



Tolterodine to Relieve Urinary Symptoms Following Transurethral Resection of the Prostate: A Double-Blind Placebo-Controlled Randomized Clinical Trial

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Purpose: To evaluate the effect of tolterodine on early storage symptoms following transurethral resection of the prostate.

Materials and Methods: Seventy patients over 55 years of age who underwent transurethral resection of the prostate owing to benign prostatic hyperplasia were randomly assigned to receive either 2 mg of tolterodine twice daily (treatment group) or matched placebo during a 1-month study period. Before and 1 month after the procedure, they were asked to complete the International Prostate Symptom Score (IPSS) questionnaire and quality of life subscale to assess their symptoms. Also, analgesic use and adverse drug events were determined at follow-up.

Results: Of 70 allocated patients, 64 patients (91.4%), including 33 in the treatment group and 31 in the placebo group, completed the study. The mean age of the patients was 67 years. None of the patients' basic clinical characteristics were significantly different. At the end of the follow-up period, the total IPSS and quality of life score had significantly improved in the patients receiving tolterodine compared with those receiving placebo ($p=0.001$ and $p=0.036$, respectively). The treatment group compared with placebo demonstrated significant improvements in frequency and urgency but not in nocturia. The amount of consumed painkiller was also significantly lower in the tolterodine group than in the placebo group ($p=0.0001$). The rate of side effects was not significantly different between the groups.

Conclusions: Administering 2 mg of tolterodine twice daily is an effective and well-tolerated regimen to relieve early storage symptoms, quality of life, and the amount of analgesic consumption following transurethral resection of the prostate.

Keywords: Cholinergic antagonists; Complications; Transurethral resection of prostate

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Article History:

received 23 April, 2013
accepted 2 July, 2013

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common diseases in aging males. It presents in over half of males older than 60 years, and 15% to 30% of those men have lower urinary tract symptoms (LUTS) that interfere with their well-being. The treatment options include watchful waiting; medications, i.e., α -blockers, 5- α reductase inhibitors, and anticholinergics; and surgeries [1].

Transurethral resection of the prostate (TURP) is a surgery with a low rate of complications that is frequently used to manage LUTS resulting from prostate hyperplasia; however, its usage has decreased compared with minimally invasive surgical therapies [2]. Despite the medical therapies and surgeries that have been developed, TURP is considered a gold standard treatment in LUTS related to BPH [3]. Unfortunately, TURP is associated with some discomforts, including postoperative bleeding, urinary re-

tention, transurethral resection syndrome, infection, bladder pain, and urinary storage symptoms (i.e., frequency, urgency, and nocturia with or without urge incontinence), as well as negative impacts on health-related quality of life (QoL) [4-7].

Multiple investigations have been done to ascertain the effect of anticholinergics for alleviating overactive bladder symptoms and symptoms related to bladder outlet obstruction. These investigations have shown the safety and efficacy of these agents for improving urinary symptoms [8,9]. The main troublesome symptoms after TURP are similar to the overactive bladder symptoms, although their etiology and diagnosis may be completely different.

Therefore, we conducted a double-blind, placebo-controlled randomized clinical trial to evaluate the effect of tolterodine (as an anticholinergic agent) compared with placebo on the early storage symptoms including frequency, urgency, and nocturia as well as adverse effects on QoL following catheter removal after TURP during a 1-month study period.

MATERIALS AND METHODS

From January 2012 to June 2012, a total of 83 men with LUTS caused by benign prostatic enlargement who were scheduled to undergo TURP were assessed for eligibility. After consideration of the exclusion criteria, a total of 70 patients (84.3%) who underwent TURP were enrolled in this study. After institutional review board approval, all patients who provided informed consent were prospectively randomized into two groups: 35 patients were given 2 mg of tolterodine twice daily for 1 month, and the others received matched placebo for the same period. This trial was registered at www.irct.ir as IRCT201112255786N3.

The medications were packed in bottles along with the drugs' consumption order. Randomization was performed in a 1:1 ratio. All of the patients were numbered consecutively by using a randomization table and were entered randomly into one of the groups. After being randomly assigned, they received either tolterodine or placebo accordingly. Investigators and the patients were blinded to the drugs until the study completion. All patients were also given 500 mg of acetaminophen (consumed as needed) to control bladder pain and were asked to record the number of analgesics consumed. All consenting patients were informed regarding the adverse events of tolterodine; however, they were not aware of whether they were receiving a placebo or tolterodine. Additionally, the major side effects, including dryness of mouth, constipation, and headache, were reported by the patients.

