

Tolterodine in Women with Overactive Bladder, Clinical and Urodynamic Effects.

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Abstract

Objective: The aim of this study was to compare the changes in urinary symptoms and urodynamic parameters in women with OAB, after tolterodine.

Materials and Methods: The study involved fifty women diagnosed with OAB and treated with tolterodine. Urinalysis, pelvic examination, urodynamic study, and a personal interview to identify urinary symptoms prior to and 3 months after treatment were recorded and interpreted.

Results: Demographic profile showed, most patients being menopausal (76.0%; mean age 52.7 years) and multiparous (mean parity 2.9) women. Urinary symptoms such as urgency, urge incontinence and urinary frequency were decreased significantly ($p < 0.05$). Urodynamic parameters did not showed significant change except for the maximum cystometric capacity ($p < 0.05$), with a significant increase after 3 months of medication.

Conclusion: Tolterodine, at recommended doses, improves the symptoms of OAB syndrome without causing urine retention, as proved by urodynamic parameters.

Keywords: tolterodine; overactive bladder; urodynamic study; detrussor over-activity.

I. Introduction

OAB is a condition that can affect all aspects of quality of life.(1,2) OAB, as defined by the International Continence Society, is a symptomatic diagnosis with urgency as the cornerstone symptom, with or without urge incontinence, but usually with urinary frequency and nocturia, in the absence of other pathological or metabolic factors that may otherwise cause similar symptoms [3]. Overactive bladder (OAB) is a common chronic problem that often requires long-term treatment to maintain control of symptoms. Suffers have significant impairment of physical, social, emotional, and sexual functions [1,2].

Pathophysiology behind the disease is not yet understood fully but is thought to be multifactorial. The prevalence of OAB increases with age in both sexes and occurs in approximately 30% in women over the age of 65 years [4]. The age-adjusted prevalence of OAB is around 17% in the United States [4]. Conservative treatment being the mainstay of therapy for OAB, including biofeedback, bladder training, electrical nerve stimulation, and medical treatment, or a combination of these methods.

Antimuscarinic agents are the first-line medical treatment for OAB symptoms and act by blocking the muscarinic receptors on most structures in the bladder wall (urothelium, lamina propria, and detrusor muscle) [5]. Various antimuscarinic agents appear to have different effects and side effects [6], tolterodine and oxybutynin being used more commonly worldwide. Tolterodine, a newer drug designed specifically for treating OAB and has a relatively lower side effects [7].

Several studies have demonstrated the efficacy and safety of tolterodine in the treatment of OAB [6,7]. However, studies concerning the changes in urodynamic parameters and clinical symptoms after OAB treatment are limited [8,9]. Thus, completes purpose of this study to investigate changes of urodynamic parameters and urinary symptoms after tolterodine treatment.

II. Materials and methods

The study was started after the approval of the protocol by the Institutional Ethics Committee of our hospital. A statistical analysis was performed using the paired t test for continuous variables, and McNemar or Chi-square test for categorical variables. A difference was considered statistically significant when $p < 0.05$. The study period was one year conducted between December 2014 and January 2016, 68 consecutive women visiting our outpatient department who underwent tolterodine (at recommended doses, 2mg bid) treatment for OAB were included in the study. The changes of subjective urinary symptoms and urodynamic parameters after 3 months of treatment, as well as the demographic characteristics, were collected and compared. Eighteen patients were excluded from the study due to loss to follow-up.

During the first visit, detailed personal history, pelvic examination, and urinalysis was performed. A personal interview was also conducted for each woman with an OAB questionnaire in order to identify the subjective urinary symptoms. A scale of 0-5 (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = a great deal, and 5 = a very great deal) was used to record the incidences of subjective urinary symptoms. The diagnosis of OAB was made when the patient answered “somewhat” or more to any one of the questions. Any obvious etiology (such as pregnancy, genital organ prolapse, urinary tract infection, and any other diseases or medications that possibly affect the lower urinary tract functions) was excluded prior to the diagnosis of OAB.

