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Research Article

Effects of Temporary Drug Cessation in BPH/LUTS Patients Treated with Alpha-1 Adrenoceptor Blocker

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Abstract

Objective: Patients with benign prostatic hyperplasia (BPH) typically present with lower urinary tract symptoms (LUTS). We sought to confirm the safety and clinical efficacy of the α-1 blocker silodosin, and investigated the effects of a temporary drug cessation (DC) in patients who exhibited clinical efficacy considered as improvement of subjective symptoms.

Methods: Subjects were 75 BPH patients with complaints of LUTS and who were being treated on an outpatient basis. Patients were first administered silodosin (4 mg twice daily) for 8 weeks, and then we evaluated the effects based on changes in subjective symptoms and divided the subjects into continuous administration (CA) and DC groups. The groups were followed up until week 24. Silodosin administration was restarted according to subjects' request during drug cessation (R group). We evaluated the International Prostatic Symptom Score (I-PSS) and quality of life (QOL) score trends before and after administration, and also assessed the safety and status of drug re-administration.

Results: Significant differences were observed between the two groups in terms of the subject characteristics of age, I-PSS storage symptoms sub-score, maximum urinary flow rate, and mean urinary flow rate. The clinical course of the voiding and storage symptoms in the CA group differed; storage symptoms improved over time, while no further improvement in the voiding symptoms was observed over time. Symptoms rapidly improved after silodosin administration in the DC group, and the improvement in I-PSS was maintained after DC. However, the residual effects on QOL gradually diminished in this group. The deterioration in storage symptoms was particularly conspicuous in those who restarted drug administration.

Conclusion: DC was possible in patients who experienced adequate improvement in storage symptoms from the early stages of α-1 blocker administration. However, we believe that it is important for elderly patients and patients with relatively severe storage symptoms to continue oral intake of α-1 blockers to maintain improved QOL.

Keywords: Benign Prostatic Hypertrophy; International Prostatic Symptom Score; Lower Urinary Tract Symptoms; Silodosin

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Introduction

Currently, α-1 adrenergic receptor blockers (α-1 blockers), such as silodosin, are generally used as first-line drug treatment for lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) [1]. Because BPH is a chronic condition, we expect that these drugs are often used for long periods of time in clinical settings.

Several reports have documented the long-term efficacy of α-1 blockers in BPH patients [2-4]. However, there are currently no detailed investigations of the extent to which drug effects are maintained when patients who experience stable efficacy take a temporary drug cessation (DC). The latest post-marketing surveillance in Japan of silodosin has shown that there are also patients who discontinue administration due to symptomatic improvement [5].

Reports have also indicated that in routine medical practice, LUTS (particularly storage symptoms) are subject to seasonal variation [6], and there are a number of patients who discontinue oral drug intake due to symptomatic improvement in summertime. Moreover, according to a survey by Yoshida et al. [7], BPH patients prefer treatment to be completed in the shortest possible period of time, and express the wish to avoid long-term oral drug intake.

By elucidating the effects of DC during this study, we believe it may become possible to reduce the drug cost burden on patients with stable efficacy by allowing them to take a temporary DC. We also believe that investigation of drug dose reductions and DC that do not impair patient quality of life (QOL) will be extremely beneficial from the perspective of medical economics, which includes factors such as polypharmacy in elderly patients and management of unused drugs.

Materials and Methods

This clinical trial was approved by the Tokai University Ethics Committee before the study started (No.10R-099). Subjects were provided with an adequate explanation of the study before participating, and only patients who gave informed consent were designated as subjects.

Subjects were patients who were examined on an outpatient basis between November 2010 and March 2015 and were diagnosed with BPH having met the following criteria: International Prostatic Symptom Score (I-PSS) ≥ 15, QOL score ≥ 3, prostate volume (PV) ≥ 20 mL, voided volume (VV) ≥ 100 mL, and a maximum urinary flow rate (Qmax) < 15 mL/s (however, VV ≥ 150 mL was preferred).

Exclusion criteria were as follows: patients with a history of hypersensitivity to the active substance in URIEF tablets (silodosin); patients already taking anticholinergic drugs, or antiandrogen drugs (including 5α reductase inhibitors) with changing the brand or dosage during the experiment; and any patients deemed to be ineligible by the investigators. Patients that met any of these criteria were excluded.

Informed consent was obtained and BPH patients who met the inclusion criteria were administered silodosin at a dose of 4 mg twice daily for 8 weeks. Then, subjects were allocated to the following two groups based on their total I-PSS score.

