Original Article

Predictive Factors for Recurrence of Overactive Bladder after Discontinuation of an Antimuscarinic Agent

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Background: Overactive bladder (OAB) is a common disease. However, the patients who stop taking medicines after clinical improvement are at risk for symptom recurrence.

Objective: To determine the disease recurrence rates and evaluate the potential predictive factors for recurrent OAB symptoms after discontinuation of an antimuscarinic drug.

Materials and Methods: The OAB patients who discontinued antimuscarinic drugs after symptom improvement were studied prospectively. The OAB symptoms were evaluated by the International Consultation on Incontinence Questionnaire Overactive Bladder (ICIQ-OAB) questionnaire. The symptom scores were evaluated at the time of recruitment and at 1, 3, 6, and 12 months after drug discontinuation. The curve of time to symptom recurrence was plotted. The factors associated with symptom recurrence were analyzed and compared.

Results: Eighty-two patients including 40 (48.78%) males and 42 (51.22%) females, were included in the present study. Forty-one (50.0%) patients experienced recurrent symptoms within 12 months. The median time to symptom recurrence was 3.01 months (interquartile range [IQR] 1.0, 6.0). The mean symptom scores in the recurrent group at 1, 3, and 6 months were significantly higher than those in the non-recurrent group (10.75±7.39 versus 22.76±13.10, p<0.001; 10.89±8.93 versus 16.41±11.70, p=0.040; and 10.51±8.03 versus 22.33±14.59, p=0.001, respectively). The results of the univariate analyses indicated that other factors were not associated with recurrence.

Conclusion: Symptom recurrence after antimuscarinic discontinuation is common in OAB patients. The high ICIQ-OAB score might be the predictive factor for recurrence. Most of the cases of symptom recurrence were observed within three months.

Keywords: Muscarinic Antagonists, Overactive bladder, Predictive factors, Recurrence

Received 10 March 2020 | Revised 4 June 2020 | Accepted 12 June 2020

J Med Assoc Thai 2021;104(5):723-7

Website: http://www.jmatonline.com

Overactive bladder (OAB) is defined as urgency, with or without urge incontinence, usually associated with increased daytime frequency and nocturia. It is a common disease in both men and women[1]. Some studies have found a higher incidence in patients with advanced age and those with diabetes[2,3]. However, multiple factors that might be associated with this disease have not yet been confirmed.

Nowadays, antimuscarinic agents are used for treating OAB because they could effectively relieve patient's symptoms[4]. However, the patients were at risk of side effects, such as dry mouth, dry eyes, blurred vision, constipation, abdominal pain, and nausea[5]. Recent studies have focused on the factors influencing the successful treatment of OAB[6,7]. The data indicated that success was influenced by age, polypharmacy, and symptom severity at the beginning of treatment. However, there is no consensus about the factors associated with successful medication reduction or discontinuation.

The aim of the present study was to determine the disease recurrence rates and the associated factors. The findings could enhance the treatment of OAB. Drug discontinuation led to reductions of medical costs, adverse effects, and drug overuse.

Materials and Methods

A prospective cohort study was conducted in the Ramathibodi Hospital between June 2016 and May 2018 after ethical approval had been received from the Institutional Ethics Committee (COA MURA2020/113). Informed consent was obtained from each participant. The inclusion criteria were more than 18 years old, diagnosed with OAB, had

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How to cite this article:

Tangmesang S, Viseshsindh W. Predictive Factors for Recurrence of Overactive Bladder after Discontinuation of an Antimuscarinic Agent. J Med Assoc Thai 2021;104:723-7.

doi.org/10.35755/jmedassocthai.2021.05.11218

been treated with an antimuscarinic agent for at least one month, and were ordered to stop taking an antimuscarinic agent before participating in the study.