All patients underwent an urodynamic study prior to treatment; this evaluation was performed by the same experienced doctor who took the interview. The studies included spontaneous uroflowmetry, both filling and voiding cystometry with infusion of normal saline at room temperature. Any uninhibited detrusor contraction during filling cystometry was deemed positive for idiopathic detrusor overactivity (DO). Patients diagnosed with OAB were given tolterodine (2 mg bid) for 3 months. Post-treatment, urodynamic study and the complete questionnaire was performed again and interpreted by the same observer to avoid any interobserver bias. All the data of urodynamic study and the OAB questionnaire after 3 months of tolterodine treatment were collected.

III. Results

A total of 50 patients with complete data were included in this study. Demographic characteristics of all patients are shown in Table 1. The mean age was 52.7 years and 38 women (76%) were menopausal. Subjective changes of urinary symptoms are shown in Table 2. Urinary symptoms, including urinary frequency, urgency, nocturia, and urge incontinence, were improved significantly after treatment ($p < 0.05$). The number of episodes of stress urinary incontinence, incomplete bladder emptying and urinary hesitancy did not differ significantly after treatment ($p > 0.05$).

Comparisons of the urodynamic parameters prior to and after treatment are shown in Table 3. Urodynamic stress incontinence, maximum detrusor pressure, maximum flow rate, residual urine, first sensation to void, detrusor pressure at peak flow did not differ significantly ($p > 0.05$), comparing all patients prior to and after the 3-month treatment of tolterodine. The rate of DO decreased but did not reach a significant difference ($p = 0.20$). Only the maximum cystometric capacity increased in a significant manner ($p = 0.038$). Comparisons of the subjective changes of urinary symptoms between DO and non-DO patients are shown in Table 4. The subjective symptoms of urinary frequency were improved significantly in both groups. Moreover, the symptoms of urgency and nocturia were also improved in both groups; however, improvement in the symptom of urgency reached significance only in the DO group and that of nocturia only in the non-DO group. All the remaining symptoms were also decreased nonsignificantly in both the groups.

Table 1: Demographic characteristics of women (n =50) with over-active bladder symptoms.

Mean age (years)		52.7 +/- 10.2	
Mean parity	2	2.9 +/- 1.0	
Menopause		38 (76)	
Diabetes mellitus		7 (14)	
Hypertension		13 (26)	

Data are presented as mean SD or n (%).

Table 2: Urinary symptoms prior to and after 3 months of medication.

Symptoms	Pre-Tx (n = 50)		Post-Tx (n = 50)		p value*
Urinary frequency	50	(100)	18	(36.0)	<0.01
Urgency	50	(100)	32	(64.0)	<0.05
Stress urinary incontinence	34	(68.2)	35	(70.0)	NS
Urge incontinence	30	(60.0)	16	(32.0)	<0.05
Incomplete bladder emptying	09	(18.0)	10	(20.2)	NS
Urinary hesitancy	3	(6.0)	2	(4.3)	NS
Nocturia	38	(76.0)	19	(39.5)	<0.05

Data are presented as n (%). * McNemar’s test. Tx =treatment; NS =not significant.

Table 3: Urodynamic changes prior to and after 3 months of medication.

Parameters	Pre-Tx (n = 50)		Post-Tx (n = 50)		p value
	Mean	SD	Mean	SD	
DO	24 (48.0)		19 (38.0)		>0.05*
USI	34 (68.4)		31 (62.0)		>0.05*
Qmax (mL/s)	19.7	+/- 8.6	19.9	+/-12.4	>0.05**
RU (mL)	65.8	+/-35.4	77.5	+/-31.9	>0.05**
FS (mL)	145.1	+/-74.4	147.3	+/-80.9	>0.05**
MCC (mL)	311.1	+/-140.0	354.2	+/-122.2	<0.05**
Pdet (cmH ₂ O)	26.7	+/-17.7	26.0	+/-16.8	>0.05**
MDP (cmH ₂ O)	32.9	+/-18.8	31.2	+/-16.0	>0.05**

Data are presented as mean +/- SD or n (%). *McNemar's test. **Paired t test.

DO = detrusor overactivity; FS = first sensation to void; MCC = maximum cystometric capacity; MDP = maximum detrusor pressure;
 Pdet = detrusor pressure at peak flow; Qmax = maximum flow rate;
 RU = residual urine; Tx = treatment;
 USI = urodynamic stress incontinence.

