Neurourology and Urodynamics

Long-Term Efficacy of a Combination Therapy With an Anticholinergic Agent and an α1-Blocker for Patients With Benign Prostatic Enlargement Complaining Both Voiding and Overactive Bladder Symptoms: A Randomized, Prospective, Comparative Trial Using a Urodynamic Study

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Aims: We evaluated long-term efficacy and safety of a combination therapy (CT) with an anticholinergic agent and an α1-blocker for patients with benign prostatic enlargement (BPE) complaining of voiding and overactive bladder (OAB) symptoms, in comparison with those of α1-blocker monotherapy (MT), by conducting a urodynamic study (UDS). **Methods:** This was a randomized prospective study involving 120 outpatients with untreated BPE associated with urinary urgency at least once per week and OABSS of ≥3. The patients were randomly assigned to receive MT with silodosin at 8 mg/day or CT with silodosin at 8 mg/day and propiverine at 20 mg/day. Changes in parameters from baseline to 12 weeks and 1 year after administration were assessed based on IPSS, IPSS-QOL, OABSS, and voiding and storage functions as measured by UDS. **Results:** In efficacy analysis, 53 patients with MT and 51 with CT were included. Although mean IPSS and OABSS significantly improved in both groups, the CT group showed statistically significant improvement in OABSS (−3.4 in CT, −2.4 in MT, $P = 0.04$), IPSS-QOL (−1.9, −1.2, $P = 0.01$), and OAB-urgency score (−1.8, −1.2, $P < 0.01$) at the long-term evaluation. In storage function, both groups showed significant improvements, but the CT group demonstrated a greater improvement in terms of disappearance rate of detrusor overactivity (54.5% in CT, 34.2% in MT, $P = 0.07$) and bladder capacity (+61 mL, +33 mL, $P = 0.02$). **Conclusions:** Long-term combination treatment with silodosin and propiverine was effective and safe for BPE patients with voiding and OAB symptoms. *Neurourol. Urodynam.* © 2016 Wiley Periodicals, Inc.

Key words: alpha-1 blocker; anticholinergics; benign prostatic hyperplasia; combination therapy; overactive bladder; urodynamics

INTRODUCTION

The most common cause of lower urinary tract symptoms (LUTS) in men older than 50 years is benign prostatic hyperplasia (BPH).[1] LUTS associated with BPH have a significant negative effect on patient quality of life (QOL).[2,3] In particular, overactive bladder (OAB) symptoms such as urinary urgency, urinary frequency, nocturia, and occasionally, urgency urinary incontinence were reported to be more bothersome and more prone to reduce QOL than voiding and post-micturition symptoms.[4,5]

Approximately 50–75% of BPH patients with LUTS have OAB symptoms.[6] Alpha 1-blockers (α1-blockers) are widely prescribed for the management of LUTS associated with BPH. However, bothersome storage symptoms, which may be related to coexisting detrusor overactivity (DO) or increased filling sensation, may persist in some patients. We previously reported that failure to improve DO contributed to inadequate improvement of subjective symptoms after α1-blocker treatment in patients with BPH.[7]

In BPH patients with residual OAB symptoms despite α1-blocker monotherapy (MT), a combination use of anticholinergics is widely recommended in BPH guidelines in a number of countries.[8–10] Anticholinergics are widely used in the treatment of OAB, but considerations need to be taken in their use to BPH patients because of their presumed inhibitory effect on detrusor contractility and deterioration of voiding function.[11,12] Although several randomized studies have reported the efficacy of a combination therapy (CT) with an anticholinergic agent and an α1-blocker, their analyses were mainly based on symptomatic parameters.[13–16] In addition, only few papers have evaluated the changes in storage and voiding functions based on urodynamic study.[17,18] Almost all studies on α1-blocker/anticholinergics CT have short follow-up periods (usually 12 weeks), and none of these studies have assessed the outcomes of this combination for >4 months, in comparison with that of monotherapy.[19]

In this study, we performed a urodynamic study (UDS), including uroflowmetry, cystometrogram (CMG), and pressure flow study (PFS), in patients with benign prostatic enlargement

