Combination of baclofen and antimuscarinics to reduce voiding difficulty in treating women with overactive bladders

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Summary

Purposte of study: To evaluate the efficacy of baclofen in combination with antimuscarinics to treat women with an overactive bladder (OAB) with abnormal voiding patterns. *Methods:* An action research and chart review was conducted in 245 OAB women. Women were prescribed tolterodine or oxybutynin with or without baclofen after urodynamics. The complaint of voiding difficulty was followed up one week later. *Results:* There was a significant difference in the occurrence of voiding difficulty after antimuscarinic administration in OAB women with abnormal voiding patterns compared with normal patterns (18% vs 4.9%, respectively; $p = 0.013$). The clinical difference of voiding difficulty after treating with antimuscarinics between both voiding patterns disappeared after adding baclofen (abnormal voiding pattern vs normal pattern; 11.1% vs 5.6%, respectively*; p* = 1.000). *Conclusion*: Combined use of baclofen and antimuscarinic agents could reduce voiding difficulty in treating women with overactive bladders with abnormal voiding patterns.

Key words: Overactive bladder; Antimuscarinics; Urodynamics; Voiding pattern; Baclofen.

Introduction

Overactive bladder (OAB) is a symptom complex. In 2002, the International Continence Society (ICS) announced a new definition of OAB, which is regarded as a syndrome whose diagnosis is made purely on the basis of symptoms presented without the need to perform any urodynamic investigation [1, 2]. This new definition allows greater ease in clinical practice. To date, antimuscarinic agents are the most common and currently the most effective drugs for treating OAB [3].

The most common side-effect of antimuscarinic agents is dry mouth which has long attracted much attention [4]. However, their clinical use has often been found to cause also voiding difficulty such as small caliber, decreased force of urinary stream, urinary hesitancy, or strained voiding, which can be very disturbing and distressing. It being unpredictable implies that it may have a profound impact on quality of life. Worse still, emergency catheterization may be required due to acute urinary retention. So far, there has been no protocol for treating OAB that can prevent voiding difficulty. Moreover, the idea that OAB symptoms can be caused by problems of the voiding phase has become more widely accepted. It meant that dysfunction voiding may be masked by urinary frequency and urgency, which may lead to a wrong diagnosis and inappropriate treatment [5-7]. Therefore, increasing attention has been given to the occurrence of incomplete emptying or voiding dysfunction in combination with OAB symptoms [8, 9].

Baclofen is a prototypic gamma-aminobutyric acid $(GABA)_B$ receptor agonist which could decrease external urethral sphincter resistance by depressing pudendal nerve reflex through spinal cord pre-synaptic hyperpolarization. Previous research has reported that baclofen can be employed to relieve certain kinds of voiding difficulty, which arises as a result of the external urethral sphincter or pelvic floor muscle being stressed [10]. This paper examines the effectiveness of combined use of baclofen and antimuscarinic agents, tolterodine and oxybutynin in prevention of voiding difficulty in women with OAB according to clinical symptoms without urodynamic examination. Exploration of other possible measures for avoiding voiding difficulty after antimuscarinic agents is one of the aims.

Materials and Methods

The study embraced action research as well as chart review. The database contained medical records of 245 women who had one or more typical OAB symptoms for more than one year as their chief clinical complaints between January 2004 and November 2006. The symptoms of OAB are defined as urinary urgency with or without urge incontinence, usually with urinary frequency (voiding eight times or more in a 24-hour period), and nocturia (awakening two times or more at night to void) [2, 11, 12].

In the study, patients enrolled had had no symptom of voiding difficulty and no abnormal urinary routine examinations. Other inclusion criteria were: no previous history of urinary tract abnormalities or lithiasis, no prior surgery of the pelvic floor and bladder, and no medical and neurogenic diseases. Patients on medication that could affect bladder function were not included. Combined symptoms of stress urinary incontinence and voiding difficulty also constituted the exclusion criteria. In

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addition, women had no chronic pelvic pain or painful bladder symptoms. During pelvic examination, no obvious cystocele, uterine prolapse or urogenital anomaly were found. Sonographic examination revealed no significant increase in size of the uterus or pelvic mass.

