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Patient-reported Goal Achievement after Treating Male Benign Prostatic Hyperplasia with Alpha-adrenergic Antagonist: A -12week Prospective Multicenter Study

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Purpose: The study was designed to assess and predict patient-reported goal achievement after treatment of benign prostatic hyperplasia (BPH) patients with tamsulosin.

Materials and methods: From November 2013 to October 2015, 272 patients initially diagnosed with BPH were prospectively enrolled in nine different centers. Before the treatment, subjective final goals were recorded by all patients. Every four weeks, the treatment outcomes were evaluated using international prostate symptom score (IPSS) and uroflowmetry, and adverse events were recorded. Patient-reported goal achievements were assessed after 12 weeks of treatment.

Results: Of the enrolled patients, 179 patients completed the study. The pretreatment patients' goals included the frequency improvement, nocturia improvement, residual urine sense improvement, well voiding, hesitancy improvement, weak urine stream improvement, urgency improvement, and voiding-related discomfort improvement. Of the 179 patients, 129 patients (72.1%) reported that they achieved their primary goals after three months of medical therapy. Logistic regression analysis revealed that pretreatment quality of life (OR = 8.621, 95% CI: 2.154-9.834), and improvement of quality of life (OR = 6.740, 95% CI: 1.908-11.490) were independent predictors of patient-reported goal achievement after tamsulosin monotherapy.

Conclusion: Overall patient-reported goal achievement after medical therapy for BPH was high and the scores of pretreatment quality of life and improvement of quality of life can be important factors to predict the achievement of treatment goals.

Keywords: prostatic hyperplasia; adrenergic alpha-antagonists; drug therapy; lower urinary tract symptoms; patient outcome assessment

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common disease, which is present in 50% of men older than 50 years and in approximately 80% of men 80 years of age or older.[1,2] Lower urinary tract symptoms (LUTS) are the most common and bothersome problems of BPH. The LUTS due to BPH include hesitancy, a weak urine stream, incomplete voiding, frequent urination, nocturia, and urgency. In the past, LUTS due to BPH were usually managed by catheterization or surgery. However, over the past several decades, the management concept for BPH has transitioned from an acute surgical condition to a chronic medical condition.[3] The development of alpha-adrenergic blockers (α-blockers) changed the treatment patterns of BPH. It has been reported that most patients who were newly diagnosed with BPH in the USA underwent watchful waiting or medical therapy, and monotherapy with α-blockers was the most common first-line medical therapy, constituting about 80% of the treatments.[4] The physiological function of α-blockers is the relaxation of smooth muscles in the prostate and bladder neck, thereby reducing the resistance to urinary flow and improving LUTS. First-generation α-blockers

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Table 1. Baseline patients' characteristics.

Characteristics	Values[a]
No. of patients	179
Mean age (years)	62.0 ± 8.4
Mean serum PSA (ng/mL)	1.7 ± 2.6
Mean prostate volume (g)	31.7 ± 12.2
Patients' goal setting	Nocturia improvement (n = 63) WUS improvement (n = 52) Frequency improvement (n = 34) RUS improvement (n = 27) Hesitancy improvement (n = 22) Well voiding (n = 21) Urgency improvement (n = 11) Voiding related discomfort improvement (n = 2)

a Data are presented as mean±SD or number

Abbreiations: PSA, prostate-specific antigen; RUS, residual urine sense; WUS, weak urine stream