Abbreviations: α1-blocker, α1-adrenergic receptor blocker; BOO, bladder outlet obstruction; BOOI, bladder outlet obstruction index; BPH, benign prostatic hyperplasia; BPE, benign prostatic enlargement; CMG, cystometrogram; DO, detrusor overactivity; IPSS, international prostate symptom score; LUTS, lower urinary tract symptoms; OABSS, overactive bladder symptom score; OAB, overactive bladder; PdetQmax, detrusor pressure at maximum flow rate; PFS, pressure flow study; PSA, prostate specific antigen; PVR, post-void residual urine volume; Qmax, maximum urinary flow rate; QOL, quality of life; UDS, urodynamic study.

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(BPE) with LUTS accompanied by OAB (BPH/OAB) and evaluated not only short-term but also long-term efficacy and safety of CT, compared with those of MT with an α1-blocker.

MATERIALS AND METHODS

This was a single-center, randomized, prospective study. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and the protocol was approved by the ethics committee of Nagoya University Graduate School of Medicine. All the participants provided written informed consent before enrollment.

The study included treatment-naive men who visited our hospital with a chief complaint of both storage and voiding LUTS between August 2011 and June 2013. The inclusion criteria were as follows: total international prostate symptom score (IPSS) ≥ 8; IPSS-QOL score ≥ 3; total OAB symptom scores (OABSS) ≥ 3; urinary urgency episodes ≥ 1 per week; prostate volume ≥ 25 ml as determined based on transabdominal ultrasonography; maximum urinary flow rate (Qmax) < 15 ml/sec at voided volume of ≥ 100 ml; and residual urine < 150 ml; age ≥ 50 years. Patients were excluded if they received oral treatment with α1-blockers, anticholinergic agents, 5-α reductase inhibitor (5-ARI), antidepressants, anti-anxiety agents, or sex hormonal agents; had neurogenic bladder dysfunction, bladder calculi, or active urinary tract infection; and had severe cardiac disease, renal dysfunction (serum creatinine level ≥ 2 mg/dl), and hepatic dysfunction (aspartate and alanine aminotransferase concentrations more than twice the normal values). Prostate biopsy was performed in all patients who had prostate-specific antigen >4 ng/ml, and only patients without cancer were included in the study.

According to the target enrollment number, the expected mean difference (standard deviation) in the change in OABSS from baseline between the two groups was assumed to be 1.0 (0.1). Thus, we defined that the required sample size for determining this difference was 48 patients in each group when the two-sided α-level and power are assumed to be 5% and 90%, respectively. In consideration of a 20% dropout rate, 60 patients were required in each group for evaluation. In this prospective study, 120 patients who met the inclusion criteria were enrolled and assigned to receive MT with silodosin at 8 mg/day or CT with silodosin at 8 mg/day and propiverine at 20 mg/day by simple randomization using random number table. The starting dose of propiverine was 10 mg/day for the first month in consideration of safety. If no severe adverse effect was observed, 20 mg/day propiverine was administered subsequently.

To evaluate changes in subjective symptoms, the IPSS, IPSS-QOL, and OABSS were assessed at baseline, 12 weeks, and 1 year after the start of treatment. The patients also underwent UDS, including uroflowmetry, CMG, and PFS for evaluation of objective findings at baseline, 12 weeks, and 1 year after treatment. First desire to void (FDV), maximum cystometric capacity (MCC), and DO were assessed as parameters of storage function, and Qmax, post-void residual urine volume (PVR), detrusor pressure at Qmax (PdetQmax), and bladder outlet obstruction index (BOOI) were evaluated as parameters of voiding function. Patients were excluded from the analysis if they discontinued the treatment due to incidence of adverse reactions or if data of urodynamic assessments until 12 months of treatment were not collected.

