



Incidence and risk factors of recurrence of overactive bladder symptoms after discontinuation of successful medical treatment

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Purpose: To identify incidence and risk factors of recurrence after discontinuation of successful antimuscarinic therapy in patients with overactive bladder (OAB).

Materials and Methods: This was a prospective, multicenter trial. Patients who had antimuscarinic agents for more than 12 weeks and showed successful response were enrolled. Successful response was defined as answering 'benefit' for patient perception of treatment benefit and answer lesser than 3 points in patient's perception of bladder condition (PPBC). The enrolled patients discontinued the antimuscarinics, and we evaluated their recurrence with PPBC and OAB symptom score (OABSS) at 1, 3, 6, and 12 months. Primary purpose was to identify the recurrence rate and secondary purpose was to reveal risk factors.

Results: Four hundred forty-one patients enrolled and 371 patients completed 6-month follow-up. The enrolled patients showed 1.6 points in PPBC, 2.9 points in OABSS and 1.4 points in IPSS (quality of life) which represented successful response after using antimuscarinics. The cumulative rates of recurrence were 25.6%, 42.3%, and 52.2% at 1, 3, 6 months, respectively. Among 177 patients who did not show recurrence at 6 months, 41 patients were followed up and 4 patients of the 41 patients (9.7%) showed recurrence at 12 months. On univariate and multivariate analyses of recurrence, OAB wet was the risk factor for recurrence after 6 months of discontinuation.

Conclusions: Discontinuation of antimuscarinic therapy after successful treatment resulted in high recurrence rate with time and OAB wet was the independent risk factor for recurrence.

Keywords: Antimuscarinic treatment; Overactive bladder; Recurrence

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INTRODUCTION

Overactive bladder (OAB) is defined as urinary frequency, urgency with or without urgency incontinence usually with nocturia [1]. Antimuscarinic treatment, such as fesoterodine, tolterodine, oxybutynin and solifenacin are considered the primary treatment for OAB [2] and the antimuscarinic drugs are highly effective in management of the OAB symptoms [3,4]. The recurrence rate of OAB symptom after discontinuation of the antimuscarinic treatment was high [5] and longer persistence of OAB medication was important to maintain improved state of symptom [6,7]. Interestingly many patients who showed satisfactory for the OAB symptoms might wonder how long they should maintain the medication. However, time point at which to stop the medication and duration which maintained therapeutic effect after discontinuation of the agents due to successful control of OAB symptom have not yet been demonstrated. Furthermore, there was no report for risk factors of recurrence of OAB symptom after discontinuation of antimuscarinic drugs because of successful treatment in mid-term follow-up. Therefore we investigated the incidence and risk factors of symptom recurrence after discontinuation of successful antimuscarinic therapy in patients with OAB.

MATERIALS AND METHODS

This was a prospective, multicenter study conducted at 14 hospitals. Study protocol was approved by the Institutional Review Board of each center and written informed consent was received from all participants (approval number: 2013-0943).

Patients who had antimuscarinic agents due to OAB for more than 12 weeks and showed successful response were screened. The patients should be older than 18 years old, patients who had plan to change medications, such as alpha-blocker, 5 alpha-reductase inhibitor, antihistamine, antidepressant and the patients who took different types of antimuscarinic agents simultaneously were excluded. The male patients who showed prostate specific antigen (PSA) ≥ 10 ng/mL and patients who had any neurogenic problems were also excluded. Successful response was defined as answering 'benefit' for patient perception of treatment benefit (PPTB) questionnaire and answer lesser than 3 points in patient's perception of bladder condition (PPBC) questionnaire simultaneously.

The enrolled patients discontinued the antimuscarinic agent their recurrence of OAB symptoms was evaluated at

baseline, 1, 3, 6 months and limited patients were followed up until 12 months. They were asked to record PPTB, PPBC, OABSS and quality of life of International Prostate Symptom Score (IPSS-QoL) questionnaires at baseline, 1, 3, 6, and 12 months in order to evaluate the change of OAB symptom and QoL. The recurrence of OAB was defined as ≥ 4 points in PPBC and increase of OABSS ≥ 3 than baseline at the time of discontinuation of medication. To identify risk factors of recurrence of OAB symptom, patients' clinical characteristics, all the questionnaires, uroflowmetry parameters and 3-day voiding diary before starting antimuscarinic treatment were analyzed.

