A pilot study of the use of fesoterodine in the management of men with refractory overactive bladder symptoms after surgery for bladder outlet obstruction

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ABSTRACT

Objective: To assess the efficacy of long-acting fesoterodine on persistent lower urinary tract symptoms in men who have had previous surgical treatment for bladder outlet obstruction (BOO).

Materials and methods: Seventeen patients with overactive bladder (OAB) secondary to BOO, persisting for 3 months after the obstruction was surgically relieved, were treated with fesoterodine. Follow up was performed at 2 months, 3 months, and 7 months. The primary endpoint was change in the International Prostate Symptom Score (IPSS). The secondary endpoints were change in the maximum flow rate (Qmax) and postvoid residual (PVR).

Results: Patients receiving fesoterodine demonstrated trends for improvement in mean nocturia episodes (3.2 ± 2.6, p = 0.065), IPSS irritative subscore (6.2 ± 2.0, p = 0.066), and quality of life score (4.2 ± 3.5, p = 0.067) over 7 months of follow up. There was also a reduction in the mean IPSS score which was not significant over time (18.8 ± 15.1, p = 0.183). There was no significant change observed in Qmax or PVR.

Six patients (33%) had significant side effects and did not complete the study.

Conclusion: Patients with persistent OAB symptoms after surgical treatment of BOO displayed possible reductions in the IPSS, IPSS irritative subscore, and mean number of nocturia events after 7 months of follow up, as well as trends for an increased quality of life when treated with fesoterodine. Larger trials are needed to help characterize the utility of fesoterodine in the treatment of persistent lower urinary tract symptoms after surgical treatment of benign prostatic hyperplasia.

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1. Introduction

Transurethral resection of the prostate (TURP) is considered to be the gold standard in the operative management of benign prostatic hyperplasia.1–4 Sparked by a desire to improve outcomes and reduce morbidity and mortality, technological advancements have increased the surgical options available to patients. However, even after surgical treatment, as many as one third of patients have troublesome lower urinary tract symptoms following transurethral surgery. Incidence of voiding dysfunction after transurethral prostatectomy has been reported to be between 5% and 35%.1

Detrusor overactivity may play a role in the persistent postoperative symptoms following treatment for bladder outlet obstruction (BOO).5 Although the mechanism is not entirely clear, studies have shown that the increased bladder pressure often caused by obstruction can result in denervation of the detrusor muscle, causing overactivity.6,7 Another cause of detrusor denervation and overactivity can be chronic hypoxia resulting from decreased blood flow after surgery.8

Persistent LUTS is a difficult problem to manage post TURP. We investigated the role of antimuscarinics in this setting. The present study examines the efficacy of antimuscarinic medication fesoterodine fumarate (Toviaz, Pfizer Inc., New York, NY, USA) for persistent overactive bladder (OAB) symptoms after surgical treatment for BOO.

2. Materials and methods

After Institutional Review Board approval and informed written consent were obtained, 18 patients with refractory OAB symptoms secondary to treatment for BOO participated in this single center...
Pilot study. Patients were treated with fesoterodine using a United States Food and Drug Administration approved flexible dosing regimen of 4–8 mg. The primary endpoint was change in the International Prostate Symptom Score (IPSS). The secondary endpoints were change in the maximum flow rate (Qmax), postvoid residual (PVR), and IPSS quality of life (QoL) score. Follow ups were performed at 2 months, 3 months, and 7 months post treatment.

Participants were males > 40 years of age who had refractory OAB with no improvement 3 months after TURP. All patients had an IPSS score > 12 as well as an IPSS QoL score > 3 at screening. At each postop visit, patients filled out an American Urological Association symptom score questionnaire, underwent noninvasive uroflowmetry, and had PVR measured by a bladder scan. Patients completed 3-day bladder diaries between each clinic visit.