were non-selective agents, and their use was associated with frequent cardiovascular and gastrointestinal side effects. Second-generation α-blockers, including terazosin and doxazosin, showed reduced side effects but required dose titration due to various vascular sequelae, such as hypotension, dizziness, fainting, and postural hypotension. More recently, third-generation α-blockers, including tamsulosin, alfuzosin, and silodosin, have been developed, which have a high affinity and selectivity for alpha-1A adrenergic receptors in the prostate and a lower affinity for the receptors in blood vessels. Currently, these agents are widely used for the medical therapy of BPH and have been reported to effectively improve LUTS with a low risk of vascular side effects.[5] Tamsulosin, which is one of the most popular α-blockers, is an alpha-1A and alpha-1D selective adrenoceptor antagonist, and its efficacy and safety have been well established in many studies.[6-10] Several clinical tools, such as the International Prostate Symptom Score (IPSS), American Urological Association Symptom Score (AUASS), peak flow rate (Qmax), and post-void residual urine (PVR), have been used to evaluate the improvement of LUTS in BPH patients. Although these tools have been considered good measurement indices, it is still difficult to assess patients' treatment goal achievement using these tools. Therefore, we tried to evaluate the patients' goal achievement with medical therapy for BPH and performed a prospective multicenter study to assess and predict the patient-reported goal achievement after treatment with tamsulosin.

MATERIALS AND METHODS

Study design and sample size

From November 2013 to October 2015, 272 patients initially diagnosed with BPH were prospectively enrolled in nine different centers (at least 30 patients in each center). All patients were informed about the purpose and protocol of this study and provided consent. This study was approved by the Institutional Review Board of each hospital (No. 2013-12-022). The primary endpoint of this study was the score of the patient-reported goal achievement after 12 weeks of treatment, and the secondary endpoints were the changes of the total IPSS, voiding subscore, storage subscore, quality of life (QoL), Qmax, and PVR at 4, 8, and 12 weeks of treatment compared to the baseline.

Study population

The inclusion criteria of this study were as follows: male patients with the age of 40 years or older, a baseline total IPSS of □ 8, a bother score of QoL of ≥ 3, initially diagnosed patients with BPH without a history of prior □-blocker medication for the recent 12 weeks and no history of prior 5-alpha-reductase inhibitor (5-ARI) medication for the recent 12 weeks. Patients requiring surgery, those with suspicious hypersensitivity or a contraindication for □-blockers, a prior history of prostatic surgery, moderate or severe liver or renal function impairment, moderate or severe cardiovascular disorder, postural hypotension, hypotension, a history of senile dementia, combined urinary tract infection, underlying neurological disease, underlying urogenital malignancy, urethral stricture, chronic prostatitis or chronic pelvic pain syndrome, and serum prostate-specific antigen (PSA) of ≥ 4 ng/mL were excluded from this study.

Variables and follow up period

Before the treatment, all patients underwent medical history taking, physical examination, including blood pressure and digital rectal examination, a serum PSA test, urinalysis with urine culture, transrectal ultrasound, uroflowmetry, and IPSS with QoL determination. In addition, all patients were asked about their subjective final goals of treatment for BPH. Since tamsulosin 0.2 mg is recommend as initial treatment dose in East Asian patients with BPH, tamsulosin was initiated at 0.2 mg once daily, and the treatment continued for 12 weeks. After four weeks of treatment, if the parameters of uroflowmetry or IPSS were not improved, or patients were not satisfied with their voiding status, the dose of tamsulosin was escalated up to 0.4 mg. Other medications that could affect patients' LUTS, such as cholinergic drugs, anticholinergic drugs, 5-ARIs, desmopressins, and other □-blockers, were not permitted throughout the study period. Every four weeks, the treatment outcomes were evaluated using IPSS and uroflowmetry, and adverse events were recorded. After 12 weeks of treatment, patient-reported goal achievements were assessed. The scoring of the goal achievement was set by 1 (completely unachieved), 2 (unachieved), 3 (neither achieved nor unachieved), 4 (achieved), and 5 (completely achieved). In addition, all patients were divided into two groups according to the goal according score; lower score (1, 2 and 3) and higher score (4 and 5), and risk factors for lower score of goal achievement were assessed using logistic regression analysis.