CMG and PFS were performed by two of the present researchers (YM and ST) according to the standard methods defined by the International Continence Society.[20,21] Specifically, a 6-Fr single pig-tail catheter (Cook Urological) was transurethrally inserted into the bladder for the monitoring of intravesical pressure. In addition, an 8-Fr catheter was inserted into the bladder to inject physiological saline. Measurements were performed in a standing position. After emptying the bladder, physiological saline was injected into the bladder at 50 ml/min, and intravesical pressure, abdominal pressure, and detrusor pressure were measured simultaneously. When patients felt a maximal desire to void, the infusion catheter was withdrawn, and 6-Fr catheter was left to measure intravesical pressure, abdominal pressure, and detrusor pressure, and urinary flow simultaneously. The data from the UDS were deidentified and analyzed independently by two of our research group members (YF and MK) who were not involved in the UDS.

All statistical values were represented as mean ± standard deviation. The Wilcoxon rank-sum test, Student-*t* test, and χ^2 test were performed to evaluate changes in subjective symptoms, including IPSS, OABSS, and objective findings obtained by CMG and PFS. All tests were two-sided, and a *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed by using the SPSS software (IBM, Armonk, NY).

RESULTS

We randomly divided 120 patients into two groups (the MT and CT groups), which consisted of 60 patients, respectively. Of the 60 patients in each group, 4 (6.7%) discontinued treatment owing to adverse reactions, which included dry mouth (n = 1), post-ural hypotension (n = 2), and dizziness (n = 1) in the MT group, and 7 (11.7%) discontinued treatment owing to dry mouth (n = 3), constipation (n = 3), and dizziness (n = 1) in the CT group. Other six patients (10%) in the MT and five patients (8.3%) in the CT complained of ejaculatory dysfunction disorder, but continued treatment. None of the patients had urinary retention during the study period in both groups. No significant difference in the incidence of adverse effects was found between the two groups. UDS was not performed after initiating treatment in three patients in the MT group and in two patients in the CT group. As a result, the analysis included 53 patients with a mean age of 70.0 years in the MT group and 51 patients with a mean age of 70.7 years in the CT group. All of the patients were Japanese. The patients' characteristics at baseline are shown in Table I. At baseline, no significant difference was detected in the IPSS, IPSS-QOL, or OABSS between the two groups. Comparison of the baseline data obtained from UDS revealed no significant differences in FDV, MCC, Qmax, PdetQmax, PVR, and BOOI.

The changes in subjective symptoms and objective findings are summarized in Tables II and III and Figures 1 and 2. Significant decrease was observed in the total IPSS, IPSS sub-scores for voiding and storage symptoms, IPSS-QOL score, OABSS, and OABSS-urgency sub-score at 12 weeks after treatment initiation in both groups. Although further improvements were observed until after 1 year in the CT group for all parameters, the improvement effect in the total IPSS and IPSS-QOL score slightly changed for worse in the MT group. The improvement in the total IPSS, IPSS-QOL score, and OABSS in the CT group was greater as compared with that in the MT group. In particular, the mean change from the baseline total OABSS at 1 year were -2.4 in the MT group and -3.4 in the CT group. The CT group showed a greater statistically significant improvement in OABSS ($P = 0.04$), OAB-urgency score ($P < 0.01$), and IPSS-QOL ($P = 0.01$) than the MT group at the evaluation after 1 year of treatment (Table II and Fig. 1).

TABLE I. Background Between the Two Groups Before Administration

	MT group α1-blocker monotherapy	CT group α1-blocker + anticholinergics	
	Mean ± SD	Mean ± SD	*P*
n	53	51	
Age (years)	70.0 ± 6.6	70.7 ± 7.1	0.40
ProstateVol (ml)	47.3 ± 18.2	44.1 ± 16.4	0.34
IPSS	18.6 ± 6.6	18.4 ± 5.6	0.84
QOL	4.8 ± 0.8	4.9 ± 0.8	0.59
OABSS	7.7 ± 2.6	7.6 ± 2.2	0.91
FDV (ml)	102 ± 37	102 ± 50	0.99
MCC (ml)	215 ± 70	208 ± 75	0.61
Qmax (ml/sec)	7.8 ± 4.3	7.9 ± 3.7	0.85
Rv (ml)	53 ± 42	46 ± 44	0.42
Pdet Qmax (cmH20)	74.8 ± 14.7	72.9 ± 19.4	0.57
BOOI	59 ± 18	57 ± 23	0.59
Prevalence of DO	35/53 (66.0%)	33/51 (64.7%)	0.72

