Neurourology and Urodynamics 28:47–51 (2009)

Randomized Comparison of Tolterodine With Vaginal Estrogen Cream Versus Tolterodine Alone for the Treatment of Postmenopausal Women With Overactive Bladder Syndrome

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Aims: To investigate whether vaginal estrogen cream combined with tolterodine is more effective than tolterodine alone in the treatment of postmenopausal women with overactive bladder (OAB). **Materials and Methods:** This is an unblinded study without placebo. A preliminary study consisted of tolterodine 2 mg twice per day for 3 months had been conducted for 25 postmenopausal women with OAB. Over a period of 11 months, 80 postmenopausal women with OAB underwent a prospective randomized trial. These patients were equally randomized into two groups. The interventions for the 12-week treatment period included 2 mg tolterodine twice per day for the group A and 2 mg tolterodine twice per day/vaginal conjugated equine estrogen 0.625 mg twice a week for the group B. Identical pre- and post-treatment assessments included bladder diary, Urogenital Distress Inventory-6 (UDI-6), and Incontinence Impact Questionnaire-7 (IIQ-7). **Results:** All 80 women (65.2 years, range 58–73) completed this study. The between groups comparison showed that the group B had significant improvements in mean daytime frequency and voided volume after treatment (14.8–5.8 vs. 14.1–6.4, $P = 0.001$ and 115.8–141.9 vs. 108.5–134.5, $P = 0.007$, respectively). Additionally, a comparison of the final total scores of UDI-6 and IIQ-7 between the two groups revealed that the group B had a statistically significant improvement in quality of life than that in the group A (8.6–6.9 vs. 9.5–7.2, $P < 0.001$ and 9.4–6.1 vs. 10.2–6.5, $P < 0.001$, respectively). Changes in the other symptoms, including nocturia, urgency and urge incontinence, were not statistically significant but actually achieved improved in both groups. **Conclusions:** A combination of vaginal estrogen cream and tolterodine is a potential therapy for postmenopausal women with OAB. *Neurourol. Urodynam. 28:47–51, 2009.* © 2008 Wiley-Liss, Inc.

Key words: antimuscarinics; menopause; overactive bladder syndrome; vaginal estrogen cream

INTRODUCTION

Overactive bladder (OAB) is a bothersome bladder problem and it deeply affects personal quality of life. The prevalence of overactive bladder in Taiwanese women is similar to that of western country.[1] Treatment modalities include lifestyle modification, electric stimulation, bladder training, and pelvic floor exercises. Pharmacotherapy such as antimuscarinic agents may be initiated if the subjects do not respond to the above-mentioned regimens.

The most common used strategy in OAB is still the pharmacological approach, mainly with antimuscarinic drugs.[2–4] However, the use of antimuscarinic agent sometimes may cause unpleasant adverse events such as dry mouth, constipation and blurred vision, and special concerns are needed in the elderly.[2,3,5] Prior studies suggested estrogen affect urethral mucosa, smooth muscle and alpha-adrenergic tone[6] and vaginal estrogen treatment have a role in the treatment of bothersome bladder symptoms.[7–11]

The use of antimuscarinic agent in postmenopausal women with OAB[12] was seldom reported and it seems that the subjects would not benefit from antimuscarinics in conjunction with other treatments.[4,13] We intend to find if any optimal regimens which can be instituted in conjunction with antimuscarinics to improve the treatment efficacy for postmenopausal women with OAB. Only few articles addressed vaginal estrogen therapy in treating urogenital symptoms for the postmenopausal women.[7–9,14,15] In addition, based on the correlation between estrogen modulation and women body, as well as the observation of less effectiveness of antimuscarinics in the treatment of postmenopausal women with OAB syndrome, we decided to conduct the current study. The aim of this study was to determine whether the effect of vaginal conjugated equine estrogen (CEE) and antimuscarinics is better than antimuscarinics alone for postmenopausal women with OAB.

MATERIALS AND METHODS

Patients

Between January 2005 and November 2005, 80 postmenopausal women with overactive bladder (OAB) were recruited for this study. This is an unblinded study without placebo. Institutional Review Board approval and informed consents were obtained for the study.