Patients were to undergo urodynamic examinations after being diagnosed with OAB syndrome. Thus, medicinal treatment was offered subsequently. Between January 2004 and October 2005, 100 women with OAB symptoms underwent a daily regimen of 2 mg tolterodine (Pfizer Italia S.R.L, Ascoli Piceno, Italy). Follow-up was scheduled one week later in clinics. Voiding difficulty associated with the regular protocol of tolterodine administration was observed. Therefore, a changeover to short-acting oxybutynine was employed. Daily 2.5 mg of oxybutynine (Panion & BF Biotec Inc., Taiwan) was given to 27 OAB patients for the period November 2005 to April 2006. Discomfort of voiding was still mentioned by the patients. Hence the successive medicine alternative was changed to a daily combination of 2 mg tolterodine along with 10 mg baclofen (Swiss Pharmaceutical Co. Ltd., Switzerland) for one week. Twenty-three patients were administered the modified protocol between May 2006 and August 2006. For cost effectiveness, the weekly regimen was changed to 2.5 mg oxybutynine daily plus 10 mg baclofen. A total of 13 patients underwent this protocol between the time frame of September 2006 and November 2006 (Figure 1).

Urodynamic studies were performed in all symptomatic patients, and consisted of measurement of post-micturition residual, urethral pressure profilometry, EMG and cystometry according to the criteria of the ICS [13]. Uroflowmetry was performed under natural circumstances. If the patient complained that the test was not performed through self-voiding as usual, the examination would be done again. In general, typical results recorded in the uroflowmetry showed a smooth single curve with the maximum flow rate exceeding 15 ml/sec under a voided volume above 200 ml. If the curve was not smooth, had multiple interrupted peaks or showed an abnormal low flow rate, the patients were considered to be suffering from an abnormal voiding pattern regardless of whether they had clinical symptoms or not.

A three-day urinary diary had to be completed to make sure that the included subjects voided more than eight times per day, awoke two times or more at night to void, and had no fluid overload the whole day. No questionnaires were used to quantify the impact of symptoms, but all subjects had these symptoms as their chief complaints, which had affected their quality of life. Of note is that the patients did not report any voiding difficulty or discomfort when having OAB symptoms.

All statistical analyses were conducted using version 13.0 SPSS software program (SPSS, Inc., Chicago, IL, USA). Demographic characteristics of the patients are presented as the mean ± SD or percentage according to the variables. Furthermore, cross tabulation was employed to describe the relationship between voiding pattern in urodynamics, baclofen, antimuscarinic agents and voiding difficulty after treatment of OAB. Comparison of the categorical data was made by the chi-square test (χ^2) and Fisher's exact test with $p < 0.05$ considered significant.

Results

Of the 245 women with OAB symptoms in our original database, only 163 patients with complete follow-up data were enrolled in our study. Thirty patients did not meet the inclusion criteria. The remaining 52 patients did not return for follow-up or treatment after urodynamic examination. We conducted a telephone interview to explore the reasons why they refused to be followed up or receive treatment. Although we did not do any statistical analysis of their responses, we discovered two common reasons for the discontinuation of follow-up. They included discomfort felt during the invasive examination procedure and lack of knowledge concerning OAB, making them reluctant to seek medical treatment.

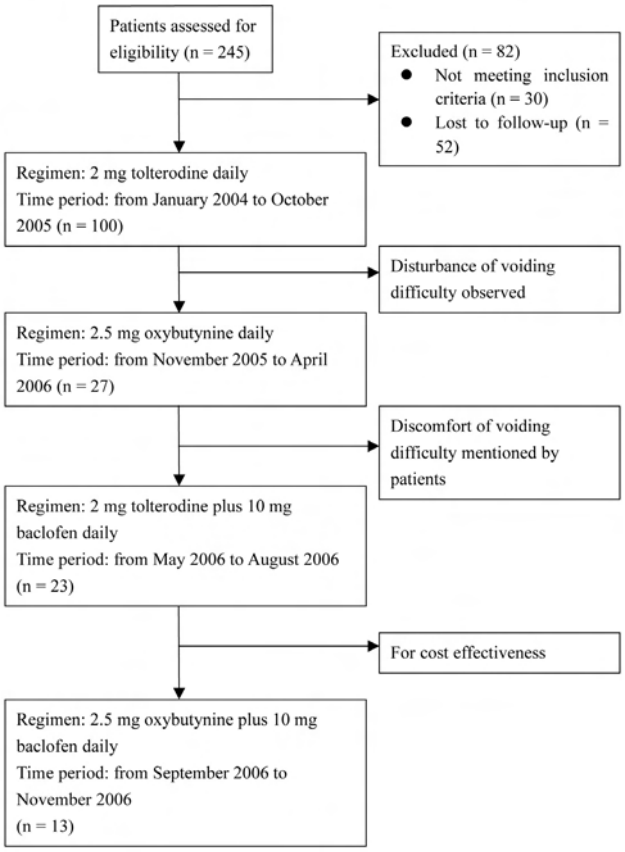

Figure 1. — Flow chart of participants through action research.