As for voiding function obtained from UDS, both groups showed significant improvements in PdetQmax and BOOI after 12 weeks and 1 year (Table III and Fig. 2). At baseline, 46 (86.8%) and 43 patients (84.3%) in the MT and CT groups showed BOO (BOOI > 40), respectively, while the number of the patients with BOO on PFS decreased to 20 patients after 1 year in each group (37.7% and 39.2%, respectively), showing a substantial improvement. No statistically significant difference in the improvement in BOO was observed between the two groups. Meanwhile, the PVR significantly decreased in the MT group but significantly increased in the CT group; residual urine volume decreased from the baseline by 20 ml (range −9 to +64 ml) after 1 year in the MT group, but significantly increased by 20 ml (range −51 to +140 ml) after 1 year in the CT group (Table III and Fig. 2).

As for storage function, FDV and MCC significantly improved in both groups (Table II and Fig. 2). The improvement in bladder capacity was significantly greater in the CT group than in the MT group at 12 weeks and 1 year. DO observed before treatment disappeared in 28.6% and 51.5% of the patients in the MT and CT groups, respectively, at 12 weeks after treatment (Fig. 2). The reduction in the prevalence of DO was significantly greater in the CT group than in the MT group ($P = 0.04$). In the long-term evaluation at 1 year, the disappearance rate of DO in the CT

TABLE II. The Changes in Subjective Symptoms Between the Two Groups

	α1-Blocker monotherapy		α1-Blocker + anticholinergics combination therapy		
	Mean ± SD (difference in mean change from baseline)	*P* (intra-group)	Mean ± SD (difference in mean change from baseline)	*P* (intra-group)	*P* (inter-group)
N	53		51		
IPSS					
Before	18.6 ± 6.6		18.4 ± 5.6		
12 Weeks	12.4 ± 6.1 (−6.2)	<0.001	11.8 ± 6.2 (−6.6)	<0.001	0.71
1 Year	13.3 ± 8.1 (−5.3)	<0.001	11.0 ± 5.1 (−7.5)	<0.001	0.09
IPSS-voiding					
Before	10.0 ± 4.9		9.6 ± 4.1		
12 Weeks	6.4 ± 4.5 (−3.6)	<0.001	6.0 ± 4.1 (−3.6)	<0.001	0.93
1 Year	7.1 ± 5.2 (−2.9)	0.003	5.6 ± 3.4 (−4.0)	<0.001	0.16
IPSS-storage					
Before	8.6 ± 2.5		8.8 ± 2.1		
12 Weeks	6.0 ± 2.6 (−2.6)	<0.001	5.8 ± 2.9 (−3.0)	<0.001	0.45
1 Year	6.2 ± 3.4 (−2.4)	<0.001	5.4 ± 2.4 (−3.4)	<0.001	0.09
IPSS-QOL					
Before	4.8 ± 0.8		4.9 ± 0.8		
12 Weeks	3.2 ± 1.0 (−1.6)	<0.001	3.4 ± 1.3 (−1.5)	<0.001	0.52
1 Year	3.6 ± 1.2 (−1.2)	<0.001	3.0 ± 1.2 (−1.9)	<0.001	0.01
OABSS					
Before	7.7 ± 2.6		7.6 ± 2.2		
12 Weeks	5.4 ± 2.5 (−2.3)	<0.001	4.7 ± 2.3 (−2.9)	<0.001	0.14
1 Year	5.2 ± 2.6 (−2.4)	<0.001	4.2 ± 2.2 (−3.4)	<0.001	0.04
OABSS-urgency					
Before	3.0 ± 1.9		3.0 ± 1.0		
12 Weeks	1.9 ± 1.1 (−1.1)	<0.001	1.4 ± 1.0 (−1.6)	<0.001	0.01
1 Year	1.8 ± 1.2 (−1.2)	<0.001	1.2 ± 1.0 (−1.8)	<0.001	0.006

