Efficacy of Tamsulosin in the Treatment of Lower Urinary Tract Symptoms (LUTS) in Women

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OBJECTIVE: We attempted to determine whether tamsulosin is an efficacious therapy for the treatment of lower urinary tract symptoms (LUTS) in women.

METHODS: A total of 140 women, aged 27–69 years old with LUTS entered a randomized double-blind study comparing tamsulosin (70) versus placebo (70) for 1 month. The outcome variables were mean change from baseline of International Prostate Symptom Score (IPSS), mean change from baseline of mean and maximum urinary flow rate and any adverse effects.

RESULTS: Mean change from baseline of IPSS (standard deviation, SD) were −5.6 (6.3) in the tamsulosin group and −2.6 (6.1) in the placebo group. The difference was statistically significant (p = 0.008). Mean change from baseline of mean urinary flow rate (SD) was 0.7 (2.7) mL/second in the tamsulosin group and −0.5 (2.6) mL/second in the placebo group. The difference was also statistically significant (p = 0.013). However, the difference in mean change from baseline of maximum urinary flow rate between the two groups was not statistically significant (p = 0.506). There were two patients in the tamsulosin group who experienced dizziness and asthenia. No other adverse effect was detected.


Key Words: lower urinary tract symptoms, tamsulosin, urinary flow rate

Introduction

There are many drugs that have been used to treat lower urinary tract symptoms (LUTS) in women, such as anticholinergics and α1-adrenergic receptor (AR) antagonists, but there is yet no evidence of any drugs which can be classified among the gold standards. Despite α1-AR antagonists not being officially registered for the treatment of LUTS in women, they are used to relieve bothersome symptoms in these patient groups.

Both men and women experience a similar high prevalence of LUTS, which increases with age.1–4 LUTS appears to be a social problem and affects the quality of life in almost half of affected women.4 It means that if we can treat LUTS in women, their quality of life will improve. LUTS also have some common underlying aetiologies in both men and women. One of these aetiologies is that they have the same α1D-AR in bladder and α1A-AR in prostate gland (men) and urethra (women) which might be involved in causing LUTS.5 Based on these findings, α1-AR antagonists should theoretically be an efficacious treatment in both men and women. Moreover, α4A/D-AR antagonist should be more efficacious than α1A-AR antagonist used alone.

Several randomized controlled trials have demonstrated that tamsulosin, a new long acting selective α1A/D-AR antagonist, is a safe and effective therapy for the treatment of LUTS suggestive of benign prostatic obstruction (BPO).
Tamsulosin has been shown to significantly increase urinary flow rate and improve symptom scores and quality of life relative to placebo in men with LUTS suggestive of BPO.

The severity of urinary symptoms associated with LUTS has been quantified using different symptom indexes. The International Prostate Symptom Score (IPSS) has been validated and presently represents the most widely accepted instrument for assessing the severity of LUTS in men, and when captured by it, the aged-dependent prevalence of LUTS is equivalent in both men and women.12–14 A recent study has also shown that it is a good indicator of the degree of bothersome symptoms and affects the quality of life throughout various age groups of women and is independent of coexisting incontinence.15 All of these observations suggest that the development of LUTS might be age-specific and not gender-specific. If this hypothesis is valid, women with LUTS may also benefit from tamsulosin.

Only two limited clinical studies have been reported with α₁-AR antagonists in women with LUTS.16,17 They used α₁A-AR antagonists in the treatment of women with LUTS. The results of these studies are in different directions and inconclusive.

We therefore performed this randomized controlled trial to determine the efficacy of tamsulosin for the relief of LUTS symptoms in women.

Methods

Patients and procedures

This prospective, randomized double-blind placebo controlled trial was carried out at the Ramathibodi Hospital, Faculty of Medicine, Mahidol University, between April 2004 and March 2005 (enrollment of patients ended in February 2005). The inclusion criteria were new cases of women with LUTS, age > 20 years, IPSS ≥ 8, normal urinalysis and provision of written informed consent. The exclusion criteria were pregnant women, stress urinary incontinence, urinary tract infection, neurological diseases including diabetes mellitus with neuropathy, postradiation to pelvic organs, bladder cancer and contraindications for α₁-AR antagonists. The study design was reviewed and approved by the ethics board of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

Using 35% difference in mean change from baseline of IPSS between terazosin and placebo from the previous study16 by assuming that tamsulosin was at least as efficacious as terazosin and a power of 80%, the type I error was set at 0.05 and the sample size in each treatment group was set at 70. Therefore, 140 women were enrolled in the study and were randomly allocated in 1:1 ratio to either the tamsulosin group or to the placebo group in double blind fashion. Block randomization size of four was carried out by computer-generated random number and was done before the women received any treatment. The tamsulosin group consisted of 70 women, five of whom were lost to follow-up (three due to symptoms not improved and two due to adverse effect), leaving 65 women who could be evaluated. Of the 70 women in the placebo group, two were lost to follow-up due to symptoms not improved. All 140 women were included in the intention to treat analysis.