Statistical methods

Statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL, USA). Continuous variables, such as IPSS, QoL score, Qmax and PVR were compared by Student's t-test and these variables of each time point (0, 4, 8 and 12 weeks) were compared by one-way analysis of variance (ANOVA). When the value was found to be significant after an assessment using the ANOVA statistical test, the Tukey's post-hoc comparison was performed. Univariate and multivariate analyses were performed to determine the risk factors for tamsulosin dose escalation and lower score of patient-reported goal achievement. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Of the enrolled patients, 179 patients completed the

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Table 2. Changes in symptom scores including quality of life and uroflowmetric parameters after 12 weeks treatment of tamsulosin.

Variables[a]	Baseline	4-week Treatment	8-week Treatment	12-week Treatment	P value[b]
IPSS (total)	17.5 ± 7.0	13.6 ± 6.7	12.5±6.4	11.0 ± 6.4	< 0.001
Voiding subscore	10.4 ± 4.8	7.9 ± 4.4	7.4 ± 4.1	6.2 ± 4.1	< 0.001
Storage subscore	6.9 ± 3.4	5.7 ± 3.2	5.2 ± 2.9	4.8 ± 2.9	0.001
QoL	4.0 ± 1.0	3.1 ± 1.2	2.8 ± 1.2	2.5 ± 1.2	< 0.001
Qmax (ml/sec)	12.5 ± 5.8	14.8 ± 6.4	15.3 ± 5.2	16.3 ± 5.8	0.001
PVR (ml)	36.5 ± 55.0	27.5 ± 43.7[c]	26.8 ± 44.7[c]	17.9 ± 26.7	< 0.001

[a] Data are presented as mean ± SD or number

[a] Continuous variables were compared by independent samples *t*-test

[b] *P* value was determined by ANOVA test

[c] These values were not statistically different compared with that of baseline by Tukey's post-hoc analysis ($P > 0.05$)

Abbreviations: IPSS, international prostate symptom score; QoL, quality of life; Qmax, peak flow rate; PVR, post-void residual urine

study and reported their goal achievement score after 12 weeks of tamsulosin monotherapy. The reasons for dropping out of the study included a treatment failure (n = 14), adverse events (n = 6), a follow-up loss (n = 65), and PSA elevation (n = 8). The adverse events that occurred in the dropped-out patients were one case of each dizziness, fever, vomiting, and general weakness and two cases of ejaculatory disorders. The mean age, mean serum PSA level, and mean prostate size of the patients who completed the study are recorded in **Table 1**. Of the 179 patients, 42 patients set multiple goals (32 patients with 2 goals, 9 patients with 3 goals and 1 patient with 4 goals) and the goals set by the patients included the nocturia improvement (n = 63), weak urine stream improvement (n = 52), frequency improvement (n = 34), residual urine sense improvement (n = 27), hesitancy improvement (n = 22), well voiding (n = 21), urgency improvement (n = 11), and voiding-related discomfort improvement (n = 2).

After four weeks of treatment, the mean Qmax, and total IPSS values, as well as the mean QoL score, significantly improved, and the tamsulosin dose was escalated to 0.4 mg for 74 patients. The logistic regression analysis showed that less improvement in Qmax [odds ratio (OR) = 1.1, 95% confidence interval (CI): 1.0–1.2, $P = .043$] and that in PVR (OR = 1.0, 95% CI: 1.0–1.0, $P = .017$) were independent risk factors for tamsulosin dose escalation. After 8 and 12 weeks of treatment, all the parameters further improved (**Table 2**). After 12 weeks of treatment, the scores of patient-reported goal achievements were as follows: 5 in 21 patients (11.7%), 4 in 108 patients (60.3%), 3 in 33 patients (18.4%), 2 in 7 patients (3.9%), and 1 in 10 patients (5.6%). Higher score group had shorter mean duration of LUTS (16.4 vs 36.6 months, $P = .002$), lower pretreatment total IPSS (15.7 vs 18.6, $P = .017$), lower pretreatment IPSS voiding subscore (9.3 vs 11.4, $P = .014$), and lower pretreatment QoL score (3.8 vs 4.1, $P = .028$) than lower score group. Post-treatment total, voiding and storage subscores of IPSS and QoL were also significantly lower in higher score group compared to lower score group. Improvement of total, voiding and storage subscores of IPSS and QoL were significantly higher in higher score group. However, mean age, mean PSA level, mean

Table 3. Comparisons of demographic, medical and voiding characteristics between higher and lower score groups.