TABLE III. The Changes in Objective Findings Between the Two Groups

	α1-Blocker monotherapy	P (intra-group)	α1-Blocker + asnticholinergics combination therapy	P (intra-group)	P (inter- group)
N	53		51		
FDV (ml)					
Before	102 ± 37		102 ± 50		
12 Weeks	128 ± 36 (+26)	<0.001	145 ± 53 (+43)	<0.001	0.03
1 year	133 ± 32 (+31)	<0.001	150 ± 48 (+47)	<0.001	0.11
MCC (ml)					
Before	215 ± 70		208 ± 75		
12 Weeks	243 ± 67 (+28)	0.04	259 ± 84 (+51)	0.001	0.04
1 Year	248 ± 50 (+33)	0.005	269 ± 92 (+61)	<0.001	0.02
B-comp (ml/cmH2O)					
Before	16.5 ± 21.3		13.9 ± 15.8		
12 Weeks	20.8 ± 16.9 (+4.3)	0.25	21.4 ± 30.2 (+7.5)	0.12	0.49
1 Year	20.2 ± 16.2 (+3.7)	0.31	26.3 ± 26.9 (+12.4)	0.005	0.05
Qmax (ml/sec)					
Before	7.8 ± 4.3		7.9 ± 3.7		
12 Weeks	9.9 ± 3.7 (+2.1)	0.006	9.4 ± 4.4 (+1.5)	0.06	0.23
1 Year	10.1 ± 3.8 (+2.3)	0.003	9.6 ± 4.4 (+1.7)	0.03	0.27
PdetQmax (cmH2O)					
Before	74.8 ± 14.7		72.9 ± 19.4		
12 Weeks	58.0 ± 16.6 (−16.8)	<0.001	60.0 ± 18.3 (−12.9)	<0.001	0.09
1 Year	58.9 ± 16.2 (−15.9)	<0.001	57.8 ± 15.4 (−15.0)	<0.001	0.71
PVR (ml)					
Before	53 ± 42		46 ± 44		
12 Weeks	32 ± 38 (−21)	0.009	69 ± 58 (+23)	0.03	<0.001
1 Year	35 ± 35 (−17)	0.02	66 ± 54 (+20)	0.04	<0.001
BOOI					
Before	59.3 ± 18.0		57.1 ± 23.2		
12 Weeks	38.1 ± 20.1 (−21.2)	<0.001	41.1 ± 23.1 (−15.9)	<0.001	0.06
1 Year	38.7 ± 19.8 (−20.7)	<0.001	38.6 ± 20.4 (−18.5)	<0.001	0.45
DO case, disappearing rate (%)					
Before	35/53		33/51		
12 Weeks	25/53 (28.6%)	0.04	16/51 (51.5%)	<0.001	0.04
1 Year	23/53 (34.2%)	0.02	15/51 (54.5%)	<0.001	0.07

group tended to be superior to that in the MT ($P = 0.07$; 54.5% vs. 34.2%).