Continuous administration (CA) group: if the I-PSS decreased by < 50% of baseline and the score was ≥ 8 points, then administration of the 4-mg dose was continued twice daily for a further 16 weeks.

DC group: if the I-PSS decreased to < 8 points, then DC was permitted and follow-up observation was performed for the next 16 weeks. Also, every 4 weeks, we asked patients in the DC group whether or not they wanted to restart oral drug intake, and silodosin administration was resumed at the patients' request.

Restart (R) group: patients who requested to restart silodosin intake during drug cessation.

The primary outcome was the change in the total I-PSS score in each group. Secondary outcomes were the subjective symptoms (QOL score), objective findings (including Qmax; average urinary flow rate, Qave; post-void residual volume of urine, PVR; systolic blood pressure, SBP; and diastolic blood pressure, DPB), safety (clinical symptoms and abnormal laboratory tests), DC duration, and drug re-administration rate.

Statistical analysis was performed with EZR (Easy R; Saitama Medical Center, Jichi Medical University, Saitama, Japan) [8], a graphical user interfaces for R (The R Foundation for Statistical Computing, Vienna, Austria). More pre-

cisely, EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Changes before and after administration were evaluated using the Wilcoxon signed-rank test. We performed an analysis of variance (ANOVA) to compare the three groups, and then evaluated the results using either the Mann–Whitney U test or the chi-square test. All data are shown as the mean ± standard deviation, and a statistically significant difference was defined by a P value < 0.05 (two-sided).

Results

We enrolled 75 BPH/LUTS patients who gave informed consent to participate in this study. The I-PSS improved by ≥ 50% in 45.3% (34/75) of these patients after 8 weeks of silodosin administration, and decreased to < 8 points in 31 patients.

Based on the evaluation in week 8, 23 patients were allocated to the CA group and 29 patients were allocated to the DC group; 6 patients from the DC group restarted silodosin administration on request (R group). Administration was restarted by 4 subjects after 4 weeks (1 resumed the DC after another 8 weeks), by 1 subject after 8 weeks, and by 1 subject after 12 weeks; mean DC duration was 6 weeks. In this study, 12 of the enrolled patients were excluded because of missing data, and 6 were excluded for protocol violations. Administration was discontinued in 6 patients due to adverse drug reactions (ADRs) and in 10 patients for

Table1: Baseline characteristics of benign prostatic hyperplasia patients with lower urinary tract symptoms.

	CA-group (n=23)	DC-group (n=23)	R-group (n=6)	P value
Age	74.5 ± 5.6 (22)	68.6 ± 8.5* (23)	73.5 ± 7.3 (6)	0.025
Height	164.6 ± 4.6 (14)	166.1 ± 7.4 (17)	161.0 ± 6.1 (3)	0.423
Weight	60.4 ± 8.8 (14)	62.9 ± 8.2 (17)	62.3 ± 9.5 (3)	0.707
Duration	21.8 ± 30.0 (12)	23.5 ± 22.4 (14)	19.5 ± 23.3 (2)	0.972
Prostate volume	41.9 ± 21.1 (21)	41.3 ± 17.7 (23)	62.7 ± 29.8 (6)	0.074
IPSS				
Voiding	9.4 ± 3.5 (23)	9.9 ± 4.5 (23)	8.3 ± 2.3 (6)	0.682
Storage	9.8 ± 3.2 (23)	6.9 ± 3.3* (23)	6.5 ± 2.6* (6)	0.006
Total	22.1 ± 6.6 (23)	19.6 ± 7.4 (23)	16.8 ± 4.3 (6)	0.180
QOL index	4.9 ± 0.9 (23)	5.0 ± 1.0 (23)	4.0 ± 0.9 (6)	0.073
Max. flow rate	7.0 ± 2.8 (18)	10.7 ± 4.7* (16)	9.6 ± 3.2 (4)	0.024
Ave. flow rate	3.9 ± 1.3 (17)	6.0 ± 2.1* (16)	4.7 ± 0.6 (3)	0.006
PVR	74.2 ± 94.2 (19)	66.7 ± 69.6 (18)	63.3 ± 26.2 (4)	0.946
SBP	138.2 ± 14.7 (13)	141.5 ± 20.1 (15)	122.7 ± 30.0 (3)	0.307
DBP	75.6 ± 14.4 (13)	83.9 ± 14.9 (15)	63.3 ± 18.0 (3)	0.080
HR	75.8 ± 12.7 (12)	74.0 ± 16.7 (15)	74.7 ± 13.3 (3)	0.955
Pre- medication*	3 / 23	4 / 23	1 / 6	0.975

*Pre-medication of α-1 blocker: tamsulosin (1), naftopidil (2) in CA-group, tamsulosin (4) in DC-group, tamsulosin with naftopidil (1) in R-group, respectively. Numbers in parentheses means number of patients.

