Original Article

Comparison of Tolterodine with Estazolam versus Tolterodine alone for the treatment of women with overactive Bladder Syndrome and Nocturia: A non-randomized prospective comparative study

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ABSTRACT

Objectives: Overactive bladder (OAB) is chronic condition that significantly affects quality of life in patients. The goal of treatment of OAB is to improve the lower urinary tract symptoms (LUTS) and enhance the quality of life (QOL). This study aims to investigate whether tolterodine combined with estazolam is more effective than tolterodine alone in the treatment of women with overactive bladder (OAB) and nocturia, advancing the management of OAB via a prospective review of 407 female cases with OAB symptoms.

Methodology: After we excluded other causes for storage symptoms, 407 consecutive female patients with OAB and nocturia were prospectively studied, of which 197 cases were given tolterodine alone while the other 210 cases were given tolterodine combined with estazolam for the treatment of OAB. Data on urgency, incontinence, micturition frequency, nocturia episodes and voided volume were collected before and after 4 weeks' pharmacological treatment using a 3-day micturition diary.

Results: The two groups of OAB patients were given tolterodine alone, tolterodine combined with estazolam for 4 weeks respectively. At weeks 4, the number of urgency episodes per 24 hours in the intervention group decreased by 3.5 (-46.7%), incontinence episodes by 2 (-66.67%), day-time frequency by 2.8 (23.3%), nocturia episodes by 1.8 (47.4%) and the volume voided per micturition increased by 50ml (31.2%), while in the control group the number of urgency episodes per 24 hours decreased by 2 (-28.6%), urgency incontinence episodes by 1.2 (-42.9%), day-time frequency by 2 (16.1%), nocturia episodes by 0.6 (17.1%) and the volume voided per micturition increased by 40.8ml (25.8%). The differences of changes of LUTS between the 2 groups has statistical significance ($P<0.05$). ÿWe used a 5% significance level and found the range of p-value with the table of critical t-values, then if the $P<0.05$, we considered the differences of LUTS between the two groups were significant.

Conclusion: A combination of toterodine and estazolam is a potential therapy for female patients with OAB and nocturia, improving significantly the OAB symptoms.

KEY WORDS: Tolterodine, Estazolam, Overactive bladder, Women.

Abbreviations: **OAB:** Overactive Bladder. **LUTS:**Lower Urinary Tract Symptoms. **NOBLE:** National Overactive Bladder Evaluation.

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INTRODUCTION

Overactive bladder is a symptom complex that is characterized by urinary urgency, with or without urgency incontinence, usually with frequency and

Table-I: Pre-treatment baseline demographics for the study population.

	Tolterodine 2mg bid+Estazolam 1mg qn	*Tolterodine 2mg bid*	*p*
Number of subjects (n)	210	197	
Age (yrs), Mean (Sd)	56.5(9.2)	57(8.9)	>0.05
Baseline OAB symptom levels, Mean (Sd)			
Urgency episodes/24 hr	7.5(2.4)	7(2.8)	>0.05[a]
Urgency incontinence episodes/24hr	3(1.8)	2.8(1.6)	>0.05[a]
Day-time frequency/24hr	12(2.2)	12.4(2.4)	>0.05[a]
Voided volume (ml)	160.5(18.4)	158.0(18.0)	>0.05[a]
Nocturia episodes	3.8(1.2)	3.5(1.0)	>0.05[a]

[a]T test

nocturia.[1] Based on the National Overactive Bladder Evaluation (NOBLE) study, the prevalence of OAB was 16.9% in women >/=18 years of age in the United States and rose with age.[2] OAB appears to be multifactorial in both etiology and pathophysiology.

The etiology of OAB comprises lower urinary tract and neurologic conditions. The symptoms of OAB are usually associated with involuntary contractions of the detrusor muscle. Overactivity of the detrusor-neurogenic, myogenic, or idiopathic in origin—may result in urinary urgency and urgency incontinence. OAB affects patients' overall quality of life, causing depression and emotional distress, which in turn exacerbate symptoms of OAB. The management of OAB includes both behavioral modification and pharmacological methods.[3] Antimuscarinic agents, such as tolterordine, are the mainstay of pharmacological treatment of OAB.[4,5]

The aims of this study were to investigate the effects of tolterodine combined with estazolam in the treatment of women with OAB and nocturia, advancing the strategies for medical management of OAB.