The study was conducted during a 1-month period. Two visits were planned: an inclusion visit (D0) and end-point visit (D30). During the treatment phase (D0–D30), patients were randomized to receive either tamsulosin (0.2 mg) or placebo. Study medications were packaged in a concealed card to maintain blinding in the pharmacy unit. Patients took one capsule daily in the evening after food. IPSS was filled in by patients themselves using validated IPSS Thai version. All uroflowmetry recordings were carried out using the same device (Life-Tech Janus IV®). The various uroflowmetry parameters of maximum flow rate (mL/second), void volume (mL), and flow time (second) were measured. Mean flow rate (mL/second) was calculated by dividing the void volume (mL) by the flow time (second). Uroflowmetry was considered valid if the void volume was of at least 150 mL. If the void volume was not sufficient, the patient was asked to drink 300–500 mL of fluid and undergo a second uroflowmetry 1 hour later. General clinical safety was assessed by the collection of spontaneously reported adverse events at the end-point visit. For compliance, the doctor asked at the end-point visit if the treatment was taken on a regular basis and counted the remaining tablets/drug. For co-intervention, patients were asked at the inclusion visit not to take any other treatment or drug for LUTS, and at the end-point visit, the patient was asked whether she had taken other medication for the treatment of LUTS.

The primary outcome was improvement in IPSS after 4 weeks of treatment. The mean change from baseline at the 4th week of IPSS between tamsulosin and placebo were compared. The secondary outcomes were improvement in maximum and mean urinary flow rate (determined
by uroflowmetry). The mean changes from baseline at the 4th week of maximum and mean urinary flow rate were compared between tamsulosin and placebo.

**Statistical analysis**

All data were analysed on an intention-to-treat basis with all recruited patients who had at least one study medication after randomization. Missing data were checked in the data management report. The demographic and baseline quantitative data were presented as mean, standard deviation, minimum, maximum, median and quartiles as appropriate.

For the primary outcome of mean change from baseline of IPSS, Mann–Whitney U test was used to compare between the two treatment groups.

For the secondary outcome of mean change from baseline of maximum and mean urinary flow rate, Mann–Whitney U test was also used to compare between the two treatment groups.

Adverse events were reported as numbers and percentages.

All statistical analyses were performed using SPSS/PC Version 11 (SPSS Inc., Chicago, IL, USA). A two-sided significance level of 0.05 was used for all analyses.

**Results**

A total of 140 women with LUTS were enrolled in the study. Seventy patients were randomly allocated to each group (tamsulosin and placebo groups).

The baseline characteristics of the patients in both groups were comparable regarding age, body weight, duration, IPSS and maximum and mean urinary flow rate (Table 1).

Owing to a statistically significant difference in baseline IPSS between the two groups \((p = 0.001)\), a scatter plot and Spearman’s rank correlation were performed. It was found that there was a very weak correlation between baseline IPSS and mean change from baseline in IPSS in both groups (Spearman’s rank correlation coefficient = 0.39, \(p = 0.9\) in tamsulosin group and 0.31, 0.1 in placebo group respectively). It was then assumed that the difference in baseline IPSS between the two treatment groups had no significant effect on difference in mean change from baseline in IPSS between groups.

Five patients in the tamsulosin group (7%) were lost to follow-up due to adverse effects (2 patients) and symptoms not improving (3 patients).

Two patients in the placebo group (2%) were lost to follow-up due to symptoms not improving.

All the patients from both groups took the study medications for 4 weeks and no other treatment of LUTS was used during the study.

For the primary outcome, change from baseline (post–pre) at 4th week in IPSS was analysed since improvement in each patient’s symptom score was of interest rather than IPSS at the end of the study. Use of change from baseline also helped remove any difference between the two treatment groups with regard to pretreatment IPSS. Table 2 displays IPSS before and after treatment and the difference in each treatment group.

