European Journal of Obstetrics & Gynecology and Reproductive Biology 197 (2016) 91–97

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

A prospective randomized trial comparing the use of tolterodine or weighted vaginal cones in women with overactive bladder syndrome

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ARTICLE INFO

Article history:
Received 19 June 2015
Received in revised form 18 October 2015
Accepted 23 November 2015

Keywords:
Overactive bladder
Tolterodine
Vaginal cone
Efficacy
Pelvic floor exercise

ABSTRACT

Objective: To compare the efficacy of pelvic floor muscle exercises (PFME) using weighted vaginal cones (WVC) on the symptoms, clinical findings, urodynamic findings and quality of life (QoL) in overactive bladder (OAB) patients with tolterodine.

Study design: Thirty-nine patients with urinary frequency (≥8/day), nocturia (≥2/night), urgency and a total score of ≥8 to the overactive bladder-awareness tool (OAB-V8) were diagnosed as OAB and were randomized into two treatment groups; WVC and extended release tolterodine (tolterodine ER) 4 mg/day for 8 weeks. Results of the clinical findings, 3-day urinary diary, validated questionnaires for symptom bother and QoL (Urinary distress inventory (UDI-6), incontinence impact questionnaire (IIQ-7), OAB-V8, Wagner questionnaire) and urodynamic examination before and after treatment were compared.

Results: A reduction of frequency, nocturia and urinary incontinence was observed in WVC group ($p = 0.006$, $p = 0.034$ and $p = 0.008$, respectively) and in tolterodine group ($p < 0.001$, $p = 0.002$ and $p = 0.035$, respectively). 24-h dry pad test results were improved significantly in both groups ($p = 0.003$ and $p = 0.001$, respectively). Pelvic muscle strength was significantly improved in WVC group but not in tolterodine group ($p = 0.010$ and $p = 0.180$, respectively). UDI-6, IIQ-7, OAB-V8 scores were improved significantly in both groups. Improvements in Wagner questionnaire were observed in WVC group but not in tolterodine group ($p = 0.002$ and $p = 0.591$, respectively). First sensation of bladder filling was significantly improved after WVC treatment but not in tolterodine group ($p = 0.035$ and $p = 0.550$, respectively). After treatment, detrusor overactivity (DO) resolved in 8 patients in the WVC group ($p = 0.003$) and in 2 patients in the tolterodine group ($p = 0.426$).

Conclusions: WVC treatment seems to be an efficacious therapeutic option for the improvement of overactive bladder syndrome (OABS).

Introduction

OABS is characterized by urinary urgency, with or without urgency urinary incontinence (UUI), usually with daytime frequency and nocturia, in the absence of urinary tract infection (UTI) or other obvious pathology [1]. It is a common disorder with a prevalence of 12–17.4% [2,3]. OAB represents a spectrum of underlying multiple pathophysiologic conditions such as increased sensitivity of bladder afferents in the urothelial/suburothelial layer of the bladder, increased involuntary contractions of the detrusor muscle or abnormal central nervous system processing of bladder afferent signaling [4].

Different treatment options for OAB include lifestyle changes, bladder training (BT), pharmacotherapy, electrical stimulation/neuromodulation and PFME [5]. Although PFME were initially designed and used for the treatment of stress urinary incontinence (SUI), later it was realized that it can also be used in the treatment of UUI, and now it is recommended as first line therapy in all types of incontinence [5,6]. The goal of PFME in SUI is to strengthen and coordinate perivaginal muscles, thereby occluding the urethra during increases in intraabdominal pressure. In OAB, the most accepted explanation on the effect of PFME on the bladder is 'the reciprocal inhibition reflex theory', which suggests that voluntary pelvic floor muscle (PFM) contraction and increased intra-urethral pressure inhibit the parasympathetic excitatory pathway for the

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http://dx.doi.org/10.1016/j.ejogrb.2015.11.034
0301-2115/

micturition reflex via Onuf's ganglion leading to a relaxing effect on the bladder [7,8].

PFME using WVC is one way of increasing PFM strength by increasing muscle tonus and coordination [9]. A recent Cochrane review suggested that use of WVC may improve urinary incontinence (UI) symptoms and that it may have similar efficacy with PFME and electrostimulation (ES) [10]. However, data is very scarce regarding the efficacy of WVC use in the management of OAB. Although different types of methods have been shown to be effective in PFM strengthening [11], its efficacy in reducing symptom bother and improving QoL in OAB is still controversial [12,13].

Anticholinergic drugs are currently the mainstay of treatment for UUI and it has been reported that no antimuscarinic drug is superior to an alternative antimuscarinic drug for cure or improvement of UUI [5]. Tolterodine is one oral anticholinergic drug that has been extensively studied [14]. Especially the ER form has been reported to have less adverse effects and to significantly improve symptoms of urgency, urge urinary incontinence, urinary frequency and mean voided volume compared to placebo over a period of 8 weeks [5,15,16]. A Cochrane review has suggested that antimuscarinic drugs with ER formulations seem to be superior in terms of QoL improvements than immediate release (IR) forms [17]. In addition, guidelines also recommend that while choosing an anticholinergic drug, the most important criteria is to use an ER form rather than an IR formulation due to lower rates of dry mouth [18].