DISCUSSION

This is the first study to evaluate the long-term efficacy of CT with an anticholinergic agent and an α1-blocker in BPH/OAB patients based on subjective symptoms and urodynamic findings, in comparison with those of MT with a α1-blocker. Drake et al.[19] reported that long-term (52 weeks) treatment with an anticholinergic agent (solifenacin) and an α1-blocker (tamsulosin) was well tolerated and efficacious in men with LUTS in the NEPTUNE study. However, they evaluated the long-term efficacy and safety of CT in a single-arm trial, without comparison with MT. We showed not only the subjective efficacy but also the objective efficacy based on urodynamic finding of the CT in comparison with those of the MT, both in the short- and long-terms. In this study, the improvement in the total IPSS, IPSS-storage, and IPSS-voiding sub-score at 12 weeks in the MT group returned to be worse in the long-term. By contrast, the further improvement in these scores was sustained in the long-term in the CT group. The actual difference was small such as 0.4 points in IPSS or 0.6 points in OABSS at the evaluation of 12 weeks. But the difference of improvement increased furthermore (i.e., 2.2 points in IPSS, 1.0 points in OABSS) at the long-term. Especially, as for OABSS, it has been reported that the minimum clinically important change (MCIC) for the OABSS is 3.0 points,[22] meaning that a change in the OABSS of more than 3.0 points is a clinically significant or beneficial improvement for OAB patients. In the present study, the mean change in the OABSS was −3.4 in the CT group whereas −2.4 in the MT group at the long-term evaluation. This suggests that CT is clinically beneficial to BPH/OAB patients, but MT is not. Additionally, in the objective evaluation, storage functions such as bladder capacity and the prevalence of DO improved significantly in both groups, while the improvement was greater in the CT group. In addition, voiding function such as BOOI and Qmax improved significantly in both groups in the short- and long-terms, without significant difference between the two groups. Although PVR increased significantly in only the CT group (mean increase of 20 ml), only seven patients (13.7%) had an increase of PVR of more than 50 ml, and mean increased volume of 20 ml is thought to be clinically insignificant. Regarding adverse effects, no significant difference was observed between the two groups, and none of the patients had urinary retention in both groups. Based on these results, the long-term CT with an anticholinergic agent and an α1-blocker appeared to be safe and more effective than MT with a α1-blocker in terms of improving LUTS, QOL, and storage function. In meta-analysis of studies that compared the two pharmacotherapies for BPH/OAB, although the CT was reported to be dominated by storage symptoms and QOL in many studies in the short-term evaluation, these findings tend to consolidate those from the long-term evaluation according to this paper.[13]