The exclusion criteria were post-void residual volumes (PVR) of more than 50 mL, treatment with more than one type of antimuscarinic agent or drugs other than antimuscarinic agents, and the presence of urinary tract infection. The following demographic and clinical characteristics were considered: gender, age, weight, height, body mass index, duration of drug use, type of antimuscarinic drug, symptom score at the beginning of the study, comorbidities, history of smoking, history of alcohol drinking, history of pelvic surgery, post-void residual urine measured by a portable ultrasound bladder scanner, and, for the women, the number of dependents and history of hormonal replacement therapy. At the time that each participant was ordered to stop taking an antimuscarinic agent, they were being asked for participating in the study. The participants were then followed up at 1, 3, 6, and 12 months after drug discontinuation. Symptom presence and characteristics were assessed with the International Consultation on Incontinence Questionnaire Overactive bladder (ICIQ-OAB) questionnaire[8], which was completed by the participants themselves or by a researcher to whom they provided the answers to the questions. For the participants who could not visit the outpatient clinic, the symptoms were accessed by telephone interviews. Symptom recurrence was defined as a return of OAB symptoms and the participant asking for medication resumption.

The participants were placed into two groups, recurrent and non-recurrent. The non-recurrent group was composed of patients who had remained symptom free throughout the follow-up period. Those with recurrent symptoms during the follow-up period were placed into the recurrent group. Patient characteristics with continuous variables were compared by Student's t-test or Mann-Whitney test and categorical variables were compared by chi-square or Fisher's exact test. The curve of time to symptom recurrence was plotted with the Kaplan-Meier estimator. The factors associated with symptom recurrence in the recurrent and non-recurrent groups were analyzed and compared through a Cox regression model. The hazard ratio (HR) with a 95% confidence interval (CI) was obtained for each independent variable. The statistical analyses were performed with Stata, version 14.1 (StataCorp LP, College Station, TX, USA). The parametric and non-parametric comparisons were performed with the paired sample t-test and paired sign test, respectively. The p-value of less than 0.05 was considered significant.

Table 1. Baseline characteristics of the patients who discontinued the antimuscarinic drug

Characteristics	Total (n=82); n (%)
Sex	
Male	40 (48.78)
Female	42 (51.22)
Age (year); median (IQR)	71 (62, 77)
BMI (kg/m^2), mean±SD	25.03±3.80
Comorbid	
No	11 (13.41)
Yes	71 (86.59)
Pelvic surgery	25 (30.49)
Prostate surgery (n=40)	5 (12.50)
Menopause (n=42)	36 (85.71)
Duration of the drug use (months); median (IQR)	11.7 (6.1, 22.2)
Drug types	
Tolterodine	40 (48.78)
Solifenacin	17 (20.73)
Trospium	21 (25.61)
Oxybutynin	4 (4.88)
Symptom scores at the beginning of the study; mean±SD	14.82±8.80

BMI=body mass index; IQR=interquartile range; SD=standard deviation

Results

Eighty-two participants, including 40 (48.78%) males and 42 (51.22%) females, were enrolled in the present study. The median age was 71 years (62, 77), and the mean body mass index was 25.03±3.80 kg/m^2. The duration of drug use was 11.7 months (6.1, 22.2). The symptom score at the beginning of the study was 14.82±8.80. The detailed demographic data is presented in Table 1.

Forty-one (41/82, 50.0%) patients were placed in the non-recurrent group, and 41 (41/82, 50.0%) who experienced recurrent OAB symptoms within 12 months were placed in the recurrent group. The median time to symptom recurrence was 3.01 months (IQR 1.0, 6.0). The time to symptom recurrence is shown in Figure 1. The cumulative recurrence rates were 20.73%, 36.59%, 48.78%, and 50.00% at 1, 3, 6, and 12 months, respectively. The mean symptom scores for the recurrent group at 1, 3, and 6 months were significantly higher than those for the non-recurrent group (10.75±7.39 versus 22.76±13.10 p<0.001, 10.89±8.93 versus 16.41±11.70 p=0040, and 10.51±8.03 versus 22.33±14.59 p=0.001, respectively) (Table 2). The results of the univariate

Table 2. ICIQ-OAB symptom scores at each follow-up between non-recurrent and recurrent groups