*P < 0.05 versus CA group (Mann–Whitney U-test or chi-square test). CA, continuous Administration; DC, drug cessation; HR, heart rate; IPSS, International prostatic symptom score; PVR, post-void residual volume; SBP, systolic blood pressure; DBP, diastolic blood pressure; QOL, quality of life.

other reasons (such as not attending hospital visits; multiple reasons for discontinuation could be given).

Table 1 shows the patient characteristics. ANOVA revealed significant differences between the three groups in terms of age, I-PSS storage symptom subscores, Qmax, and Qave. Compared with the CA group, patients in the DC group were younger, had milder storage symptoms, and higher Qmax and Qave values. Compared with the DC group, patients in the R group had larger PV values and lower total I-PSS and QOL scores.

Figure 1 shows the clinical course of the subjective symptoms (total I-PSS and QOL scores). Patients who experienced early symptomatic improvement due to silodosin administration (4 mg twice daily) achieved maximum improvement within 8 weeks, and the I-PSS was also maintained after the DC up to week 24. Patients in the R group experienced rapid symptomatic deterioration during DC, although the I-PSS decreased again when silodosin was re-administered. We also observed significant improvement in the CA group compared with before administration, but the degree of improvement was also inadequate at 24 weeks compared with the DC group.

We observed definite improvement in QOL scores in the CA group, but the improvement occurred gradually over the course of time. Additionally, there was early improvement in the DC group, which was similar to the I-PSS results, and the values were approximately the same as those in the CA group after 24 weeks. We also confirmed that QOL scores in the R group deteriorated immediately after DC and decreased after re-administration, and these findings were also similar to the I-PSS results.

Figure 2 shows the I-PSS subscore trends (voiding symptoms, storage symptoms). Voiding symptom and storage symptom trends in the CA group differed; storage symptoms improved over time, but there was no further improvement in voiding symptoms over time. Both voiding and storage symptoms in the DC group improved soon after administration and the effects were maintained after

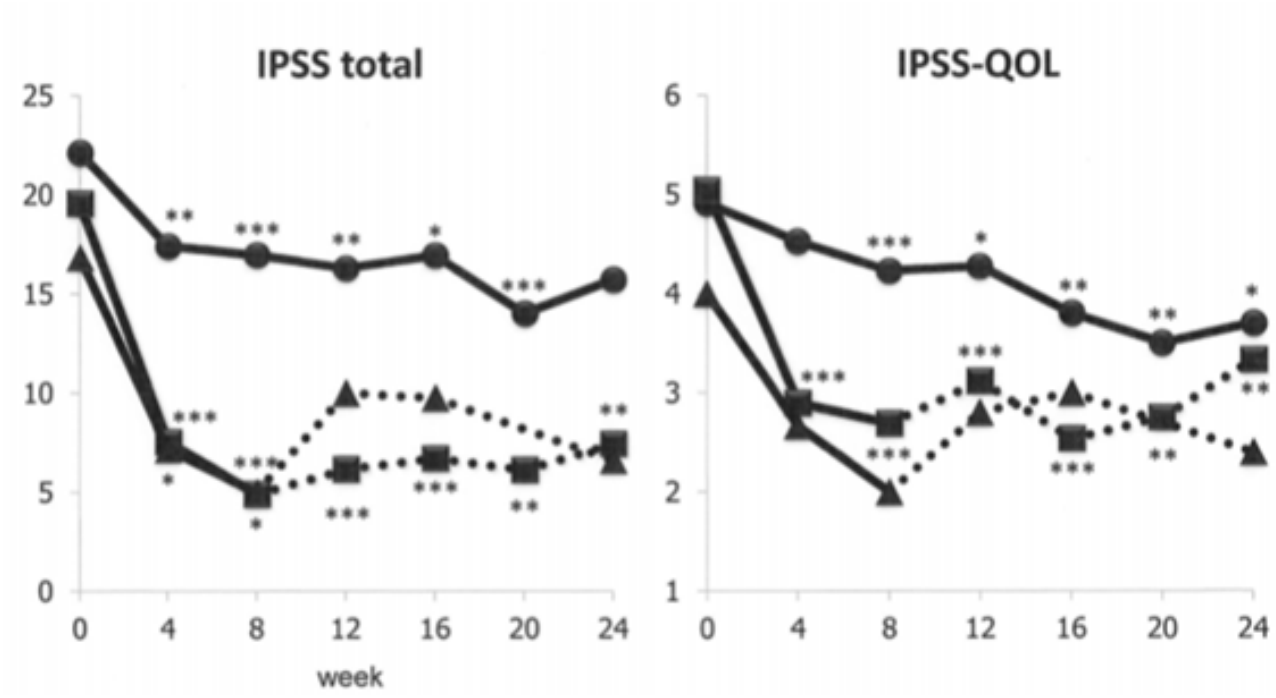

Figure 1: Changes in International Prostatic Symptom Score (I-PSS) total score and quality of life (QOL) index.