Study Design

All the enrolled subjects underwent a clinical interview and physical examination. The interview included questions

No conflict of interest reported by author(s).
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E-mail: 3g7330@yahoo.com.tw
Received 9 January 2008; Accepted 12 February 2008
Published online 15 December 2008 in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/nau.20583

related to age, parity, medical illness, and previous surgery. Drug history was also obtained to exclude the cause that may aggravate the symptoms. Physical examination included height, weight, and pelvic examination to detect the presence of pelvic organ prolapse. Digital examination and pin prick test were performed to assess the S2–4 dermatome. Patients with abnormal neurological sign such as Babinski sign during pelvic examination or unsteady gait were assessed for their underlying diseases. All women in the study group had baseline assessment including urinalysis, post-void residual checked by ultrasonic bladder scan (BVI 3000, Diagnostic Ultrasound Corporation, Bothell, WA) and a 3-day bladder diary including the times of micturitions, voided volumes, incontinence episodes, pad usage and other information such as fluid intake, the intensity of urgency and incontinence was completed. Transvaginal ultrasonography was arranged for the subjects to exclude the possibility of endometrial lesions of which is one of the contraindication for estrogen use. Treatment options including lifestyle modification, bladder training and pelvic floor exercises are also proposed in case that they would change their decision for treatment. The quality of life assessment including the use of Urogenital Distress Inventory-6 (UDI-6) and Incontinence Impact Questionnaire-7 (IIQ-7) was performed before and after treatment. Videourodynamic study was arranged if neurological condition suspected. All nomenclatures were made according to ICS terminology.

Menopause was defined by 12 months of amenorrhea after the final menstrual period or an elevated serum follicle stimulating hormone concentration (over 30–40 mIU/ml) for women had undergone hysterectomy. OAB is defined as a condition characterized by urgency, with or without urge incontinence, usually with frequency and nocturia, if there is no proven infection or obvious pathology.[16] Additionally, ''how long the symptoms have been through'' and ''which are the most bothersome symptoms'' were also questioned.

Women were excluded from the study if they had anyone of the following conditions: (1) Women with both storage and voiding symptoms and unable to tell the priority. (2) Women with advanced pelvic prolapse, severe constipation, elevated post-void residual, or neurological deficit. Advanced pelvic organ prolapse was defined as the prolapse greater than stage II of the pelvic organ prolapse quantitation system (POP-Q).[17] Women with above conditions were at risk for elevated post-void residual urine and might further attenuate the efficacy of antimuscarinic agents.[18] (3) Women who had medical illness and contraindication for using tolterodine included: significant hepatic and renal disease; abnormal cardiac conduction, rate or rhythm; narrow-angle glaucoma; myasthenia gravis; obstructive uropathy; decreased gastrointestinal motility. Additional concerns for using estrogen included: a history of cerebrovascular disease; thromboembolic disorders; gallbladder disease; known or suspected breast carcinoma; estrogen-dependent neoplasm or undiagnosed abnormal genital bleeding. Women who were on HRT within 3 months were also excluded from the study.

Randomization and Sample Size Calculation

After enrolment, the patient was randomly allocated, via permuted block method with a block of 4, into two groups. ''Blocks'' having equal numbers of As and Bs (A = tolterodine, B = tolterodine/estrogen) were used, with the order of treatments within the block being randomly permuted. A random number sequence was used to choose a particular block, which set the allocation order to the first four subjects. Similarly, treatment group was allocated to the next four patients in the order specified by the next randomly selected block. The process was then repeated. Patients allocated in group A received 2 mg tolterodine twice per day (n = 40) and patients in group B received 2 mg tolterodine twice per day/ vaginal conjugated equine estrogen (CEE) 0.625 mg twice a week (n = 40). (Premarin vaginal cream, Ayerst, New York, NY).For this trial, a preliminary study that consisted of tolterodine 2 mg twice/day during a 3-month period being given to 25 postmenopausal women with OAB had revealed a 25% response rate. Moreover, we hypothesized that vaginal CEE 0.625 mg twice a week which was added on to the tolterodine 2 mg twice a day would increase a 30% response rate for those women who had had 25% of response rate in the preliminary study. That was to attain an absolute complete response rate of 46% [=25% + (1–30%) × (30%)].[19] With a type I error of 0.05, a power of 0.80, 95% of confidence intervals and anticipated that groups of equal size were required. The total sample size required to achieve these objectives was at least 40 subjects.