Table 4: Urinary symptoms in women with and without DO prior to and after 3 months of medication.

Symptoms	DO (n = 24)				No DO (n = 26)			
	Pre-Tx	Post-Tx	p value*		Pre-Tx	Post-Tx	p value*	
Urinary frequency	24 (100)	11 (45.8)	<0.05		26 (100)	10 (38.4)	<0.01	
Urgency	24 (100)	13 (54.1)	<0.05		26 (100)	21 (80.7)	>0.05	
SUI	22 (91.6)	20 (83.3)	>0.05		20 (76.9)	18 (69.9)	>0.05	
Urge incontinence	16 (66.7)	9 (37.5)	>0.05		16 (61.5)	10 (38.4)	>0.05	
Incomplete emptying	6 (25.0)	8 (33.3)	>0.05		9 (34.6)	9 (34.6)	>0.05	
Urinary hesitancy	2 (8.3)	2 (8.3)	>0.05		3 (11.5)	2 (7.6)	>0.05	
Nocturia	15 (62.5)	9 (37.5)	>0.05		23 (88.4)	10 (38.4)	<0.01	

* McNemar's test. Data are given as n (%). DO = detrusor overactivity; SUI = stress urinary incontinence; Tx = treatment

IV. Discussion

The action of tolterodine in OAB patients is that it acts by blocking competitively the muscarinic receptors on the detrusor muscle, which are stimulated by acetylcholine released from activated parasympathetic nerves. As a result, it inhibits the contractile ability of the bladder. This blocking activity occurs mainly during the storage phase of the bladder, increasing the total bladder capacity [10]. Demographic data showed that the majority of our patients were of advanced age (mean age 52.7 years), postmenopausal (76.0%), and of greater parity (mean parity 2.9).

The subjective symptoms of urinary frequency, urge incontinence, and nocturia improved significantly (p < 0.05), but the numbers of episodes of stress urinary incontinence, incomplete bladder emptying, and urinary hesitancy did not differ significantly after treatment. The symptom of urgency was improved nonsignificantly, which may be attributed to the limited number of patients included in the study. Several studies have shown a significant increase in the bladder capacity after anticholinergic medication [8,9]. Therefore, the maximum bladder capacity has been suggested to be a useful marker of the efficacy of treatment [11]. Similar results were seen in our study, proving the need of tolterodine in OAB.

No statistically significant changes were found in the urodynamic parameters of voiding function, including maximum flow rate, maximum detrusor pressure, and detrusor pressure at peak flow. Hsiao et al [12,13] also reported similar findings. As discussed above, blocking the contraction of the bladder may also decrease the power of voiding and cause urine retention. In our study, the mean volume of residual urine was increased nonsignificantly (p = 0.38) after treatment. Showing similar results to other authors [9,10]. So, the concern that tolterodine (in short-term use) may increase the risk of urine retention can be ignored but attention is warranted to those women with large residual urine volume prior to treatment.

The rate of DO decreased nonsignificantly after treatment (48.0% vs. 38.0%, p = 0.16), similar to our study [14]. The detection rate of DO by urodynamic study varies greatly, because of many factors, including the type of infusion medium used, posture of the patient during the test, temperature of the medium, rate of

infusion, and pro-vocative tests used, cause detrusor contraction [15]. Thus, the percentage of DO may not be a good predictor to evaluate the efficacy of treatments.

Tolterodine was found to be effective in improving the symptoms of frequency in both DO and non-DO group, but it had greater impact on urgency in the DO group. Also, it does not cause deterioration of voiding function as there was no change in urinary hesitancy and a nonsignificant increase of incomplete bladder emptying in the DO group, but no change in the non-DO group. Lack of changes in the urodynamic parameters revealed that anticholinergic agents had no adverse effect on the voiding function. Undoubtedly, a greater impact on the therapeutic effects was observed in DO patients. The main limitation of this study is the small size of study samples. By contrast, a fixed protocol of urodynamic examination, performed by the same experienced doctor and interpreted by the same observer, can avoid any interobserver bias. Also, completion of the entire questionnaire by the patients themselves also minimizes the bias from other persons' opinions. In conclusion, tolterodine, at a recommended dosage, is an effective antimuscarinic agent for women with OAB, without causing urinary retention.

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