Closed circles indicate the continuous administration group, closed squares indicate the drug cessation group, and closed triangles indicate the restart group.

*P < 0.05, **P < 0.01, ***P < 0.001 versus pre-medication (Wilcoxon signed-rank test)

DC, though this tendency was more conspicuous for voiding symptoms. Furthermore, symptomatic deterioration immediately after DC in the R group was more conspicuous for storage symptoms than for voiding symptoms.

We observed non-significant improvement in Qmax and Qave due to silodosin administration with marked variation (standard deviation), and there were no obvious differences between the trends in the two groups. VV also improved after silodosin administration, although there was also marked variation; no obvious effects as a result of DC or restarting administration were noted. No clinically significant changes were observed in SBP, DBP, or HR during the experiments.

ADR incidence after the maximum silodosin administration period of 24 weeks was 8% (6/75 patients). Three patients developed diarrhea, 2 patients had syncope, and 1 patient had nasal congestion; all of ADRs appeared almost within 2 weeks (aged 53-72 years old), and all these patients discontinued administration. However, none of the ADRs were serious and all patients recovered after administration was discontinued.

Discussion

During this study, we investigated the utility of DC in patients who confirmed the effects of silodosin, a drug used to treat BPH/LUTS, and who exhibited objective efficacy. We confirmed that the I-PSS improved by ≥ 50% in approximately half of these patients after 8 weeks of silodosin administration (4 mg twice daily) with marked improvement in subjective symptoms soon after silodosin administration, and that this was associated with improved micturition-related QOL.

In total, DC was possible in 31 of 75 patients (total I-PSS < 8 points), and comparing their characteristics with those in the CA group showed that these patients were younger and had milder storage symptoms and less impaired voiding function (urinary flow). Our findings suggest that these patients more readily experienced benefits starting from the early period of silodosin administration and a short period of DC was possible. Nevertheless, there were some patients who restarted drug administration af-