Statistical Considerations

Values were given as mean (SD). Independent sample *t* tests (for continuous variables) and Chi-Square tests (for categorical variables) were performed on the variables that evaluated differences between groups as appropriate. All tests were performed using SPSS-PC software (SPSS, Inc., Chicago, IL). A P value <0.05 was regarded as significant.

RESULTS

Between January and November 2005, 80 consecutive women with OAB were equally randomized to receive either tolterodine with vaginal conjugated equine estrogen (CEE) or tolterodine alone. The mean patient age was 65.2 years (range 58–73) and the mean parity was 2.5 (range 1–5). All patients completed the study. Baseline demographics were presented in Table I. The two groups were generally well balanced in terms of baseline demographic variables except women in the tolterodine group had higher UDI-6 score initially. Only 12–15% of patients in each group had been treated with antimuscarinics and it happened more than 3 months ago. For the accuracy of data analysis, repeated measures analysis of variance was used.

Table II compares the pre- and post-treatment bladder diary variables and quality of life assessments between the two groups. A comparison of the final mean daytime frequency episodes between the two groups revealed that the tolterodine/estrogen group had a statistically significant decrease in numbers than that decreased in the tolterodine alone group (14.8–5.8 vs. 14.1–6.4, $P = 0.001$) (Fig. 1a). A comparison of the final mean voided volume between the two groups revealed that the tolterodine/estrogen group had a statistically significant increase in amount than that increased in the tolterodine alone group (115.8–141.9 vs. 108.5–134.5, $P = 0.007$) (Fig. 1e). For both groups, the voiding symptoms including nocturia, urgency and urge incontinence were subjectively improved after treatments although the differences were not statistically significant (Fig. 1b–d).

The subjective perception of bladder problems at baseline was slightly different in the two groups. Women in the tolterodine group had higher UDI-6 score at baseline. There was significant difference in the perception of bladder symptoms between the two groups after 12 weeks of treatment ($P < 0.001$). A comparison of the final total scores of

TABLE I. Demographic and Clinical Characteristics

	Group A, n = 40 (tolterodine)	Group B, n = 40 (tolterodine/estrogen)	*P*-value
Age	64.5 ± 7.4	66.2 ± 6.8	NS
Parity	2.6 ± 1.2	2.5 ± 1.5	NS
BMI	24.5 ± 3.9	25.3 ± 3.8	NS
History of previous antimuscarinics treatment (%)[a]	5 (12.5)	6 (15)	NS
History of hysterectomy (%)[a]	12 (30)	14 (35)	NS
Day time frequency/day	14.1 ± 1.3	14.8 ± 1.5	NS
Urgency/24 hr	4.5 ± 0.8	4.3 ± 0.7	NS
Nocturia/night	3.5 ± 0.8	3.3 ± 0.8	NS
Urge incontinence/24 hr	1.8 ± 0.7	2.2 ± 1.1	NS
Voided volume	108.5 ± 14.0	115.8 ± 15.1	NS
UDI-6 score	9.5 ± 3.9	8.6 ± 3.8	0.042
IIQ-7 score	10.2 ± 4.5	9.4 ± 3.6	NS

NS, not significant; BMI, body mass index; UDI-6, urogenital distress inventory-6; IIQ-7, incontinence impact questionnaire-7.
Numbers are given as mean ± SD.
Values are expressed as patient number and percentage is expressed in parentheses.

UDI-6 and IIQ-7 between the two groups revealed that the tolterodine/estrogen group had a statistically significant decrease in the scores than that decreased in the tolterodine alone group [8.6−6.9 vs. 9.5−7.2, $P < 0.001$; 9.4−6.1 vs. 10.2−6.5, $P < 0.001$, respectively] (Fig. 2a,b).

Adverse Events

No significant adverse effects were observed in both groups and none of them developed acute urine retention which required catheterization.

DISCUSSION

To our knowledge, this is the first randomized trial investigating a comparison of the effects of two different regimens for OAB treatment. The combination groups proved to be statistically significant decrease in day time frequency (14.8−5.8 vs. 14.1−6.4, $P = 0.001$) and increase in mean voided volume (115.8−141.9 vs. 108.5−134.5, $P = 0.007$). Subjective improvements were also appreciated in the between-group comparison of the total score of the UDI-6 and IIQ-7 (8.6−6.9 vs. 9.5−7.2, $P < 0.001$ and 9.4−6.1 vs. 10.2−6.5, $P < 0.001$, respectively). Eighty postmenopausal women (mean age 65.2 years; range 58−73) with OAB syndrome were enrolled and our study indicated the combination of tolterodine with vaginal estrogren was more effective than tolterodine alone.