Variablesa	Higher score (n=129)	Lower score (n=50)	*P* value
Age (years)	60.1 ± 8.3	62.6 ± 7.1	0.063
Duration of LUTS (months)	16.4 ± 23.4	36.6 ± 43.8	0.002
Prostate volume (g)	32.3 ± 10.4	33.0 ± 13.0	0.745
PSA (ng/ml)	1.6 ± 2.0	1.8 ± 1.8	0.688
Pretreatment Qmax (ml/s)	13.4 ± 6.4	11.8 ± 5.3	0.142
Pretreatment PVR (ml)	30.3 ± 51.9	35.3 ± 40.7	0.537
Pretreatment IPSS (total)	15.7 ± 6.4	18.6 ± 6.9	0.017
Pretreatment IPSS (voiding)	9.3 ± 4.2	11.4 ± 5.4	0.014
Pretreatment IPSS (storage)	6.3 ± 3.3	7.1 ± 3.6	0.198
Pretreatment QoL	3.8 ± 0.9	4.1 ± 0.8	0.028
No. of goals	1.3	1.4	0.096
Posttreatment Qmax (ml/s)	15.6 ± 6.0	14.2 ± 6.9	0.252
Posttreatment PVR (ml)	22.3 ± 33.9	25.7 ± 24.8	0.509
Posttreatment IPSS (total)	11.5 ± 5.9	15.8 ± 6.7	< 0.001
Posttreatment IPSS (voiding)	6.7 ± 3.8	9.3 ± 4.6	< 0.001
Posttreatment IPSS (storage)	4.8 ± 2.7	6.5 ± 3.5	0.002
Posttreatment QoL	2.6 ± 1.1	3.7 ± 1.0	< 0.001
Δ Qmax (ml/s)	3.9 ± 5.1	3.5 ± 6.3	0.754
Δ PVR (ml)	-12.9 ± 42.1	-18.8 ± 37.3	0.447
Δ IPSS (total)	-7.2 ± 5.6	-2.9 ± 6.1	< 0.001
Δ IPSS (voiding)	-4.7 ± 3.9	-2.3 ± 4.9	0.006
Δ IPSS (storage)	-2.6 ± 2.6	-1.2 ± 2.8	0.007
Δ QoL	-1.9 ± 1.2	-0.6 ± 1.1	< 0.001
Cases of dose escalation	40 (31.0%)	19 (38.0%)	0.103

[a] Data are presented as mean ± SD or number

Abbreviations: LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen; Qmax, peak flow rate; PVR, post-void residual urine; IPSS, international prostate symptom score; QoL, quality of life

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Table 4. Logistic regression analysis to determine the predictive factors of patient-reported goal achievement (higher score).

	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Pretreatment IPSS	0.8 (0.2-1.8)	0.284	0.8 (0.2-1. 9)	0.169
Pretreatment QoL	10.0 (2.5-10.1)	0.001	8.6 (2.2-9.8)	0.002
Duration of LUTS	1.0 (0.9-1.0)	0.372	1.0 (0.7-2.0)	0.155
Posttreatment IPSS	1.1 (1.0-1.1)	0.230	1.3 (0.8-2.5)	0.113
Δ IPSS (total)	1.0 (1.0-1.0)	0.859	1.0 (0.8-1.4)	0.967
Δ IPSS (voiding subscore)	1.0 (0.9-1. 2)	0.889	1.0 (0.5-1.1)	0.948
Δ IPSS (storage subscore)	0. 9 (0.8-0.9)	0.872	1.0 (0.6-2.0)	0.996
Δ QoL	7.6 (2.0-10.5)	<0.001	6.7 (1.9-11.5)	0.001