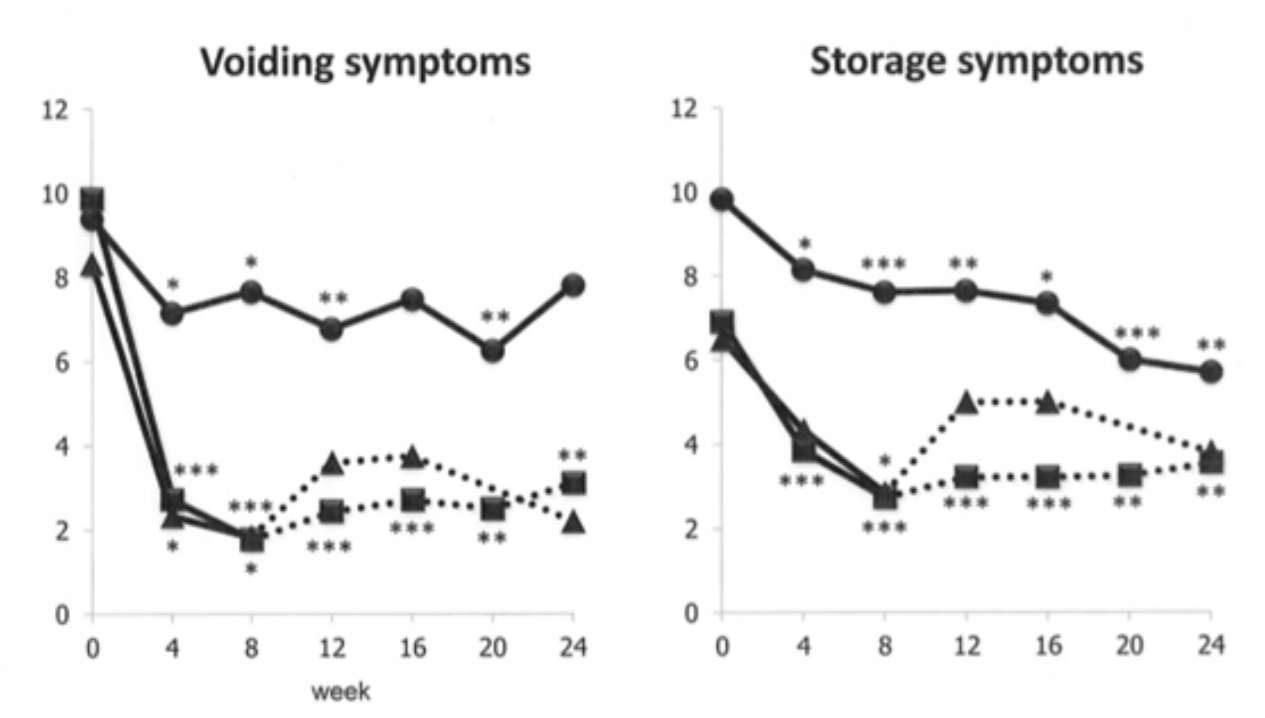

Figure 2: Changes in International Prostatic Symptom Score voiding and storage subscores.
Closed circles indicate the continuous administration group, closed squares indicate the drug cessation group, and closed triangles indicate the re-start group.
*P < 0.05, **P < 0.01, ***P < 0.001 versus pre-medication (Wilcoxon signed-rank test)

ter the DC, so we have also determined that not all patients can tolerate DC.

We examined the clinical course after silodosin administration and found that storage symptoms improved more gradually than voiding symptoms. This is because of the high prostatic selectivity of silodosin [9], exerting more potent effects on prostatic obstruction, which in turn suggests that the improvement of voiding symptoms may appear earlier than that of storage symptoms. Another cause might be that patients in the CA group were older, and may have had poorer bladder function due to long-term obstruction, which may have led to a more gradual improvement in storage symptoms than voiding symptoms after silodosin administration.

In a study with detailed investigation of patients who exhibited poor response to silodosin administration using urodynamic [10], patients who did not experience adequate symptomatic improvement after four weeks of silodosin administration characteristically exhibited improved lower urinary tract obstruction but no improvement in overactive bladder symptoms. This suggests that patients who did not experience adequate improvement in storage symptoms during the early period of silodosin administration during our study will exhibit poor therapeutic response (and will require continued administration).

Previous studies of DC after α-1 blocker administration used dutasteride (5α-Reductase inhibitor) concomitantly and reported symptomatic deterioration after α-1 blocker DC [11, 12]. Another study, which also involved concomitant administration of dutasteride, reported no significant differences between a continued concomitant administration group and a DC group after an α-1 blocker DC in terms of Qmax and the bladder outlet obstruction index. This study, however, reported that the improvement in maximum cystometric capacity decreased in the DC group [13]. The results from our study also showed a more conspicuous symptomatic deterioration in the R group (6/29 patients) than in the DC group, and the storage symptoms deteriorated more than voiding symptoms. This suggests that patients should be questioned about improvement in storage symptoms during the evaluation of effects, and if there is adequate improvement in storage symptoms, patients will then be able to take an α-1 blocker DC.

Finally, the effects on I-PSS during this study were relatively maintained after α-1 blocker administration was discontinued, although the residual effects on the QOL score tended to decrease gradually. Considering the results to date, we believe that patients with relatively mild storage symptoms before administration and patients who experience improvement in storage symptoms soon after administration are able to take a short DC. However, we believe that it is important for patients with relatively severe storage symptoms to continue oral administration of α-1 blockers even if they have experienced a certain degree of improvement in subjective symptoms, to maintain improved QOL.

This study was subject to the following limitations. The DC during this study occurred after a short administration period of 8 weeks, so we cannot rule out the possibility that patients may exhibit different characteristics during DC after long-term oral drug intake (symptoms deteriorated over a shorter period of time). In addition, recent BPH/LUTS patients are no longer treated with α-1 blockers as monotherapy, and receive concomitant drug treatment for LUTS including β-3 agonists, anticholinergic drugs, dutasteride, and phosphodiesterase type 5 inhibitors. Accordingly, it is possible that patients treated with multiple drugs who take a α-1 blocker DC may exhibit different results to those seen in our study. We hope to conduct future studies to offer patients a greater range of therapeutic options.

Conclusion

Silodosin, an α-1 blocker, causes marked improvement in subjective symptoms from the early period of administration, and these effects are associated with improved micturition-related QOL. DC may be possible in patients who experience adequate improvement in storage symptoms from the early period of α-1 blocker administration. However, we believe that it is important for elderly patients and patients with relatively severe storage symptoms to continue oral intake of α-1 blockers to maintain improved QOL.

Disclosure

The authors declare no conflicts of interest.

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