Patients with a history of interstitial cystitis, uninvestigated hematuria, Mullerian duct cysts, urethral obstruction caused by urethral tumor, radiation cystitis, genitourinary tuberculosis, bladder calculi, or detrusor-sphincter dyssynergia were excluded. Additional exclusions included evidence of urinary tract infection, and any significant hepatic or renal disease (defined as twice the upper laboratory limit in AST, ALT, ALP, BUN, or creatinine). Patients who used any electrostimulation within 30 days of screening, had a history of interstitial cystitis, uninvestigated hematuria, Mullerian duct cysts, urethral obstruction caused by urethral tumor, radiation cystitis, genitourinary tuberculosis, bladder calculi, or detrusor-sphincter dyssynergia were excluded. Additional exclusions included evidence of urinary tract infection, and any significant hepatic or renal disease (defined as twice the upper laboratory limit in AST, ALT, ALP, BUN, or creatinine). Patients who used any electrostimulation within 30 days of screening were excluded.

Statistical analyses were conducted on an intent-to-treat basis to evaluate difference of symptoms, PVR, or Qmax from baseline through 2 months, 3 months, and 7 months follow up. Means and ranges from raw data are presented. As none of the variables under consideration are normally distributed, Friedman one-way nonparametric analysis of variance was used to assess changes over time. All statistical tests were two-sided and interpreted at a 5% significance level; analyses employed the last observation carried forward method. SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

3. Results

There were 17 patients enrolled in the trial with a mean age of 72.1 (range 53–91) years and a mean body mass index of 28.25 (range 19.1–35.9). All patients had undergone either TURP or photoselective vaporization of the prostate. Thirteen patients were treated initially with laser TURP and four with TURP (Table 1). Eleven of the 17 patients enrolled completed the full 7 months. Six patients were unable to complete the 7-month trial period because of medication related adverse effects. Adverse effects leading to withdrawal from the study included constipation in three patients (17% of total enrolled), dry mouth in three patients (17%), and dry eyes in one patient (6%).

There was a trend for reductions observed in mean nocturia episodes (3.2–2.6, p = 0.065) and the IPSS irritative subscore (6.2–2, p = 0.066) and QoL score (4.2–3.5, p = 0.067) over the 7 months of follow up (Table 2). There was also a reduction in the mean IPSS score which was not significant over time (18.8–15.1, p = 0.183; Table 2). There was no significant change observed in Qmax or PVR.

To our knowledge, there has been no other study on the use of fesoterodine for the treatment of refractory OAB after TURP. The use of fesoterodine demonstrated possible reductions in the IPSS, IPSS irritative subscore, and mean number of nocturia events after 7 months of follow up (Table 2; Fig. 1). There were also trends for an increased quality of life (a lower QoL score indicating a more positive outlook; Table 2). The IPSS obstructive subscore did decrease in a similar continuous manner over 7 months, but this was not found to be statistically significant (Fig. 1; Table 2). Change in PVR after 7 months was not statistically significant. As seen in Fig. 2, PVR appears to drop and increase again after 2 months, whereas Qmax appears steady over time. Of the nine patients who remained on the trial for the full 7 months, seven patients continued treatment long term for > 15 months.

4. Discussion

Treatment with fesoterodine was tolerated in our small cohort. Six patients withdrew from the study due to side effects associated with fesoterodine, mainly constipation and severe dry mouth. No

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### Table 1

Baseline characteristics.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Laser</th>
<th>TURP</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3 (19.1–35.9)</td>
<td>13 (76.5)</td>
</tr>
<tr>
<td>Voided Volume (VV)</td>
<td>86 (20–292)</td>
<td>4 (23.5)</td>
</tr>
</tbody>
</table>

Data are presented as n (%) or median (range).

BMI — body mass index; TURP — transurethral resection of the prostate.

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### Table 2

Summary of study findings.