Inclusion criteria for the study were as follows: (1) men who were candidates for undergoing TURP, (2) a negative urine culture before TURP, and (3) older than 55 years of age. The exclusion criteria in the preoperative state were as follows: (1) neurologic diseases, (2) cardiovascular disease, (3) patients taking anticholinergics or other drugs that interfere with micturition, (4) proven or suspected pro-

static cancer, (5) patients with urinary catheters, and (6) patients who had suffered from urinary retention. A postoperative exclusion criterion was a measured postvoid residual urine (PVR) higher than 70 mL by use of ultrasound.

On the basis of the guidelines, owing to a lack of further studies and large variability, it is not possible to establish an exact PVR cutoff value in terms of making treatment decisions [10]. In addition, a PVR volume between 50 and 100 mL in the elderly is generally considered normal [11]. Also, we did not perform urodynamic study before TURP in all patients; it was done optionally for some patients on the basis of their clinical backgrounds and medical or drug histories. In other words, urodynamic study was performed according to the decision of the urologist for excluding patients and postoperative PVR was done to exclude high-risk patients as well.

Before and 1 month after TURP, all patients were examined by using the International Prostate Symptom Score (IPSS) questionnaire and QoL to evaluate symptoms and by using trans-abdominal ultrasonography to measure the amount of PVR and prostate volume (PV). The patients could not undergo surgery when they had a positive urine culture result. After the patients underwent TURP, they received a urethral catheter for a duration of 2 days.

The operations were done with the patient under spinal or general anesthesia by two surgeons using a routine and standard technique. The prostatectomy was performed by using a standard wire loop and 26-Fr continuous-flow resectoscope (Richard Wolf, Knittlingen, Germany). Concomitantly, an electrical current generator was used for coagulation. During TURP, continuous irrigation was achieved with a distilled water solution. All tissues retrieved from each patient were histopathologically examined. At the end of each operation, a 22-Fr Foley catheter was inserted for irrigation. In all patients, the bladder irrigation was continued until the hematuria was resolved. Routinely, the catheter was removed when the gross hematuria disappeared and the patients could urinate; thereafter, the patients were discharged from the hospital.

Routinely, a complete blood count, serum urea and creatinine levels, and electrolytes including sodium and potassium were also evaluated. Antibiotic prophylaxis consisted of 1 g of ceftriaxone twice a day, commencing 1 day before the procedure and continuing for 2 days postoperatively. Moreover, the patients were administered either pentazocine or morphine to control pain after the operation.

One day after discharge, ultrasound investigation was performed to measure PVR. When PVR was determined to be lower than 70 mL, the patients were given study medication in a defined manner.

The results were analyzed by using the chi-square test and Mann-Whitney U test as appropriate; a p-value of less than 0.05 was defined as being statistically significant.

RESULTS

The study was completed in October 2012. Overall, 79 pa-

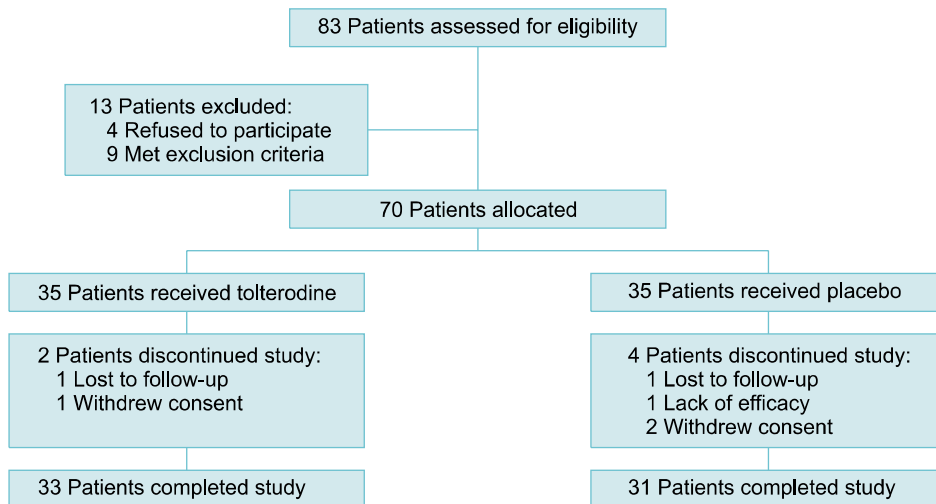


FIG. 1. Study flow diagram.