Student t-test and analysis of variance were used to compare age, sex, symptom duration, voiding diary variables, diabetes mellitus (DM) (yes or no), OAB type (wet or dry) and uroflowmetry parameters. We used the chi-square test, univariate and multivariate logistic regression to assess the relationship between OAB symptom recurrence and the variables. All statistical analyses were performed using the SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA) and p value < 0.05 was considered statistically significant.

RESULTS

A total 446 patients were screened and 441 patients enrolled. After discontinuation of antimuscarinic agents, 70 patients (15.8%) were excluded due to follow-up loss; 41, 19, and 9 patients at 1, 3, and 6 months, respectively. At time of discontinuation of antimuscarinic treatment, enrolled patients showed 1.6 points in PPBC, 2.9 points in OABSS and 1.4 points in IPSS (QoL) which represented successful response of antimuscarinic agents. Finally, 371 patients (84.2%) (male, 74; female, 297) completed follow-up until 6 months. Their mean age was 60.2 ± 13.1 years and the mean duration of symptoms 18.2 ± 20.4 months. Among the 371 patients, 76 patients (20.4%) had DM and 177 patients (47.7%) showed OAB wet. They showed 9.9 ± 2.5 times/d of urinary frequency, 4.2 ± 2.8 times/d of urgency episodes, 0.8 ± 1.1 times/d of urinary urgency incontinence episodes and 3.4 ± 1.0 points of urgency grade before antimuscarinic treatment. Their mean maximum flow rate (mL/s) was 22.7 ± 7.7 and postvoided residual urine (mL) was 32.2 ± 29.5 in uroflowmetry before antimuscarinic treatment (Table 1).

After discontinuation of antimuscarinic agents, 95, 62, and 37 patients showed recurrence of OAB symptoms at 1, 3 and 6 months, respectively and the cumulative rate of symptom recurrence was 23.8%, 41.3% and 52.9% at 1, 3, and 6 months, respectively. After discontinuation of medication their symptom scores significantly increased after 1 month

Table 1. Comparison of patient’s characteristics according to the OAB symptom recurrence at 6 months

Characteristic	Total	No recurrence	Recurrence	p-value
No. of patients	371	177	194	
Sex				0.020
Male	74	48 (67.6)	26 (32.3)	
Female	297	136 (46.2)	161 (53.7)	
Age at diagnosis (y)	60.2±13.1	59.2±12.9	61.2±13.4	0.305
Diabetes mellitus				0.269
No	295	154	141	
Yes	76	35	41	
Duration of symptom (mo)	18.2±20.4	19.1±19.3	17.4±21.6	0.592
OAB type				0.005
OAB dry	194	117 (64.7)	67 (35.2)	
OAB wet	177	73 (42.3)	104 (57.6)	
Diary variables per 24 hr (at diagnosis)				
Frequency	9.9±2.5	10.2±2.5	9.6±2.4	0.217
Urgency episodes	4.2±2.8	4.4±3.1	4.0±2.4	0.511
UUI episodes	0.8±1.1	0.8±1.2	0.8±1.0	0.886
Urgency grade	3.4±1.0	3.5±1.0	3.2±1.0	0.200
Uroflowmetry (at diagnosis)				
Maximum flow rate (mL/s)	22.7±7.7	22.3±8.5	23.5±5.9	0.508
Postvoided residual urine (mL)	32.2±29.5	31.0±30.3	34.5±28.8	0.848

Values are presented as number (%) or mean±standard deviation. OAB, overactive bladder; UUI, urinary urgency incontinence.