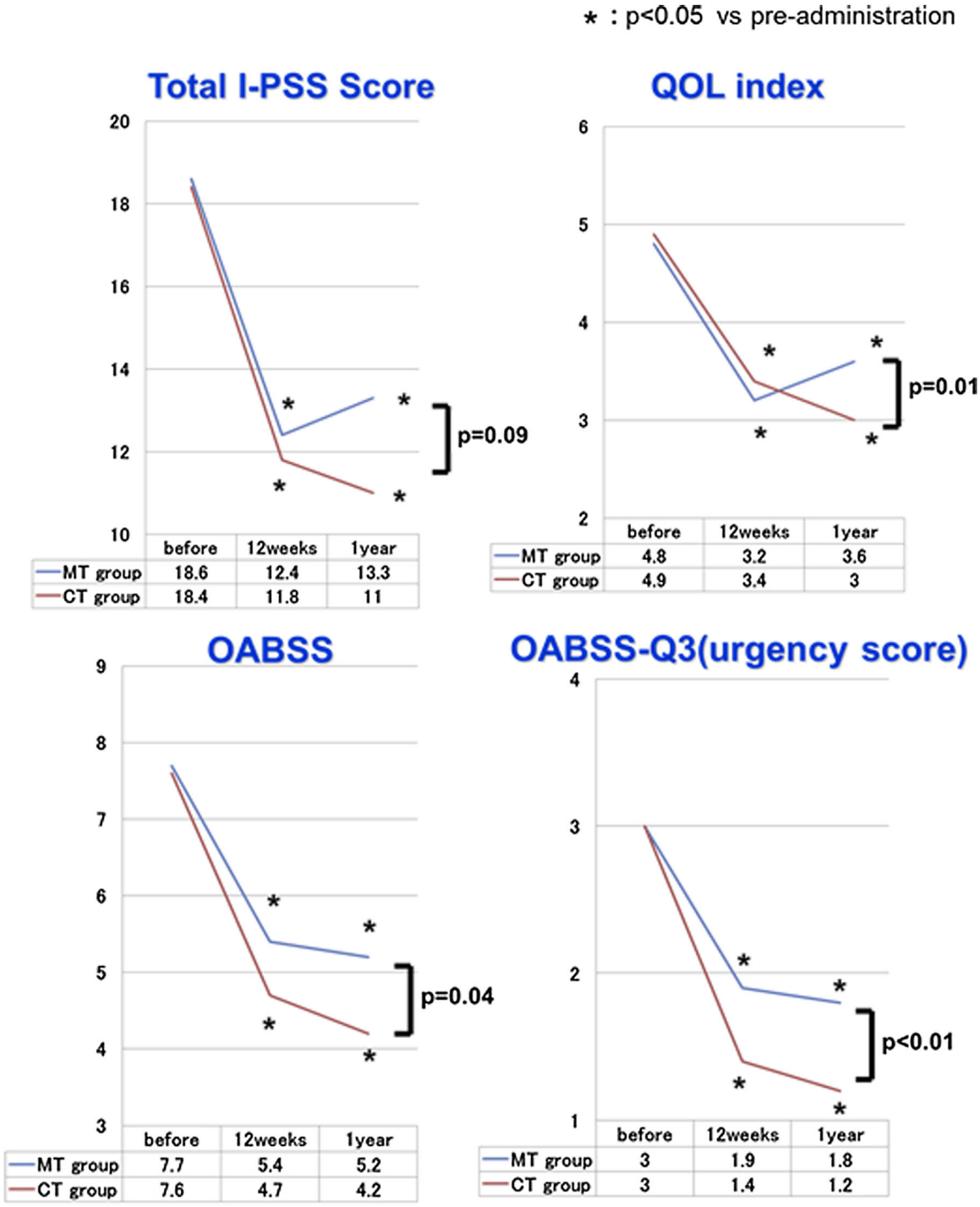

Fig. 1. The changes in subjective symptoms (total-IPSS, IPSS-QOL, OABSS, and OABSS-urgency score).

Historically, the use of anticholinergic agents in BPH/OAB patients has been limited because of concerns about the risk of voiding dysfunction and urinary retention. However, the previous clinical studies such as the NEPTUNE study and ASSIST study showed that the treatment using anticholinergics did not increase clinical risk of urinary retention.[14,23] In this study, it is interesting to note that none of the patients in the CT group had urinary retention in the long-term, despite their median prostate volume of 44.1 ml, 43 (84.3%) of the 51 patients in the CT group had BOO (BOOI > 40) at baseline. The use of anticholinergics with an α1-blocker seems to be safe and effective for long-term use in BPE patients with OAB and BOO.

We previously reported that a failure to improve DO contributed to inadequate improvement of subjective symptoms after α1-blocker treatment in patients with BPH.[7] In a large population-based study, Agarwal et al.[24]