Abbreviations: CI, confidence interval; IPSS, international prostate symptom score; QoL, quality of life; LUTS, lower urinary tract symptoms

prostate volume, pre- and post-treatment uroflowmetric parameters, the presence of underlying diseases, the number of goals, and the sorts of goals were not significantly different between higher and lower score groups (**Table 3**). Multivariate analysis revealed that pretreatment quality of life (OR = 8.6, 95% CI: 2.2-9.8) and improvement of quality of life (OR = 6.7, 95% CI: 1.9-11.5) were independent predictive factors of patient-reported goal achievement (**Table 4**). The most common adverse event was low blood pressure (systolic pressure < 110 mmHg) in 11 patients, and dizziness and ejaculatory disorder occurred in one patient each.

DISCUSSION

Although there is strong evidence for the benefit of combination therapy (α-blocker with 5-ARI), supported by several randomized, controlled trials, in terms of the symptom control, disease progression, and risk of BPH-related surgery,[11,12] monotherapy still constitutes the largest portion of medical therapy for BPH.(13,14-16) Among the drugs used as a monotherapy, □-blockers are the most common agents.[13,14-16] The availability of tamsulosin has been a major breakthrough for medical therapy of patients with BPH, due to comparable efficacy, fewer side effects, and a more optimal dose compared to previously existing α-blockers. With these advantages, monotherapy using α-blockers became more common after tamsulosin had been introduced to the clinical practice.[3]

The efficacy of α-blockers, including tamsulosin, has been usually evaluated by uroflowmetry and specially designed questionnaires, such as IPSS and AUASS, in many BPH-related studies.[17-20] Although these evaluation tools are well validated and objectively reflect the change of LUTS, they have limitations in evaluation of patients' subjective satisfaction and initial goal achievement after treatment. Since BPH is a chronic and refractory disease and medical therapy became a standard treatment for most BPH patients with mild to moderate LUTS, adherence to and persistence with therapy are considered important factors for the success of the treatment.[5,21] Therefore, assessment and prediction of the patient-reported goal achievement can be a useful indicator to predict patients' adherence to and persistence with medical therapy.

Schoenfeld et al. reported that only about 40% of the patients with BPH who initiated α-blocker monotherapy continued medication for six months, and about one-third of the patients continued it for one year.[5] However, Shortridge et al. reported that 63.5% of the patients who initiated combination therapy with α-blockers and 5-ARIs persisted with their medications for more than four years.[21] This can be explained by the fact that the addition of 5-ARIs can be more helpful in improving LUTS subjectively as well as objectively. Currently, anticholinergic agents and phosphodiesterase type 5 inhibitors are also available for medical therapy of BPH, and several studies have proven their efficacy.[1,22] In this situation, physicians should decide whether they will continue □-blocker monotherapy or add or change to other drugs after a short-term follow-up. Although several evaluating tools, such as uroflowmetry, IPSS, and voiding diary, can be helpful, patients' treatment goals and subjective satisfaction may also have important roles in determining the strategy. As seen in this study, patients with BPH have various treatment goals, including not only voiding symptoms but also storage symptoms. However, the currently available BPH-related evaluation tools, such as uroflowmetry and IPSS, may not reflect or assess patients' main treatment goals. Continuing the same medical therapy, with only improvements of uroflowmetric parameters and IPSS, regardless of patients' treatment goals and/or subjective satisfaction, can lead to early discontinuation of medical therapy and dropout of overall treatment.