The demographic characteristics of the 163 subjects are listed in Table 1. All were Taiwanese. Their mean age was 48 years with no predominant age group found. Among them, 36.8% were postmenopausal, indicating that menopause is not a significant factor for the occurrence of OAB syndrome. However, the majority (71.8%) of the OAB patients had only normal spontaneous deliveries

Table 1. — *Patient characteristics*.

Variable	Value
Age (years)	48.1 ± 13.9 (22-79)
BMI (kg/m^2)	23.6 ± 3.8 (15.2-36.9)
Postmenopausal	60 (36.8)
NSD only	117 (71.8)
CS only	17 (10.4)
NSD and CS	4 (2.5)
Nulliparous	25 (15.3)

Values are given as mean ± standard deviation (range) or n (%).
BMI: body mass index; NSD: normal spontaneous delivery, CS: cesarean delivery.

Table 2. — *Voiding pattern in urodynamics with baclofen, antimuscarinic agents, and voiding difficulty after medication.*

Uroflow pattern	Abnormal voiding pattern (n = 82)					Normal voidin pattern (n = 81)					
Voiding difficulty after medication	Yes (n = 15)		No (n = 67)		*p*	Yes (n = 4)		No (n = 77)		*p*	0.013
Baclofen used	Yes (n = 2)	No (n = 13)	Yes (n = 16)	No (n = 51)	0.503	Yes (n = 1)	No (n = 3)	Yes (n = 17)	No (n = 60)	1.000	1.000
Tolterodine	0	12	11	38	0.101	0	2	12	48	1.000	0.008
Oxybutynin	2	1	5	13	0.247	1	1	5	12	1.000	1.000

(NSD). This implies a close relationship between NSD and OAB syndrome.

Table 2 displays the relationship among the voiding difficulty experienced by our subjects after different types of medication were prescribed to treat OAB symptoms. Of the 82 women with abnormal voiding pattern demonstrated by urodynamics, 15 (18%) had voiding difficulty after medication. However four, there were 4 of 81 (4.9%) women with normal voiding patterns who had the same complaint. There was a significant difference in the occurrence of voiding difficulty after antimuscarinic administration in OAB women with abnormal voiding patterns (18% vs 4.9%, respectively; $p = 0.013$). Despite the voiding pattern, the rate of voiding difficulty after antimuscarinic administration showed no significant difference in using different antimuscarinics (tolterodine or oxybutynin) or in combination with baclofen or not. Although no significant difference was demonstrated, we found there was a tendency when using antimuscarinics plus baclofen in reducing the incidence of voiding difficulty in OAB women with abnormal voiding patterns. On the contrary, administration with antimuscarinics plus baclofen or not showed no benefit in treating OAB women with normal voiding patterns.

Concerning voiding difficulty after using pure antimuscarinics, 14 of 100 (14%) women with tolterodine treatment reported this side-effect, while for two of 27 women (7.4%) it occurred with oxybutynin. There was no clinical difference (14% vs 7.4%, respectively; $p = 0.29$). However, if analyzed thoroughly, taking the voiding pattern into consideration, there was a significant difference in the rate of voiding difficulty occurring after prescribing tolterodine only between different voiding patterns (abnormal voiding pattern vs normal pattern; 24% vs 4%, respectively; $p = 0.008$). In contrast to tolterodine, administration of oxybutynin only in treating OAB women did not demonstrate any relationship between voiding difficulty and different voiding patterns (7.1% vs 7.7%, respectively; $p = 1.000$). Worthy of mention is that the clinical difference of voiding difficulty after treating with antimuscarinics between both voiding patterns disappeared after adding baclofen (abnormal voiding pattern vs normal pattern; 11.1% vs 5.6%, respectively; $p = 1.000$) (Table 2).