METHODOLOGY

Patients: We prospectively collected 407 consecutive female patients who presented with any chief complaint suggestive of OAB and nocturia between August 2008 and June 2010 from the inpatient department and outpatient clinic of Dujiangyan Medical Center and West China Medical Center in China. Women aged over 18 years old who had urinary urgency and nocturia with or without urgency incontinence or frequency for at least 6 months were included in this study. Exclusion criteria included the following: urinary tract infections, interstitial cystitis, polyuria, bladder tumor and underlying neurologic abnormalities (e.g., neuropathic bladder). Before and after 4 weeks' pharmacological treatment, all the cases were evaluated with medical, surgical, obstetric and gynecologic history, 3-day micturition diary, targeted physical examination and urinaylsis. If necessary, cystoscopy, urodynamics or videourodynamics were performed to exclude other conditions causing OAB symptoms.

Study Design and Protocol: One hundred and ninety-seven patients referred to hospital with OAB and nocturia between August 2008 and July 2009 were treated with oral tolterodine 2mg twice a day for 4 weeks. The 210 patients referred between July 2009 and June 2010 were given oral tolterodine 2mg twice a day combined with estazolam 1mg per night for 4 weeks. The study was approved by the local ethical committees and was performed with the patients' informed consent.

Table-II: Post-treatment changes in OAB symptoms.

Change, Mean (Sd)						
	Urgency episodes/24 hr	*Urgency incontinence episodes/24hr*	*Day-time frequency/24hr*	*Voided volume (ml)*	*Nocturia episodes*	*p*
Tlterodine+Estazolam	-3.5(1.3)	-2(0.9)	-2.8(1.4)	50(12.3)	-1.8(0.5)	<0.05[b]
Tolterodine alone	-2(1.5)	-1.2(0.5)	-2(1.7)	40.5(11.7)	-0.6(0.3)	<0.05[b]