Therefore, we aimed to compare the efficacy of PFME using WVC on the symptoms, clinical findings, urodynamic findings and QoL in OAB patients with tolterodine ER.

Materials and methods

This was a prospective randomized trial conducted on women with OAB symptoms attending the urogynecology unit of Ankara University School of Medicine, Department of Obstetrics and Gynecology during a period of 18 months. The study was approved by the local ethics committee of the Ankara University School of Medicine. All patients were asked to give an informed consent and were instructed about the study protocol. Initially, all patients attending the unit with urogynecological symptoms were evaluated; all by the same physician. A detailed medical history was taken and a complete urogynecologic examination including the cough stress test, voided volume, postvoid residual urine (PVR) measurement, Q-tip test, pelvic organ prolapse (POP) staging, clitoral-anal reflex examination and digital evaluation of PFM strength was performed.

Simplified Pelvic Organ Prolapse Quantification (POP-Q) staging was performed in the lithotomy position as described by the International Continence Society (ICS) Committee on Standardization of Terminology [19]. PVR was measured by catheterization in 5 min after micturition. PFM strength was evaluated by digital examination according to the Modified Oxford Scoring [20].

The higher frequency of OAB symptoms in patients with POP and the reported significant symptomatic improvement after the reconstructive surgery for POP is suggestive for the causative role of POP on OAB symptoms [21,22]; therefore, in order to minimize the bias associated with POP, we excluded patients with advanced stages of POP (Stages 3 and 4, $n = 4$).

All patients completed the 3-day urinary diary and validated questionnaires for lower urinary tract symptoms (LUTS), sexual dysfunction and QoL, including the short form of UDI-6, IIQ-7, Wagner's Questionnaire for QoL and the OAB-V8.

Patients with urinary frequency ($\geq$8/day), nocturia ($\geq$2/night), urgency and a total score of $\geq$8 to the OAB-V8 were diagnosed as OAB and were included in the study. Although the selection criteria for the study reduced the number of included patients significantly, we used the OAB-V8 to identify further OAB patients and achieve a more homogeneous and 'pure' OAB patient population, as this validated screening tool has been shown to have a a high OR for probable OAB of 95.7 (95% CI: 29.3; 312.4) for scores $\geq$8, with a sensitivity of 98.0 and specificity of 82.7 [23].

Exclusion criteria were: Patients under 18 years of age, patients with a positive cough stress test, positive Q-tip test (>30 degree), PVR $\geq$100 ml, POPQ stage $\geq$3, pregnant women, the presence of urinary tract infection, neurological disease, uncontrolled metabolic disease, glaucoma, and patients who had received anticholinergic therapy and PFME in the last 3 months.

Patients meeting the inclusion criteria completed a 24-h pad test described by Sullivan et al. [24]. The pads used in the 24-h period were placed in sealable plastic bags and were weighed on a balance with a precision of 0.01 g. The multichannel urodynamic examination followed the standards recommended by the ICS [1]. The patients were then randomized with a computerized program into two therapeutic options; PFME with WVC or tolterodine ER tablets 4 mg per day.

Treatment protocol

In the vaginal cone group, four vaginal cones of the same volume and size with varying weights (20 g, 34 g, 50 g and 68 g) were used (Elanee Pelvic Floor Training Aids-Phase 1,GRÜNSPECHT Naturprodukte e.K., Ingolstadt, Germany). At the initial visit, the patients were taught how to insert and hold the weighted vaginal cone while standing. Starting from the lightest cone the patient could be able to hold, the patients were instructed to stand up, walk and do housework/exercise after inserting the vaginal cone twice daily and each set for 10 min according to the manufacturer's instructions. A heavier cone was used once the patients were be able to retain the current weight for >10 min. At the initial visit, patients were both instructed by demonstration on how to use vaginal cones and and then application of cone was observed under supervision. The patients in the other group were given tolterodine ER 4 mg per day. After 4 weeks of treatment, the patients were called for follow-up to check compliance and side effects. Treatment efficacy was evaluated after 8 weeks of both treatments with 3-day voiding diary, questionnaires, urogynecologic examination, 24-h pad test, and urodynamic examination.

Statistical analysis

The sample size calculation was based on an expected 50% decrease in UI episodes [25]. The mean number of UI episodes in a small group of women with OABS in our study was 3.5/day with a standard deviation of 2.8. To detect a 50% decrease in the number of UI episodes, 20 patients were required for each group with 80% power and a two-sided type I error rate of 0.05.

Statistical analysis was performed with SPSS version 14.0 for Windows (SPSS, Inc., Chicago). Descriptive statistics were expressed as mean $\pm$ standard deviation or median for continuous variables. The significance of the difference between two groups was analyzed with Student's t test for continuous variables consistent with normal distribution and the Mann–Whitney U test for continuous variables that were not normally distributed. The significance of the difference between pre-treatment and post-treatment measurements within groups was analyzed with the Significance of Difference Between Two Pairs Test (dependent t-test) for normally distributed continuous variables and with the Wilcoxon Sign Test for not normally distributed continuous variables. Categorical data were compared using Fisher's Exact Probability test. Bonferroni adjustment was performed for all possible intra-group comparisons. A p value < 0.05 was considered statistically significant.