Nocturia improvement was the most common treatment goal (27.2%) in this study, followed by the weak urine stream improvement (22.4%). Seventy-eight patients (43.6%) wanted to improve their storage symptoms as initial treatment goals. This indicates that not a few patients with BPH want to improve their storage symptoms. Traditionally, tamsulosin was considered to provide more effect on voiding symptoms, but recent studies have shown that tamsulosin monotherapy also has effects on storage symptoms.[23,24] In this study, more than 70% of all patients achieved scores of 4 or 5, and among the patients whose initial goals were the storage symptom improvement, nearly 70% also achieved scores of 4 or 5. In addition, the mean storage subscore of IPSS was also significantly improved by the medication over time. This demonstrated that tamsulosin monotherapy is effective for storage symptoms as well as for voiding symptoms in patients with BPH. Although only patients with a mild- to moderate-sized prostate were enrolled in the present study, this study confirmed that more than 70% of the patients with BPH were able to achieve their treatment goals (scores 4 or 5) after 12 weeks of tamsulosin monotherapy, regardless of their primary treatment goals. In addition, every parameter, including the total IPSS, voiding subscore, storage subscore, QoL, Qmax, and PVR, was significantly improved over time with tamsulosin monotherapy. However, nearly 30% of the patients did not

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achieve their primary treatment goals, even with dose escalation, although their objective parameters, such as IPSS, Qmax, and PVR, improved compared to the pretreatment state. Based on several previous studies, a relatively low dose of tamsulosin (0.2 mg daily) was recommended as the standard regimen for the treatment of LUTS in Asian patients with BPH.[7,9,25] However, recent studies have shown that tamsulosin at 0.4 mg once daily can be more effective for the patients who do not respond to 0.2 mg once daily, especially for the improvement of Qmax without any increase in cardiovascular events.[10,26] Therefore, all patients started tamsulosin at 0.2 mg daily as the initial dose, and the dose was escalated to 0.4 mg after four weeks of treatment if the patients did not demonstrate their LUTS improvement in this study. By the analysis of risk factors for dose escalation, our study showed that patients with less improvement of Qmax and PVR could have higher risks for dose escalation.

For the rest of the patients, who did not achieve their treatment goals (scores 1 or 2), a change in their treatment strategies needs to be considered, such as the addition or change of drugs, according to the state of their LUTS, even if their IPSS or uroflowmetric parameters significantly improved; otherwise, there may be a higher risk of discontinuation of treatment. Thus, the patient-reported goal achievement can be used to determine a change or addition of other drugs after initial treatment of patients with BPH/LUTS. However, this evaluating tool also has disadvantages. The patient-reported goal achievement usually reflects changes of patients' subjective symptoms. Although IPSS and uroflowmetric parameters tend to correlate with changes of subjective symptoms, some patients may complain about less improvement of their voiding symptoms even if their IPSS, Qmax, and PVR were significantly improved, or vice versa. Therefore this patient-reported goal achievement cannot be used alone for the evaluation of objective changes in patients with BPH/LUTS. In addition, this study demonstrated that patients with higher pretreatment QoL and less improvement of QoL may have fewer chances of goal achievement after medical therapy. Therefore, close monitoring will be needed for these patients, and changing the treatment strategy should be considered.

There are several limitations in this study. Although this study was performed prospectively based on multi-institutional patient enrollment, a case-controlled trial or comparative study with other BPH drugs was not conducted. In addition, patients with only mild- to moderate-sized prostate were enrolled, even though this was not intended. A relatively high dropout rate due to a follow-up loss and the lack of long-term follow-up results, can also be limitations of this study. However, to the best of our knowledge, this is the first trial to assess the patient-reported goal achievement after the treatment with tamsulosin monotherapy for patients with BPH. It can be the base of a new evaluation tool to increase the adherence to and persistence with medical therapy for BPH/LUTS. Based on the results of this study, a larger, population-based, longer-term follow-up and randomized controlled trial with/without other BPH drugs will be needed for the future study.

CONCLUSIONS

In conclusion, medical therapy with tamsulosin is safe and effective as an initial treatment for patients with BPH. Nocturia and a weak urine stream are the most common lower urinary tract symptoms that patients with BPH want to be relieved by the treatment. More than 70% of our patients reported satisfactory goal achievement after 12 weeks of tamsulosin monotherapy, regardless of the patients' treatment goals. This study demonstrated that the scores of pretreatment quality of life and improvement of quality of life can be important factors to predict the achievement of treatment goals.

CONFLICT OF INTERESTS

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