ORIGINAL RESEARCH

THE EFFICACY OF TROSPIUM CHLORIDE IN WOMEN WITH AN OVERACTIVE BLADDER

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ABSTRACT

Objective: The efficacy of trospium chloride on lower urinary tract symptoms and urodynamic parameters in women with OAB were investigated.

Material and Methods: Forty-four consecutive women with OAB were enrolled in this study. Before and after 8 weeks of TC treatment, OAB-V8 scores of the patients related to the current symptoms were collected. Urodynamic studies were performed in 28 patients (63.6%). Primary and outcome variables were OAB symptom score and urodynamic findings. The difference in response to TC according to the lower urinary tract symptoms between the patients with or without proven detrusor overactivity was analyzed.

Results: Mean OAB-V8 score of the patients after the treatment with TC was significantly lower than before the treatment (11.9±6.3; 24.9±5.1; p<0.05). After treatment, when compared to the mean OAB-V8 score of patients without DO (14.2±5.3), the mean symptom score of those with proven DO (10.3±4.1) was found to be statistically lower (p<0.05).

Conclusion: Trospium was much more effective in improving symptoms in women with proven DO than in women without DO.

Keywords: Overactive bladder, Voiding dysfunction, Pharmacotherapy

AŞIRI AKTİF MESANE SENDROMU OLAN KADINLARDA TROSPIUM CHLORIDE TEDAVİSİNİN ETKİNLİĞİ

ÖZET

Amaç: Aşırı aktif mesane sendromu bulunan kadınlarda trospium tedavisinin etkinliğini ve bu etkinin ürodinamik bulgular ile ilişkisi araştırıldı.

Yöntem: Aşırı aktif mesane sendromu bulunan 44 kadın hasta çalışmaya alındı. 8 haftalık trospiyum tedavisinden sonra, hastaların tedavi öncesi ve sonrası OAB-V8 semptom skoru, ürodinamik bulguları karşılaştırdı.

Bulgular: Ortalama OAB-V8 semptom skoru tedavi ile birlikte anlamlı olarak düşük bulundu (11.9±6.3; 24.9±5.1; p<0.05). Detrusor aşırı aktivitesi bulunan kadın hastaların (10.3±4.1) detrusor aşırı aktivitesi olmayan kadın hastalara (14.2±5.3) göre trospium tedavisinden daha fazla fayda göруldüğü saptandı.

Sonuç: Trosipium tedavisi ispatlanmış detrusor aşırı aktivitesi olan kadın hastalarda daha etkili bulunmuştur.

Anahtar Kelimeler: Aşırı aktif mesane, İşeme disfonksiyonu, Farmakoterapi
INTRODUCTION

Overactive bladder (OAB) is defined as urgent with or without incontinence, usually with frequency and nocturia by the International Continence Society (ICS), and it affects nearly 17% of the general adult population.

Although the pathophysiology of OAB is not still completely understood, it is almost certainly multifactorial. The voiding process can be visualized as complex neural circuits in the brain and spinal cord that coordinate the activity of smooth muscle in the bladder and urethra. Although the treatment of choice has been anticholinergics in the management of overactive bladder, these cause a wide spectrum of undesirable side effects. Trospium chloride (TC) is a quaternary ammonium compound that is a non-receptor selective anticholinergic drug with primarily peripheral (antimuscarinic) activity, but also, at least in vitro, some ganglionic (nicotinic) effects. When taken orally, up to 60% of metabolically active, absorbed trospium is excreted in the urine, and it has not been shown to cross the blood-brain barrier in humans.

Although urodynamic study has been accepted as a useful tool in the diagnosis of the overactive bladder, the variations in the technique and the intrinsic variability of the physical factors being tested can undermine the overall value of urodynamic testing. In this preliminary study, the efficacy of TC on lower urinary tract symptoms and urodynamic changes in patients with OAB were investigated.

MATERIAL AND METHOD

Patient characteristics

Between January 2003 and 2005, a total of 44 consecutive women admitted to the outpatient clinic (mean age of 52.8+7 years, range 18 to 73 years) with overactive bladders based on a detailed history, physical examination, routine laboratory tests including urine analysis, were enrolled in this study after an informed consent was signed.

All the patients were 18 years or older and they had complaints of urgency with or without incontinence, usually with frequency and nocturia for at least 6 months. Patients with predominantly stress incontinence, neurogenic bladder, post-voiding residual volume greater than 100 ml, closed angle glaucoma, significant renal disease or other severe systemic diseases and any contraindications to antimuscarinic therapy were excluded from the study. Also patients using any previous anticholinergic drugs for the treatment of OAB were not included.

Study Protocol

Before and after 8 weeks of treatment with TC (15 mg, three times daily), all patients underwent physical examination with measurements of blood pressure and pulse rate. The OAB-V8 scores related to the current symptoms of the patients were collected. Urodynamic studies were performed by an experienced technician at the beginning and at the end of the treatment period in 28 patients (63.6%), who had all signed the consent form, and the data were interpreted by a single observer to avoid bias.