TABLE II. Comparison of Bladder Diary Variables and Quality of Life Assessments Before and After Treatment

	Group A, n = 40 (tolterodine)	Group B, n = 40 (tolterodine/estrogen)	*P*-value
Day time frequency/day			
Pre-	14.1 ± 1.3	14.8 ± 1.5	NS
Post-	6.4 ± 1.9	5.8 ± 0.9	0.001
Urgency/24 hr			
Pre-	4.5 ± 0.8	4.3 ± 0.7	NS
Post-	3.5 ± 0.5	3.3 ± 0.6	NS
Nocturia/night			
Pre-	3.5 ± 0.8	3.3 ± 0.8	NS
Post-	2.9 ± 0.6	2.6 ± 0.7	NS
Urge incontinence/24 hr			
Pre-	1.8 ± 0.7	2.1 ± 1.1	NS
Post-	1.5 ± 0.5	1.5 ± 0.5	NS
Voided volume			
Pre-	108.5 ± 14.0	115.8 ± 15.1	NS
Post-	134.5 ± 15.8	141.9 ± 16.1	0.007
UDI-6 score			
Pre-	9.5 ± 3.9	8.6 ± 3.8	0.042
Post-	7.2 ± 2.9	6.9 ± 2.7	<0.001
IIQ-7 score			
Pre-	10.2 ± 4.5	9.4 ± 3.6	NS
Post-	6.5 ± 2.7	6.1 ± 2.5	<0.001

NS, not significant; BMI, body mass index; UDI-6, urogenital distress inventory-6; IIQ-7, incontinence impact questionnaire-7.
Numbers are given as mean ± SD.

Our preliminary study.

Our original attempt was to find if there was any regimen which could be used in combination with antimuscarinics to improve the treatment efficacy for those postmenopausal women with OAB at the expense of no additive side effects. Postmenopausal estrogen deficiency causes atrophic change of urogenital tract and is associated with irritating urinary symptoms, incontinence and recurrent infection.[8,9,11,24]

Moreover, recent studies suggested vaginal estrogen therapy effectively reduces OAB symptoms in postmenopausal women or for those following anti-incontinence surgery.[14,15] It is interesting that the corner stone symptom of OAB, urgency, does not show any significant difference between the two groups and the same is true for nocturia, which is also a bothersome symptom, nevertheless there was a statistically significant improvement in quality of life for the combination therapy. The bladder behavior in women with OAB may be more complex than we had previously considered.

Obviously, the criteria that we used to detect patients for this study will not guarantee all cases of overactive bladder syndrome. Our study were limited with lack of control on the methodology of women receiving estrogen only and the lack of a placebo cream in the control arm. Another pitfall of our