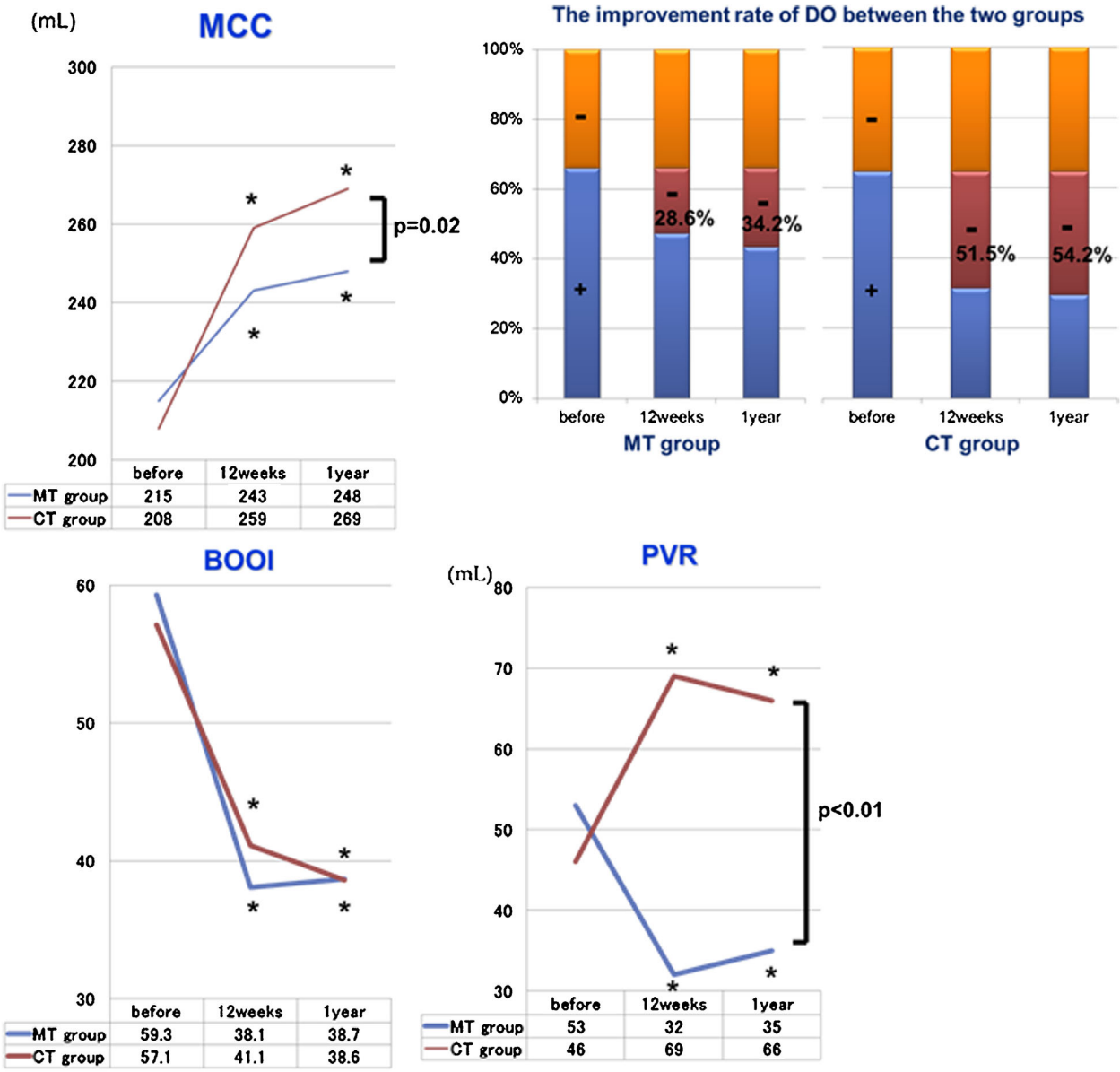

Fig. 2. The changes in objective findings on UDS (MCC, DO, BOOI, and PVR).

reported that urinary urgency was the most common troublesome symptom. In this study, long-term total IPSS and IPSS-QOL worsened in the MT group after initial improvement at 12 weeks, but further improvement was sustained in the CT group. In this background, the improvements in storage symptom and function such as urinary urgency and DO were thought to be more important factors to achieve patient satisfaction in the treatment of LUTS. Most of the clinical studies of CT with an α1-blocker and an anticholinergic agent have been conducted in the manner that an anticholinergic agent is added on after initial treatment by an α1-blocker, and this add-on CT is a common way to treat BPH/OAB patients in real clinical setting.[23,25] However, the results of the present study suggest that initial administration of both an α1-blocker and an anticholinergic agent will provide a significant advantage to BPH/OAB patients with a minimal risk.

The present study has several limitations. Firstly, this was an open-label and not a placebo-controlled study. Therefore, placebo effects cannot be completely excluded in terms of changes in subjective symptoms as well as UDS evaluation. Additionally, the habituation effect may appear in repeated urodynamic examinations. However, we think these effects are minimal and do not cause a major problem in the objectivity of the present study. Furthermore, observer bias when analyzing UDS may have been present, but we believe that this did not seriously affect out study outcomes because the data from UDS were analyzed independently by two of our research group members who were not involved in UDS. Another limitation is that the follow-up period of the present study was only 1 year. Since pharmacotherapy for LUTS should generally been continued for much longer period, further long-term efficacy and safety of CT need to be clarified in future studies. In addition, the efficacy and safety of a β3-adrenoceptor in

comparison with those of an anticholinergic agent for the treatment of BPH/OAB will be an issue in the future.

CONCLUSIONS

Long-term treatment with silodosin and propiverine significantly improved not only subjective symptoms but also storage function and bladder outlet obstruction in BPE patients with voiding and OAB symptoms. Long-term efficacy of CT is more effective than MT in subjective symptoms and objective storage function, and there is no difference in the improvement of voiding function between CT and MT. Initial CT will be a reasonable choice of treatment for BPH patients complicated with OAB.

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