Symptom scores	Non-recurrent	Recurrent	p-value	HR (95% CI)	p-value
At the beginning of the study (n=82)	13.78±8.15	15.87±9.39	0.283	1.02 (0.98 to 1.05)	0.266
1 month after discontinuation (n=74)	10.75±7.39	22.76±13.10	<0.001	1.11 (1.07 to 1.14)	<0.001
3 months after discontinuation (n=61)	10.89±8.93	16.41±11.70	0.040	1.04 (1.00 to 1.07)	0.028
6 months after discontinuation (n=47)	10.51±8.03	22.33±14.59	0.018	1.08 (1.03 to 1.13)	0.001
12 months after discontinuation (n=35)	10.73±7.94	13 (1 person)		1.02 (0.83 to 1.25)	0.813

HR=hazard ratio; CI=confidence interval

Table 3. Predictive factors associated with recurrent overactive bladder

Characteristics data	Non-recurrent (n=41); n (%)	Recurrent (n=41); n (%)	p-value	HR (95% CI)	p-value
Sex					
Male	18 (43.90)	22 (53.66)	0.337	1	
Female	23 (56.10)	19 (46.34)		0.88 (0.47 to 1.62)	0.675
Age (year); median (IQR)	70 (61, 76)	72 (63, 79)	0.457	1.01 (0.98 to 1.04)	0.393
BMI (kg/m^2); mean±SD	24.74±3.67	25.30±3.95	0.509	1.02 (0.94 to 1.11)	0.607
Comorbid					
No	7 (17.07)	4 (9.76)	0.331	1	
Yes	34 (82.93)	37 (90.24)		1.69 (0.59 to 4.77)	0.321
Pelvic surgery	13 (31.71)	12 (29.27)	0.810	0.85 (0.43 to 1.67)	0.647
Prostate surgery (n=40)	2 (11.11)	3 (13.64)	0.999	0.80 (0.23 to 2.76)	0.720
Menopause (n=42)	19 (82.61)	17 (89.47)	0.673	1.81 (0.41 to 7.89)	0.429
Duration of the drug use (months); median (IQR)	11.2 (5.8, 22.2)	12.0 (6.3, 22.2)	0.702	1.01 (0.98 to 1.02)	0.530
Drug type					
Tolterodine	19 (46.34)	21 (51.22)	0.560	1	
Solifenacin	10 (24.39)	7 (17.07)		0.74 (0.30 to 1.84)	0.524
Trospium	9 (21.95)	12 (29.27)		1.31 (0.64 to 2.67)	0.455
Oxybutynin	3 (7.32)	1 (2.44)		0.49 (0.06 to 3.63)	0.484

HR=hazard ratio; CI=confidence interval; BMI=body mass index; IQR=interquartile range; SD=standard deviation

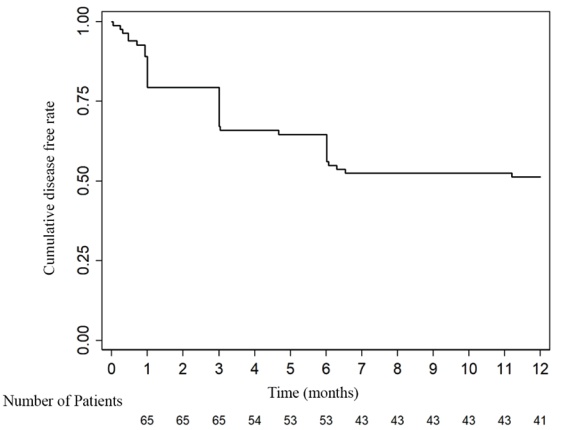

Figure 1. Time to overactive bladder symptom recurrence curve.

The Y axis was the cumulative disease-free rate and the X axis was the follow-up time. The graph showed disease recurrence and decrease in a number of remaining disease-free patients over the time. The number which showed below the graph indicated the remaining disease-free patients at each specific month.

analysis indicated that factors such as age, gender, body mass index, comorbidity, history of previous surgery, and duration and type of medication were not associated with recurrence (Table 3).