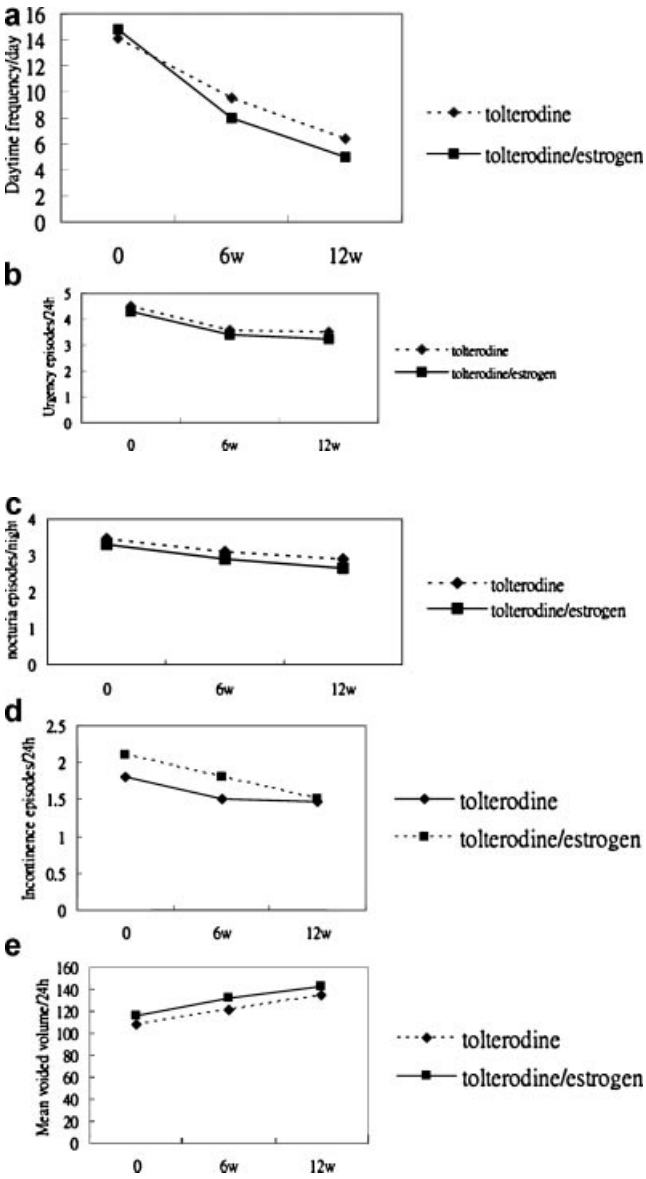

Fig. 1. Comparisons of the changes in the bladder diary variables. Data presented as mean. **a**: Mean daytime frequency/day. A comparison of the final mean daytime frequency episodes between the two groups revealed that the tolterodine/estrogen group had a statistically significant decrease in numbers than that decreased in the tolterodine alone group (14.8−5.8 vs. 14.1−6.4, $P = 0.001$). **b**: Mean urgency episodes/24 hr. **c**: Mean nocturia episodes/night. **d**: Mean incontinence episodes/24 hr. **e**: Mean voided volume/24 hr. A comparison of the final mean voided volume between the two groups revealed that the tolterodine/estrogen group had a statistically significant increase in amount than that increased in the tolterodine alone group (115.8−141.9 vs. 108.5−134.5, $P = 0.007$).

study was the limited no. of women enrolled and we did not apply the patient-reported outcome measures for patients with OAB such as Overactive Bladder Questionnaire (OAB-q), Patient Perception of Bladder Condition (PPBC), Urgency Questionnaire (UQ), or Primary OAB Symptom Questionnaire (POSQ).[25] These instruments are condition specific for incontinence and therefore, may not be as well suited for women with OAB-dry.

Although our findings suggested vaginal estrogen cream combined with antimuscarinics was more effective than

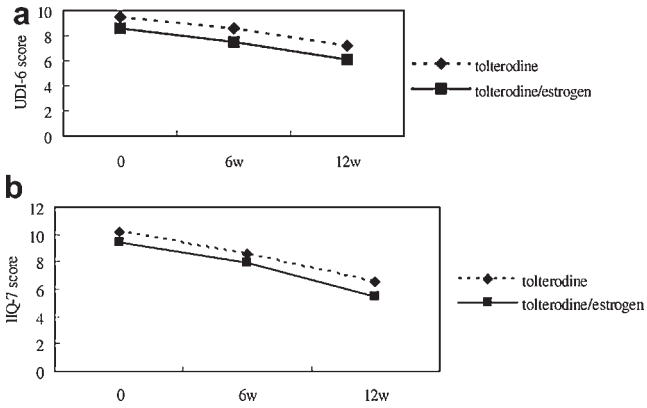

Fig. 2. Comparisons of the changes in quality of life assessments. A comparison of the final total scores of UDI-6 and IIQ-7 between the two groups revealed that the tolterodine/estrogen group had a statistically significant decrease in the scores than that decreased in the tolterodine alone group [8.6−6.9 vs. 9.5−7.2, $P < 0.001$; 9.4−6.1 vs. 10.2−6.5, $P < 0.001$, respectively]. Data presented as mean. **a**: Mean UDI-6 score. **b**: Mean IIQ-7 score.

antimuscarinics alone. Further study including a large number of subjects is warranted to improve the significance of difference between the two groups.

CONCLUSIONS

A combination of vaginal estrogen cream and tolterodine is a potential therapy for postmenopausal women with OAB. Further controlled studies with large series and longer study period are necessary for obtaining the conclusive evidences.

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