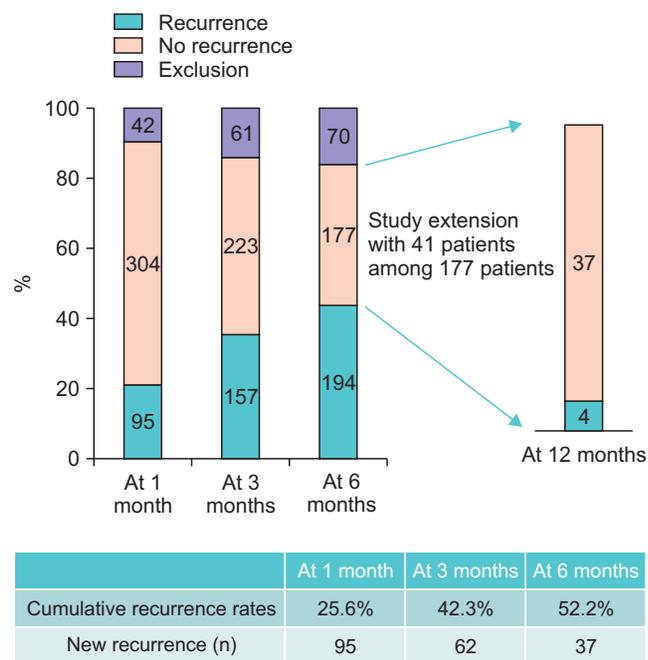


Fig. 1. Cumulative rates and new cases of overactive bladder symptom recurrence after discontinuation of antimuscarinic treatment.

of discontinuation; from 16 to 22 in PPBC, from 2.9 to 3.9 in OABSS, from 1.4 to 1.8 in IPSS (QoL). The recurrence rate of symptoms was high within 1 month and afterwards gradually decreasing with time. Among 177 patients who did

not show OAB symptom recurrence at 6 months, 41 patients were followed up until 12 months. Four patients (9.7%) of the 41 patients showed OAB symptom recurrence at 12 months (Fig. 1).

When we compared patients with or without recurrence of OAB symptom, we found no significant differences between these 2 groups in age, DM status, duration of OAB symptoms, variables in voiding diary and parameters in uroflowmetry. However, there were significant differences of symptom recurrence in sex (male 32.3% vs. female 53.7%, $p=0.020$) and OAB type (OAB dry 35.2% vs. OAB wet 57.6%, $p=0.005$) (Table 1). On multivariate analysis of symptom recurrence, OAB wet was an independent risk factor for symptom recurrence after 6 months of discontinuation of successful antimuscarinic treatment (odds ratio, 2.265; 95% confidence interval, 1.137–4.509, $p=0.020$) (Table 2).

DISCUSSION

OAB is one of the most frequent urological disorders [8,9] and large scale, randomized, placebo-controlled studies have shown that patients receiving antimuscarinic treatment report significant reductions in OAB symptoms [10,11]. Interestingly, it is very common to observe patients wondering the duration of maintenance of the therapy after

Table 2. Uni- and multivariate analyses on predictors of symptom recurrence at 6 months

Variable	Univariate	Multivariate analysis	
	p-value	OR (95% CI)	p-value
Age	0.304		
Sex	0.029		0.225
Men		Reference	
Women		1.687 (0.725-3.927)	
Duration of symptom	0.590		
Diabetes mellitus	0.420		
OAB type	0.007		0.020
OAB dry		Reference	
OAB wet		2.265 (1.137-4.509)	
Uroflowmetry			-
Maximum flow rate	0.504	-	
Postvoided residual urine	0.846	-	
Voiding diary			-
Frequency (/d)	0.216	-	
Urgency episodes (/d)	0.508	-	
UUI episodes (/d)	0.884	-	
Urgency grade (mean)	0.199	-	
Symptom questionnaires			-
PPBC	0.608	-	
OABSS	0.606	-	
IPSS (QoL)	0.359	-	

OR, odds ratio; CI, confidence interval; OAB, overactive bladder; UUI, urinary urgency incontinence; PPBC, patient’s perception of bladder condition; OABSS, OAB symptom score; IPSS, International Prostate Symptom Score; QoL, quality of life.

improvement of OAB symptom. However the duration of its sustained therapeutic efficacy after successful treatment has not been demonstrated by well constructive longitudinal long-term follow-up studies. Therefore we demonstrated incidence and risk factors of recurrence of OAB symptom after discontinuation of the antimuscarinic treatment. To our knowledge, this is the first prospective long-term study for that issue.