A urodynamic study was performed according to the report from the standardization subcommittee of the ICS with an 8 F dual lumen vesical catheter and an 8 F rectal balloon catheter using saline, with the patient in upright position, at a filling rate of 40 ml/min. First of all, post-void residual urine was measured with the catheter before examination. During bladder filling, patients were asked simply to report their sensations to the examiner. The first sensation of bladder filling, maximum cystometric capacity and bladder compliance as well as any possible unstable detrusor contractions were noted. Detrusor overactivity was diagnosed when detrusor contractions were seen in the presence of urgency or urinary leakage while the woman was attempting to inhibit micturition.

Outcome variables

The primary outcome variables were the lower urinary tract symptoms of patients.
assessed with OAB-validated 8-question awareness tool (OAB-V8). This included eight questions regarding urinary frequency, urgency, nocturia and incontinence in order to assess the patients’ symptoms. The secondary outcome variables were urodynamic parameters such as the volume at first desire (FDV), bladder compliance, and maximum cystometric capacity.

Statistical analysis

Values were expressed as mean ± SD, and the Wilcoxon test analysis was used to compare variables before and after the treatment. Spearman’s Rho correlation test was used to correlate the OAB symptom scores and urodynamic changes. P value less than 0.05 was considered statistically significant.

RESULTS

There were similar results in the pulse rate and systolic and diastolic blood pressure values between before and after the treatment (p>0.05). While the mean OAB-V8 score of the patients before treatment with TC was 24.9±5.1 (range 14 to 34), the OAB-V8 the score after treatment was 11.9±6.3 (range 5 to 28) (Table I). The mean OAB-V8 score after treatment was found to be statistically significantly lower than that of the patients before the treatment (p<0.05). Thirty-seven of the patients, (84%) were found to have improved with the treatment, and in these patients clinical symptoms either resolved or decreased markedly. Only 7 (16%) patients treated with trospium chloride showed no improvement in their OAB-V8 scores.

According to the stratification of the patients after the findings of the urodynamic study, the mean volume at first desire (FDV) was found to have increased from 79.2±13.2 to 110±8.5 ml (p<0.05). The mean maximum cystometric capacity (MC) increased significantly with TC from 216±34 to 320±31.1 ml (p<0.05). Furthermore, mean bladder compliance (BC) increased significantly after treatment (21.1±4.5) with TC compared to pretreatment values (13.3±2.5) (p<0.05) (Figures 1-2). Eleven of the patients (39.2%) who underwent urodynamic study before the treatment, were found to have detrusor overactivity, and after treatment only 4 (14.2%) still had detrusor overactivity (p<0.05).

Table I: The urodynamic parameters and the symptom score values before and after the treatment of women with overactive bladder (OAB-V8: OAB-validated 8-question awareness tool, BC: Bladder compliance).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean OAB-V8 scores</td>
<td>24.9±5.1</td>
<td>11.9±6.3</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>First sensation of bladder filling (ml)</td>
<td>79.2±13.2</td>
<td>110±8.5</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Maximum cystometric capacity (MC) (ml)</td>
<td>216±34</td>
<td>320±31.1</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Bladder compliance (ml/cmH20)</td>
<td>13.3±2.5</td>
<td>21.1±4.5</td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>Detrusor overactivity (no. pts (%))</td>
<td>11 (39.2%)</td>
<td>4 (14.2%)</td>
<td>p&lt;0.05</td>
</tr>
</tbody>
</table>
Concerning the baseline OAB-V8 scores, patients with proven detrusor overactivity had a statistically higher symptom score (27.5±4.2) compared to those without detrusor overactivity and without urodynamics (22.4±4.0 and 23.9±3.6, respectively). After treatment, when compared to the mean OAB-V8 score of patients without detrusor overactivity (14.2±5.3), the mean symptom score of those with proven detrusor overactivity (10.3±4.1) was found to be statistically lower (p<0.05).

In the case of correlation between OAB symptom scores and urodynamic changes, there was a negative correlation between OAB-V8 score and mean BC and FDV (p<0.05). The presence of a higher symptom score did not result in a lower MC value, but the correlation was not significant (p>0.05).

According to the spontaneous reporting of undesirable effects, only 8 patients (18%) were found to have experienced adverse effects. Dryness of mouth was the major side effect seen in 5 patients (11%). Constipation was spontaneously reported by 4 patients (9%) and blurred vision by 2 (4.5%) of the patients treated with TC. All these adverse effects reported by the patients were transient and reversible with the discontinuation of the treatment.