Since the mean change from baseline in IPSS, mean and maximum flow rate in both tamsulosin and placebo groups were not normally distributed, Mann–Whitney U test was performed. The mean change from baseline of IPSS in the tamsulosin group was significantly higher than in the placebo group (−5.6 vs. −2.6, exact \(p = 0.008\)).

### Table 1. Demographic characteristics and baseline data

<table>
<thead>
<tr>
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<th>Tamsulosin ((n = 70))</th>
<th>Placebo ((n = 70))</th>
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</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45.3 (12.9) 44 27, 69</td>
<td>49.8 (13.0) 48 27, 69</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>50.6 (9.3) 50 38, 67</td>
<td>51.8 (7.8) 50 35, 66</td>
</tr>
<tr>
<td>Duration (mo)</td>
<td>35.0 (34.8) 24 6, 120</td>
<td>38.0 (36.9) 30 4, 144</td>
</tr>
<tr>
<td>IPSS*</td>
<td>18.2 (5.1) 19 10, 28</td>
<td>21.3 (5.8) 22.5 9, 31</td>
</tr>
<tr>
<td>Max flow rate (mL/sec)</td>
<td>18.0 (6.1) 17 9, 30</td>
<td>18.8 (6.1) 19 9, 31.7</td>
</tr>
<tr>
<td>Mean flow rate (mL/sec)</td>
<td>7.0 (3.1) 7 3, 14.2</td>
<td>7.7 (3.8) 7 1, 17.3</td>
</tr>
<tr>
<td>Void volume (mL)</td>
<td>284.4 (118) 258 154, 482</td>
<td>289.9 (98.3) 283 156, 453</td>
</tr>
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</table>

*\(p = 0.001\). IPSS = International Prostate Symptom Score; SD = standard deviation; min = minimum; max = maximum.
The mean change from baseline of mean flow rate in the tamsulosin group was also significantly higher than in the placebo group (0.7 vs. −0.5, exact $p = 0.013$) (Table 3). The mean change from baseline of maximum flow rate in the tamsulosin group was not significantly higher than in the placebo group (1.0 vs. 1.1, exact $p = 0.506$) (Table 4).

There was a statistically significant difference in both mean change from baseline of IPSS and mean flow rate but not in mean change from baseline of maximum flow rate, there was a weak correlation among mean change from baseline of IPSS, mean and maximum flow rate (Spearman’s rank correlation coefficient = −0.1, $p = 0.1$ and −0.03, $p = 0.8$, respectively). However, there was a strong correlation between mean change from baseline of mean and maximum flow rate (Spearman’s rank correlation coefficient = 0.76, $p = 0.0001$).

There were two patients in the tamsulosin group who had dizziness and asthenia (2%) and were lost to follow-up. No patient in the placebo group had adverse effect.

**Discussion**

LUTS in women, including urinary incontinence, is highly prevalent in the community (up to half of women may have some degree of urinary incontinence), but it is considerably under-diagnosed and treated. There are many drugs which have been used to treat LUTS in women such as anticholinergics and $\alpha_1$-AR antagonists, but there is no evidence to know which drugs are used for standard treatments. The rationale for investigating $\alpha_1$-AR antagonists for the treatment of women with LUTS was based upon the observation that men and women had the same propensity for LUTS, suggesting that some aetiology might be identical. Recently, data have clearly shown that the human prostate (female urethra) predominantly expresses $\alpha_{1A}$-ARs and human detrusor contains mainly $\alpha_{1D}$-ARs, although the expression of $\alpha_1$-ARs, is low. $\alpha_{1D}$-ARs, which are predominately present in the spinal cord, might also be involved in the development of LUTS.
Moreover, the $\alpha_{1A}$-ARs in prostate (female urethra) might be involved in producing bladder outlet obstruction and the $\alpha_{1D}$-AR in the bladder might be the subtype responsible for bladder overactivity.

These would furthermore suggest that an $\alpha_{1A/D}$-selective compound such as tamsulosin would be expected to reduce both obstruction and improve voiding and storage symptoms in women as issues that are well documented in the controlled clinical trials with this compound in men.

Only limited clinical studies have been reported with $\alpha_{1A}$-AR antagonists in women with LUTS. One placebo-controlled study showed no better effects of the $\alpha_{1A}$-AR antagonist terazosin in 29 women. This study used $\alpha_{1A}$-AR antagonist not $\alpha_{1A/D}$-AR antagonist and was underpowered to detect clinical significance. Another study was an open nonrandomized trial that used $\alpha_{1A}$-AR antagonist doxazosin. This study showed that the $\alpha_{1A}$-AR antagonist doxazosin is at least as effective as anticholinergic hyoscyamine in reducing the total IPSS ($-30\%$ vs. $-34\%$, respectively). Similarly, a very small open Japanese study in five women with LUTS suggested that tamsulosin reduced the total IPSS and residual volume, and improved the quality of life and urinary flow rate in women with LUTS.