Importantly we designed the study according to usual situation in outpatient clinic in order to apply our study results to daily practice. The enrolled OAB patients discontinued the antimuscarinic treatment of 12 weeks if they showed improvement of symptom. Afterward we observed the recurrence of OAB symptom at 1, 3, 6, and 12 months. We used patients reported outcome, such as OABSS and PPBC to evaluate recurrence of OAB symptoms. As a result, the cumulative rate of recurrence of OAB symptoms 25.6%, 42.3%, and 52.2% at 1, 3, and 6 months, respectively. The results represented that recurrence of OAB symptoms was most frequently observed at 1 month (n=95), afterward the number of patients with new recurrence of OAB symptoms decreased to 62 patient at 3 months and to 37 patients at 6 months. Furthermore we could see the

significant aggravation of OAB symptoms after 1 month of discontinuation of antimuscarinic agents and the aggravated symptoms persisted until 6 months without change. Interestingly, patients who did not show symptom recurrence until 6 months tended to persist the status until 12 months of discontinuation of the therapy. Two previous studies also showed similar high recurrence rate of OAB symptom, however they had small cohort with only women (n=68, 108) and short follow-up period of discontinuation (1, 3 months) [5,12]. In those studies the authors demonstrated risk factors of recurrence of OAB symptoms, such as health-related quality of life, old age and urgency scores. We demonstrated that female sex and OAB wet were risk factors for recurrence of OAB symptom, therefore we investigated the incidence of OAB wet in each sex. We found that there was significant difference for the incidence of OAB wet in sex (male 26.5% vs. female 53.1%, p<0.05). High incidence of OAB wet in female could affect the results that sex (female) was a risk factor for the recurrence of OAB symptom. We demonstrated that OAB wet was only one independent risk factor for the recurrence of OAB symptom through multivariate analysis. The DM was also reported as one of the important factor for OAB symptom [13], however

it was not independent factors for the recurrence of OAB symptom in the present study. Based on the retrospective review of our cohort, almost patients (98%) in DM patients in our cohort showed normal level of blood sugar. We guess the patients might be active hospital visitors, therefore they managed blood sugar level and OAB symptom.

The clinical information can help us when we use antimuscarinic agents to treat OAB patients. Because many patients who showed improvement for the OAB symptoms might wonder how long they should maintain the medication. With OAB wet, a person may be unable to stop leakage before reaching the toilet. It has significant effects on health-related QoL in both men and women, affecting their ability to work, physical activity, sexual function, and sleep [14-16]. When we treated the female patients with OAB wet, long-term maintenance of antimuscarinic agents should be recommended based on the result from the present study.

These OAB symptoms could be controlled but not cured. There are several hypotheses for recurrence of OAB symptom after successful response. Detrusor overactivity (DO) is frequently associated with OAB symptoms and is urodynamically characterized by involuntary detrusor contractions during bladder filling [17]. DO and OAB do not always coexist, but one study reported that more than 80% of patients with DO had symptoms of OAB, and more than 60% of patients with OAB symptoms had DO. The causes of DO are multifactorial and might involve both peripheral and central signaling [18-20]. It has been suggested that antimuscarinic drugs act at muscarinic receptors on detrusor muscle cells to reduce spontaneous myocyte activity during the storage phase [21,22] which meant that the drug could not manage of central signaling. Another hypothesis which was involved with systemic etiology of OAB suggested that reduction of OAB symptom was associated the reduction in urinary nerve growth factor (NGF) levels in successfully treated patients with OAB [23]. However the level of NGF/creatinine increased after 1 month of discontinuation of antimuscarinic treatment. The result might be due to incomplete resolution of the underlying pathophysiology for OAB, such as existence of a residual inflammation in the central nerve system (CNS) [24]. Furthermore, because muscarinic receptor over-expression is not the only one cause of OAB, some bladder etiology responsible for OAB that do not involve the muscarinic receptor pathways might not be affected by antimuscarinic treatment. On the other hand, there were 50% patients who did not show recurrence of OAB symptoms. Even though there were several hypothesis which were involved with CNS role to explain the pathophysiology for OAB [25,26], other hypothesis have been

proposed that myogenic causes and peripheral autonomic causes [27,28]. The controlled state by using antimuscarinic treatment could affect afferent signaling [29] suggesting that alterations in the sensory transduction leads to stabilize afferent noise.

Limitations of the study were insufficient number of patients' voiding diaries and only 41 patients were followed up until 12 months. This can cause selection bias.

CONCLUSIONS

Recurrence of OAB symptoms was most frequently observed at 1 month, afterward the number of patients with new recurrence of OAB symptoms and almost 50% patients showed OAB recurrence after 6 months of discontinuation of antimuscarinic therapy after successful treatment. Female and OAB wet were the risk factors for OAB symptom recurrence.

CONFLICTS OF INTEREST

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