**DISCUSSION**

Overactive bladder (OAB) with an overall prevalence of around 16-17% in Western Europe and United States is also a major economic burden for patients, healthcare providers and society as a whole. It was found that patients with OAB are known to have worse quality of life scores than patients with other chronic diseases such as diabetes. The main goal of pharmacological treatment for OAB is to inhibit detrusor overactivity and thereby to increase the functional bladder capacity. Although anticholinergic agents are the most common and currently the most effective drugs used to treat OAB, their lack of selectivity is responsible for the classic peripheral anticholinergic side effects of dry mouth, constipation, blurred vision, tachycardia and effects on cognitive function. In our study, with spontaneously reporting only, 18% of the patients experienced some side effects, and the major side effects were dry mouth in 11% of the group, constipation in 9% and blurred vision in 4.5%. These results were found to be consistent with other studies in literature. There was no discontinuation because of the adverse effects of TC.
There is a lack of information regarding the natural history and the long-term outcome of an overactive bladder. Additionally, there is no published, well-designed longitudinal study of a long-term follow up of these patients to date. However, Zinner et al. performed a placebo controlled, multicentric study with 523 patients, and they showed that patients treated with TC are likely to experience a clinically meaningful decrease in lower urinary tract symptoms attributable to OAB\textsuperscript{16}. Since most OAB-related symptoms showed significant improvement by the end of week 1, it was concluded that this rapid onset of action increases the compliance of patients to therapy. Likewise, Rudy et al. found that TC was significantly and sustainably effective in their multicentric placebo-controlled study including 658 patients\textsuperscript{17}. In their study, all the effects of TC had occurred by the end of week 1 and all patients improved and sustained this improvement throughout the 12-week study. In a study comparing the effects of oxybutynin with TC, they demonstrated that both of these drugs were equal in decreasing urinary frequency but trospium had less severe adverse effects\textsuperscript{18}. Because of the rapid onset of action, we investigated the patients by the end of 8 weeks, and of 44 patients treated with TC, 37 (84\%) were found to have improved with the therapy. Only 7 patients treated with TC did not have any improvements in their symptoms.

Although some studies suggest that, during cystometry, phasic detrusor overactivity was found in only 40\% to 60\% of the patients with OAB symptoms\textsuperscript{19}, most urodynamic evaluations have revealed a premature filling sensation with decreased bladder capacity\textsuperscript{20}. The use of urodynamics was found to be controversial in patients with OAB. Some authors suggest that patients with OAB can be safely treated according to their history, without the need for invasive urodynamics, whereas others concluded that urodynamic evaluation is an essential tool in the management of women with OAB\textsuperscript{21}. The principal urodynamic feature of overactive bladder is presumed to be detrusor muscle overactivity\textsuperscript{22,23}. Urodynamic studies act as diagnostic tests to identify etiologies such as involuntary detrusor contractions or low bladder compliance underlying OAB. The present study showed that women with proven detrusor overactivity had a higher pre-treatment OAB-V8 symptom score than the others.

We have used the urodynamic evaluation in 28 patients to evaluate the results in an objective way as well as considering the subjective symptoms of patients. According to our study, the mean maximum cystometric capacity (MC) and mean bladder compliance (BC) were found to increase significantly after treatment with TC, compared to pretreatment period. Of the patients who underwent urodynamic study, around 40\% were found to have detrusor overactivity at the beginning, but only 14\% still had detrusor overactivity after the treatment. There are other studies showing a significant increase in mean maximum bladder capacity from around 80 to 140 ml in patients using trospium compared to placebo\textsuperscript{24}. The findings in these studies showed that TC has a significant effect on the urodynamic parameters including the bladder capacity, bladder compliance, bladder stability and the first sensation of bladder filling.

As there are few studies concerning the correlation between the OAB symptom scores and urodynamic findings, we investigated this correlation in the present paper. We found that there was a negative correlation between the OAB-V8 score and both mean bladder capacity and the first desire volume. But there was no correlation between the symptom score and maximum cystometric capacity. Although the weak point in our study for evaluating women with OAB who underwent trospium treatment, is that the study was not placebo-controlled, it is to our knowledge, the first study in the literature evaluating the efficacy of TC in OAB by comparing the lower urinary tract symptom scores of patients with detrusor overactivity to those of patients without detrusor overactivity and also with patients who had not undergone urodynamics. Other studies have revealed that the placebo effect of TC is high in OAB, and
it was demonstrated that the placebo effect in decreasing the patients’ symptom score and urge incontinence episodes at 3 months was around 12-18% and 45%, respectively. Dry mouth and constipation in patients with placebo treatment were found to be 5.2% and 5.8%, respectively. In conclusion, trospium chloride was found to be effective and safe in the treatment of women with overactive bladders in regard to the improvement of urodynamic parameters and of symptoms. It was much more effective in the treatment of women with proven detrusor overactivity than in women without detrusor overactivity. Placebo-controlled studies with a larger number of patients should document the outcome assessment of trospium on the quality of life and urodynamic findings in patients with OAB to support our results.

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REFERENCES