[b]T test

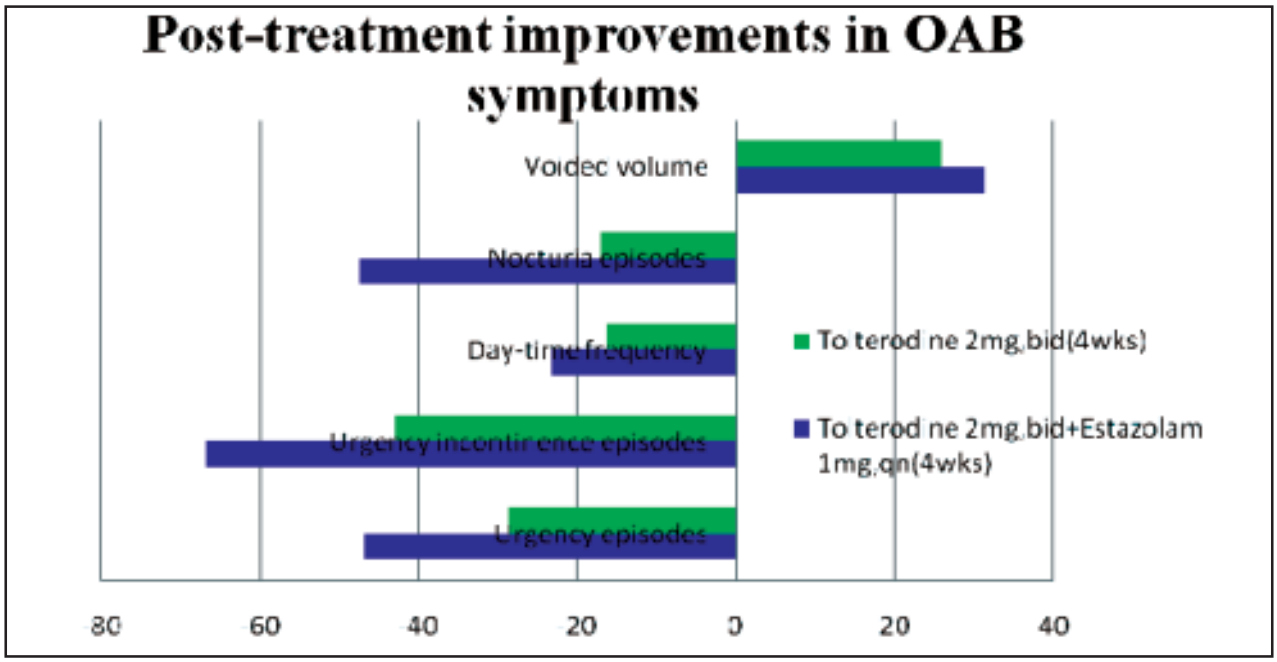

Fig-1: Post-treatment improvements in OAB symptoms.

Before and after 4 weeks' pharmacological treatment, all the enrolled subjects were asked to complete a 3-day micturition diary. Data on urgency, urgency incontinence, daytime micturition frequency, nocturia episodes and voided volume were collected. Urgency, the hallmark of OAB, is the complaint of a sudden compelling desire to pass urine which is difficult to defer. Daytime frequency is the patient's perception of urinating too often. Nocturia is defined as the need to wake one or more times per night to void. Urgency incontinence is the complaint of involuntary leakage accompanied by or immediately preceded by urgency.

Statistical Methods: For statistical analysis the unpaired Student's t-test was used to test for significant differences between the two groups in symptoms changes from pre-treatment to post-treatment urgency, urgency incontinence, daytime frequency, nocturia episodes and voided volume. SPSS version 16.0 was used for all analyses. A p value<0.05 was considered statistically significant.

RESULTS

Baseline characteristics and OAB symptoms for the study population are summarized in Table-I. A total of 407 women with OAB and nocturia were enrolled in the study between August 2008 and June 2010, of which 210 cases were in the intervention group while the other 197 cases in the control group. Patients in the intervention group were given oral tolterodine 2mg twice a day combined with estazolam 1mg per night for 4 weeks while those in the control group were given oral tolterodine 2mg twice a day for 4 weeks. Changes from baseline to endpoint in urgency, urgency incontinence, day-time frequency, voided volume and nocturia are summarized in Table-II.

At weeks 4, the number of urgency episodes per 24 hours in the intervention group decreased by 3.5 (-46.7%), urgency incontinence episodes by 2 (-66.67%), day-time frequency by 2.8 (23.3%), nocturia episodes by 1.8 (47.4%) and the volume voided per micturition increased by 50ml (31.2%), while in the control group the number of urgency episodes per 24 hours decreased by 2 (-28.6%), urgency incontinence episodes by 1.2 (-42.9%), day-time frequency by 2 (16.1%), nocturia episodes by 0.6 (17.1%) and the volume voided per micturition increased by 40.8ml (25.8%). The differences of changes of LUTS between the intervention and control groups has statistical significance (P<0.05). Compared with control group, tolterodine 2mg twice a day combined with estazolam 1mg per night resulted in a more significant improvement in all of the OAB symptoms and noctuira.

DISCUSSION

OAB can have a profound effect on quality of life. It can have an impact on daily activities, such as

work, travel, interpersonal activities, physical activity, sexual function, and sleep.[6] Drug treatment has an important role in the management of women with OAB, and tolterodine is an effective and safe antimuscarinic drug for OAB.[7,8] This study demonstrates that a combination of oral tolterodine and estazolam is a potential therapy for women with OAB and nocturia. OAB frequently causes profound psychological and social consequences as well as restricted social activities. Nocturia in OAB patients results in poor sleep quality, negative moods, and decreased quality of life, which can aggravate OAB symptoms forming a pernicious cycle,[9] and estazolam possesses anxiolytic and sedative properties, which can ease anxiety and improve sleep interrupting the pernicious cycle of OAB symptoms. Hence, tolterodine combined with estazolam is more effective than tolterodine alone in the treatment of women with OAB and nocturia. However, the exact mechanism still needs to be investigated and further controlled studies with large series and longer study period are necessary for obtaining the confirmative conclusion.

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