Discussion

OAB, a common disease worldwide, occurs predominantly in women[2,9-11]. The patients might suffer from its symptoms and have a negative impact on the quality of life[12]. Currently, they are being treated with antimuscarinic drugs that provide effective symptom relief and improve the quality of life[13,14]. However, the long-term use of antimuscarinic drugs can result in higher medical costs and increased complications[5,15-17]. With symptom improvement, most OAB patients will be advised to stop taking these drugs. However, some will suffer from symptom recurrence after drug discontinuation[18]. Thus far, there is no consensus on symptom recurrence rates

and the appropriate timing for drug discontinuation. Therefore, the present study was conducted to determine the recurrence rates and the associated predictive factors in OAB.

The present prospective study established a 1-year follow-up period after drug discontinuation to observe symptom recurrence in OAB patients. The median time to symptom recurrence was 3.01 months. The cumulative recurrence rates were 20.73%, 36.59%, 48.78%, and 50.00% at 1, 3, 6, and 12 months, respectively. The present study result is similar to the findings of previous studies. Kim et al[19] reported cumulative symptom recurrence rates of 25.6%, 42.3%, and 52.2% at 1, 3, and 6 months, respectively. Symptom recurrence was most frequently observed at one month. Lee et al[20] observed that antimuscarinic drug discontinuation occurred within three months after successful treatment. The cumulative rates of patients requesting retreatment at one and three months were 53% and 65%, respectively. Wang et al[21] also studied the effects of medication discontinuation in OAB patients; however, the patients had used mirabegron instead of an antimuscarinic drug. The mean duration from mirabegron discontinuation to resumption was 2.25±1.17 months. The recurrence rate for OAB symptoms was 45.3%.

The present study found that the only predictive factor associated with recurrence and retreatment was high ICIQ-OAB symptom scores. The other factors, such as age, gender, body mass index, comorbidity, history of previous surgery, and duration and type of medication, were not. As was indicated in previous studies, the urge severity score was associated with recurrence and antimuscarinic treatment duration was not associated with retreatment[21]. In contrast, some studies have found predictive factors of recurrent OAB symptoms, such as age, gender, and OAB-wet[19].

The OAB patients in the present study exhibited high rates of recurrence after the discontinuation of antimuscarinic drugs. Patients should therefore be followed up within three months for symptom evaluation. The strength of the present study is its prospective nature. The follow-up period was one year, which was longer than that in some studies. Most of the patients completed the follow-up visits. The limitation was the small sample size, which might have led to insignificant results because of the lack of power. Thus, a large-scale sample study is required to obtain representative results.

Conclusion

Symptom recurrence and treatment resumption are common after antimuscarinic discontinuation. The high ICIQ-OAB symptom score might be the predictive factor for recurrent OAB symptoms. In most cases, symptom recurrence was observed within three months. Patients should therefore be followed up within this period after antimuscarinic drug discontinuation for the evaluation of symptom recurrence.

What is already known on this topic?

OAB is a common disease in both men and women. The natural history of the disease is variable. It can be progressive, stable, or remissive. Antimuscarinic agents effectively relieve OAB symptoms. However, there is no consensus about the factors associated with successful medication reduction or discontinuation.

What this study adds?

The present study demonstrated that symptom recurrence and treatment resumption are common after antimuscarinic discontinuation. ICIQ-OAB symptom score can be used to predict recurrent OAB symptoms. In most cases, symptom recurrence was observed within three months. Therefore, patients should be followed up within this period after antimuscarinic drug discontinuation for the evaluation of symptom recurrence.

Acknowledgement

The authors heartily thank Miss Suraida Aeesoa for her encouragement and her guidance on the statistical analysis. The authors acknowledge everyone who supported us throughout the present project.

Funding disclosure

The presented research project is supported by the Faculty of Medicine Ramathibodi Hospital Mahidol University (RF_60080). The funding covered the costs of English proofreading and the phone charges that the researcher paid for calling participants to collect data. The funding also supported participants transporting costs for each followed-up time. The funders had no role in the study design, study completion, data analysis, and writing of the manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

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