To our knowledge, our study represented the only randomized placebo-controlled trial to investigate the therapeutic benefit of an $\alpha_{1A/D}$-AR antagonist tamsulosin in women with LUTS. A total of 140 patients were enrolled in the study which reached the power of 80% to detect clinical significance. Seventy patients were randomly allocated to tamsulosin and placebo groups. The baseline characteristics of patients in each group was not statistically significant except for baseline IPSS which was higher in the placebo group than in the tamsulosin group ($p = 0.001$).

Owing to this significant difference, scatter plot and Spearman’s rank correlation were performed and it was found that there was a very weak correlation between baseline IPSS and mean change of IPSS in both groups. We then assumed that the difference in baseline IPSS between the two treatment groups had no significant effect on the difference in mean change from baseline in IPSS between groups.

The primary outcome in the study was mean change from baseline of IPSS. Our study showed that there was a statistically significant difference in mean change from baseline of IPSS between the tamsulosin and placebo groups, but that might not be clinically significant because the difference in mean change of IPSS was only 3 points. Similar analyses were performed for the voiding and storage part of IPSS. These were both not statistically significant (results not shown). These results imply that improvement in total IPSS may be the components of both voiding and storage symptoms.

The secondary outcome in the study was mean change from baseline of mean and maximum flow rate. Our study showed that there was a statistically significant difference in mean change from baseline of mean flow rate between the tamsulosin and placebo groups but not in mean change from baseline of maximum flow rate independent of void volume. There was no statistically significant difference among baseline, post-treatment and difference in void volume in both groups (results not shown). The changes in the flow rate are perhaps not clinically significant despite statistical significance (at least for the changes in the mean flow rate). Therefore, the improvement in IPSS may not be due to improvements in flow rates.

Although there was a statistically significant difference in both mean changes from baseline of IPSS and mean flow rate but not in mean change from baseline of maximum flow rate, there was a weak correlation among mean change from baseline of IPSS, mean and maximum flow rate. However, there was a strong correlation between mean and maximum flow rate.

These findings also suggest that the level of improvement in urinary symptoms was not directly related to the improvement in urinary flow rate, indicating that the mechanism for symptom improvement might not be mediated exclusively by relieving bladder outlet obstruction.

All of these findings were different from the previous studies because our study was more detailed and used tamsulosin ($\alpha_{1A/D}$-AR antagonist) that theoretically is more efficacious than $\alpha_{1A}$-AR antagonist.

Overall, tamsulosin was fairly well tolerated at the daily single dose of 0.2 mg. Asthenia and dizziness developed in two patients in the tamsulosin group and was sufficiently troublesome to result in premature withdrawal from the study. No patient in the placebo group developed side effects.

A criticism of the study was the primary outcome (mean change from baseline of IPSS). IPSS was a surrogate outcome that might not reflect the actual benefit to the patients from taking the $\alpha_{1A/D}$-AR antagonist tamsulosin. Quality of life would have been more appropriate.
IPSS was also a subjective outcome. Despite trying to minimize the bias when filling the IPSS, there were some misunderstandings of the patients that reflected the reliability of the IPSS. The last one is that the study should have included anticholinergics that have been used to treat LUTS in women efficaciously so that there were three treatments in the study to make the results more interpretable.

This study suggested that the \( \alpha_{1A/D} \)-AR antagonist tamsulosin was more efficacious for relieving LUTS than placebo in an unselected female population. It could improve IPSS and urinary flow rate but there was no correlation between them suggesting that improving only urinary flow rate did not mean that tamsulosin could clinically improve IPSS that was the major problem in the female patients and vice versa. Although men and women had the same predisposition for LUTS, the pathophysiology for the symptomatology was gender-specific. It was conceivable that a subgroup of women with LUTS (that was women with bladder neck dysfunction) might respond to selective \( \alpha_{1A/D} \)-AR antagonists (improve urinary flow rate and IPSS). Based on this study, tamsulosin should be used carefully in selected female patients because of its rather low efficacy and high cost.

Further studies should be directed towards a subgroup of female patients with bladder neck dysfunction, comparing tamsulosin with anticholinergics and determining the pathophysiology of urinary symptoms in women, which may lead to the development of new pharmacological strategies for treating LUTS.

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