<table>
<thead>
<tr>
<th>Time</th>
<th>Total</th>
<th>Obstructive</th>
<th>Irritative</th>
<th>Nocturia</th>
<th>QoL</th>
<th>Qmax</th>
<th>QAvg</th>
<th>PVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>18.8 (5.3)</td>
<td>9.1 (3.9)</td>
<td>6.6 (2.1)</td>
<td>3.2 (1.6)</td>
<td>4.2 (1.1)</td>
<td>15.3 (18.0)</td>
<td>n/a</td>
<td>42.9 (43.2)</td>
</tr>
<tr>
<td>2</td>
<td>15.8 (7.9)</td>
<td>7.5 (5.1)</td>
<td>5.6 (2.6)</td>
<td>2.8 (1.6)</td>
<td>3.8 (1.3)</td>
<td>10.2 (3.5)</td>
<td>5.1 (2.0)</td>
<td>33.1 (39.4)</td>
</tr>
<tr>
<td>3</td>
<td>16.2 (6.3)</td>
<td>8.4 (4.1)</td>
<td>5.1 (2.2)</td>
<td>2.6 (1.3)</td>
<td>3.5 (1.5)</td>
<td>10.6 (3.9)</td>
<td>6.1 (2.6)</td>
<td>48.2 (64.8)</td>
</tr>
<tr>
<td>7</td>
<td>15.1 (6.7)</td>
<td>7.9 (4.3)</td>
<td>4.4 (2.4)</td>
<td>2.6 (1.3)</td>
<td>3.5 (1.5)</td>
<td>10.5 (4.2)</td>
<td>6.2 (3.0)</td>
<td>55.2 (56.1)</td>
</tr>
</tbody>
</table>

PVR — postvoid residual; QAvg — average flow rate; Qmax — maximum flow rate; QoL — quality of life.

* Data are expressed as mean (standard deviation) at each time period for 17 patients using the last observation carried forward for six patients who dropped out of the trial.

* Subscore is missing for one patient.
serious complications were observed. This side-effects profile corresponds to that shown by both Chapple et al. and Nitti et al.

Konstantinidis et al. conducted a randomized prospective study comparing fesoterodine extended-release in combination with tamsulosin to tamsulosin alone, for 47 men with persistent OAB after 1 week of tamsulosin. Patients who received the addition of fesoterodine displayed significantly reduced troublesome LUTS and storage symptoms after 4 weeks as measured by IPSS. In a double-blind placebo controlled study conducted by Weiss et al., the use of fesoterodine for overactive bladder symptoms, particularly nocturnal urinary urgency, resulted in reduced micturition-related nocturnal urgency episodes. This corresponds to our findings of decreased mean nocturia episodes over 7 months. In a subanalysis of pooled data enrolled in two double-blind, placebo-controlled Phase III trials, Herschorn et al. found fesoterodine 4 mg and 8 mg to be effective for overactive bladder symptoms in 358 men. It was well tolerated with the side effects consisting of mainly constipation and dry mouth.

This pilot study has several limitations. These include small study size and the nonrandomized and nonblinded administration of the drug. Also, patients may have had some resolution of their irritative symptoms over time. The inclusion of different surgical procedures in a small cohort of patients creates the potential for a different incidence of postoperative OAB and different, time-dependent, self-limiting storage symptoms.

This study was conducted using 3-day voiding diaries. Although consistent with most other trials, a 7-day diary may have unmasked other changes in voiding habits, incontinence episodes, etc. Larger trials that are both randomized and blinded are needed to further characterize the role of fesoterodine in the cohort.

5. Conclusion

The use of the antimuscarinic medication fesoterodine fumarate demonstrated possible reductions in the IPSS, IPSS irritative subscore, and mean number of nocturia events after 7 months of follow up, as well as trends for an increased quality of life (a lower score indicating a more positive outlook) in our small cohort of patients with refractory OAB after surgical treatment for benign prostatic hyperplasia. There was a dropout rate of 33%. Additional larger trials are needed to further analyze the utility of fesoterodine for this difficult-to-manage indication in this cohort.

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

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