Discussion

According to our original data, of 245 OAB women underwent urodynamic examination, 117 (47.8%) had involuntary detrusor contractions similar to the findings reported earlier [14, 15]. That is, not all clinical OAB symptoms can be attributed to involuntary detrusor contractions. Hence, the idea that OAB symptoms can be caused by problems of the voiding phase has become more widely accepted. In the past, voiding dysfunction among women was often ignored or attributed to anti-incontinence surgery and pelvic organ prolapse. With better understanding of pelvic floor dysfunction, dysfunctional voiding is known to be the result of spastic external sphincter urethra or levator ani muscle. It is common among women with wrong voiding habits, habitual refraining from voiding, or chronic pelvic pain [4, 16-18]. Often these women have complaints similar to the typical OAB symptoms [4, 5].

Antimuscarinics are the first-line pharmacotherapy for OAB, however, urine retention is one of the side-effects, although the incidence is rare (1.1 to 6%) [19, 20]. Owing to the experience of voiding dysfunction after the standard dosage of administration, is why we chose a low-dose in this study. Even so, we still observed 19 of 163 women (11.7%) with voiding difficulty, which implies administration of antimuscarinics in treating OAB has to be precautious. Moreover, low-dose antimuscarinics appeared to be sufficient for the Taiwanese women in this study. The discrepancy of dosage used in most published reports and our study might be due to the difference in body frame between Western and Eastern populations.

Overactive bladder can be diagnosed according to medical history, physical examination and clinical symptoms without the aid of urodynamic examination. In this study, OAB women with abnormal voiding patterns suffering from voiding difficulty after antimuscarinic treatment had a higher incidence compared to those with normal voiding patterns (18% vs 4.9%, respectively; $p = 0.013$). If no urodynamic examination is performed before giving patients prescriptions, these patients could be given an antimuscarinic agent directly (according to the routine protocol) and be caused a higher rate of voiding difficulty. In view of this, physicians should pay greater care to the use of antimuscarinic agents for treating OAB syndrome diagnosed purely on the basis of clinical symptoms.

Even though urodynamics plays an important role in confirming abnormalities in both the storage and voiding phases, its invasive nature and discomfort causes patients to shrink back at the sight. Of 245 OAB patients who underwent urodynamic examination during the study period, 52 (21.2%) opted not to continue with the follow-up or receive treatment. Telephone interviews of these

cases revealed that most patients complained of discomfort felt during the examination. To avoid possible infection during examinations and discomfort caused by placing the catheter, non-invasive uroflowmetry examination followed by measuring residual urine after voiding by ultrasonography could be performed. This alternative can offer accurate assessment of the voiding function instead of a troublesome full course of urodynamics.

In this study, our subjects were OAB patients without clinical voiding difficulty. Even so, there were 50.3% (82 of 163 patients) with abnormal voiding patterns revealed by urodynamics in the final analysis. Therefore it is no wonder that using longer acting antimuscarinic agents such as tolterodine caused more voiding difficulty in OAB patients with an abnormal voiding pattern compared with a normal voiding pattern (24% vs 4%, respectively; $p = 0.008$). The incidence of voiding difficulty after prescribing short acting oxybutynin with low dosage made no difference despite the voiding pattern. Baclofen is a muscle relaxant and has been used for a long time as an agent for voiding difficulty resulting from spasm of the external urethral sphincter. Results shown in Table 2 reveal that combined use of baclofen with antimuscarinic agents could reduce the incidence of voiding difficulty among patients with abnormal voiding patterns. In other words, baclofen has beneficial effects when used in combination with an antimuscarinic agent for treating OAB patients with abnormal voiding patterns in terms of reducing or eliminating side-effects of voiding difficulty.

The results of our study also showed that OAB might be caused by many more complicated factors and the pathological mechanism merits further investigation. Administration with antimuscarinics in treating OAB women with abnormal voiding patterns had a higher incidence of voiding difficulty than in OAB women with normal voiding patterns. In view of this, the clinical use of antimuscarinic agents for treatment of OAB syndrome should be applied with care and at least after performing uroflowmetry examination or measuring residual urine. A urodynamic study is not a requirement for diagnosis of OAB. The combined use of baclofen with antimuscarinic agents might be a practical way to treat OAB with prevention of voiding difficulty. This was a preliminary study involving only a small number of patients; we believe larger studies with more patients are required to investigate the feasibility and effectiveness of this regimen are crucial before definite conclusions can be drawn.

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