.8%)	5 (4.4%)	0.722
Thirst	6 (2.7%)	2 (1.9%)	4 (3.5%)	0.684
Loose stool or diarrhea	7 (3.2%)	3 (2.8%)	4 (3.5%)	0.746
Urinary incontinence	3 (1.4)	1 (0.9%)	2 (1.8%)	0.588

with severe LUTSs in terms of improvement in the total IPSS, IPSS voiding subtotal score, and QoL score. In addition, adverse events were observed less common in the 4 mg of silodosin group than in the 8 mg of silodosin group.

In a study comparing QD vs BID of 4 mg of silodosin, Seki et al. [14] prospectively analyzed 268 Japanese men with BPH and reported similar results with ours. They found in both groups significant reduction in IPSS voiding and storage subtotal scores, total IPSS, QoL index, PVR, and increase in Q_{max}. However, only QoL index among those gained significantly more benefit from 8 mg/day usage of silodosin. Both treatments did not affect VV significantly in their study. Although rates of adverse events in their study were lower in the 4 mg QD group, it did not reach statistical significance. Seki et al. [14] also used Overactive Bladder Symptom Score (OABSS) questionnaires along with IPSS and found that both treatments gave benefit to the OABSS total score. However, daytime symptom scores reduced significantly much more with 4mg BID usage of silodosin due to more likely administrating one of the dose after breakfast. Consequently, they concluded that 4 mg BID administration of silodosin was not superior to QD of that in IPSS but more

beneficial in the OABSS. In our study, even though QD usage of 4 mg of silodosin has similar results with 8 mg in patients with moderate LUTSs, 8mg is more effective on total IPSS, IPSS voiding subtotal, and QoL scores in patients with severe LUTSs. An another (SILVER) study conducted in Korea by Choo et al. [13] reported that 8mg QD administration of silodosin had similar results with 4mg BID one in terms of safety, efficacy, and adverse reactions. Similar study investigated on Indonesian patients confirmed the findings of the SILVER study.[15]

LUTSs/BPH and sexual dysfunctions are concomitantly seen by increasing parallel with aging.[20,21] On the other hand, the effect of a1-blockers given for the treatment for LUTSs/BPH on erectile function is inconsistent.[22] In that meta-analysis, van Dijk et al. [22] investigated the a1-blocker–associated erectile dysfunction. They analyzed the studies including alfuzosin, doxazosin, tamsulosin, and terazosin. They concluded that a1-blockers had similar effects with the placebo on erectile function. In addition, they specified that impotence, which is not a specific word unlike erectile dysfunction, might be seen in some patients under a1-blocker treatment with a similar rate among those.[22]

In a study conducted in Italy, researchers investigated the effect of silodosin on sexual functions by IIEF orgasmic function subdomain.[23] They were asked the emergence of erectile dysfunction after 3 month treatment by the response of yes or no. They did not use IIEF erectile function subdomain. Of the patients, 11 (11%) had erectile dysfunction concomitant impaired ejaculatory and orgasm functions, which might be perceived as erectile dysfunction (ED) by them. As a result of literature search, our study is the first in terms of use of IIEF-5 score for evaluation of erectile function in patients treated with silodosin. It revealed that both silodosin dosages did not affect the IIEF-5 scores. Ejaculatory disorder was seen in a rate of 6.5% for the patients receiving 4 mg of silodosin and 9.7% for those using 8 mg of silodosin in our study. There are different rates for the ejaculatory disorder due to silodosin in literature. It was shown in a systematic review and meta-analysis including 3 studies comparing tamsulosin vs silodosin and 2 studies comparing placebo vs silodosin that ejaculatory dysfunction caused by 8 mg of silodosin was varying from 9.7% to 28.1%.[18] A study conducted by Sertkaya and Ozkaya [24] revealed in their study that sexual adverse events of silodosin were related to nocebo effect. They allocated the patients into two groups as those who were informed about the sexual adverse effects of 8 mg of silodosin treatment in Group 1 and those who were not informed about sexual side effects in Group 2.[24] After 3 months of treatment, the anejaculation rate in Group 1 was 22.7%, while 14.3% in Group 2 with lower frequency.[24] In addition, the rates belonging to their cohorts were including the patients who ceased the treatment.[24] In our study, we do not know the reason why the patients left the follow-up because they did not come back to the control visit and did not answer our phone calls. It may be ejaculatory disorder. If so, the actual rate will be higher as approximately 2-fold in the present study. On the other hand, it was found as 5.2% and 8.7% similar to our results in 4 mg of silodosin and 8 mg of silodosin, respectively, in the study conducted by Seki et al [14] in the Japanese population. Morever, in a similar study published recently, ejaculation disorder rates were 6.7% in 8 mg of silodosin QD and 5% in 4 mg of silodosin BID in Indonesian patients with BPH.[15]

Although our study is the first of its kind, it has some inherit drawbacks. Firstly, this study is limited by a relatively small sample size despite having enough number of patients according to the result of power analysis. Secondly, we could not evaluate urinary incontinence, nocturnal polyuria, and postmicturition symptoms because the IPSS questionnaire does not include these parameters. Thirdly, the pharmacokinetic assessment of both administrations such as their concentrations in plasma, half-life of their eliminations, and area under the plasma concentration–time curve was not investigated. Even if 4 mg QD administration may not provide adequate dosage for 24 hours according to the study which reviewed the pharmacology, pharmacokinetics, drug dosage, and administration of silodosin in adult male patients with BPH,[25] it is enough to significantly reduce complaints in patients with moderate symptoms. More likely, moderate symptoms may not disturb the patients as much as severe symptoms. Another point, we gave the medication after dinner. During adequate dosage at night, well-being associated the improvement in nocturia which is usually the most disturbing symptom of the patients may result in increase in QoL and also decrease in IPSS scores in our study.

5. Conclusion

The present study indicates that 4 mg of silodosin QD is as effective as 8 mg of silodosin QD with lower adverse event frequencies in patients with moderate LUTSs secondary to BPH. However, 8 mg of silodosin QD causes significantly more reduction in total IPSS, IPSS voiding subtotal, and QoL scores in patients with severe LUTSs. Morever, both treatment modalities do not affect erectile functions according to IIEF-5. We can infer from our study that administration of 4 and 8 mg of silodosin QD may be more appropriate in patients with moderate and severe LUTSs, respectively. Further well-designed placebo-controlled studies with larger sample size are required.

Author contributions

All authors performed the research.

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Conflicts of interest

All authors declared no conflict of interest.

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