TABLE 1. Baseline characteristics of the patients in the tolterodine and placebo groups

| Characteristic | Tolterodine | Placebo | p-value |
|------------------------------|-------------|------------|--------------------|
| No. of patients | 33 | 31 | - |
| Age (y) | 66.00±6.43 | 68.00±8.36 | 0.499 ^a |
| Prostate volume (mL) | 52.8±14.3 | 48.6±14.6 | 0.287 ^a |
| Postvoid residual urine (mL) | | | |
| Preoperative | 58.0±31.6 | 62.0±30.4 | 0.742 ^a |
| Postoperative | 13.0±10.2 | 13.4±9.8 | 0.898 ^a |
| Prostate pathology | | | 0.477 ^b |
| Hyperplasia | 22 (66.6) | 18 (58.1) | |
| Hyperplasia and prostatitis | 11 (33.4) | 13 (41.9) | |

Values are presented as mean±standard deviation or number (%).
^a:Mann-Whitney U test. ^b:Chi-squared test.

tients were assessed for eligibility; 9 of those patients (11.4%) were excluded and the others were randomized into two groups. Two patients (5.7%) in the tolterodine group and four patients (11.4%) in the placebo group discontinued the study; therefore, 33 and 31 patients were analyzed in the tolterodine and placebo groups, respectively (Fig. 1).

The patients' mean age was 66.97±7.44 years, and there was no significant difference between the groups in age ($p=0.499$). Before the patients underwent TURP, the mean PV was comparable between the groups ($p=0.287$). Compared with baseline, the decrease in the mean postoperative PVR was not significantly lower in the patients taking tolterodine than in the patients receiving placebo (13±10.2 mL vs. 13.4±9.8 mL, respectively). The mean resected prostate weight was 14.98 and 13.80 g in the tolterodine and placebo groups, respectively; the difference was not statistically significant ($p=0.399$). An analysis of prostate pathology as hyperplasia alone or hyperplasia along with prostatitis showed no significant differences between the groups (Table 1).

None of the storage symptoms, including frequency, ur-

gency, and nocturia, were significantly different at baseline. Storage symptoms were lower in the patients who received tolterodine than in those who received placebo at 1 month after TURP, except for nocturia, which did not differ significantly between the groups (Table 2). We found no significant difference in the baseline total IPSSs between the groups, whereas the total IPSS at follow-up showed a significant decrease in the tolterodine group compared with the placebo group ($p=0.001$). Concerning the QoL subscale, the mean QoL score was similar at baseline; however, it was significantly improved in the tolterodine group compared with the placebo group during the 1-month period ($p=0.036$).

According to the patients' self-reported data, withdrawal due to adverse drug events was not observed, although dryness of mouth, constipation, and headache were reported in both groups. However, none of these effects differed significantly between the groups (Table 2). Other singly reported side effects in the patients receiving tolterodine included blurred vision and pruritus. Moreover, the amount of analgesic that the patients consumed from the time of catheter removal to 1 month later was significantly lower in the tolterodine group than in the placebo group (10.09±2.67 vs. 15.10±5.31, respectively; $p=0.0001$).

DISCUSSION

Although TURP is considered the gold standard treatment for alleviating LUTS caused by BPH, dissatisfaction of nearly one third of patients is reported. This could be explained by the fact that such patients with LUTS have non-prostatic conditions leading to the development of urinary symptoms, such as bladder dysfunction including detrusor overactivity or impaired detrusor contractility [1,12,13]. Patient dissatisfaction might also be attributable to an increase in the sensitivity of muscarinic receptors to acetylcholine in the smooth muscle of the bladder as opposed to a prostatic pathology that leads to overactive bladder symptoms (storage symptoms) following TURP. This asso-

TABLE 2. Clinical outcomes and symptom changes in the tolterodine and placebo groups

| Variable | Tolterodine | Placebo | p-value |
|------------------|-------------|------------|---------------------|
| Frequency | | | |
| Before TURP | 2.97±1.26 | 3.26±1.24 | 0.350 ^a |
| After 1 month | 1.52±0.62 | 1.97±0.8 | 0.018 ^a |
| Urgency | | | |
| Before TURP | 2.94±1.39 | 2.35±1.58 | 0.123 ^a |
| After 1 month | 1±0.94 | 1.71±0.97 | 0.004 ^a |
| Nocturia | | | |
| Before TURP | 2.58±1.54 | 2.68±1.60 | 0.816 ^a |
| After 1 month | 0.61±0.75 | 0.74±0.77 | 0.428 ^a |
| Total IPSS | | | |
| Before TURP | 21.82±7.43 | 22.77±5.41 | 0.475 ^a |
| After 1 month | 6.03±1.67 | 7.81±2.18 | 0.001 ^a |
| Quality of life | | | |
| Before TURP | 2.42±0.97 | 2.35±1.08 | 0.721 ^a |
| After 1 month | 1.24±0.66 | 1.48±0.68 | 0.036 ^a |
| Adverse events | | | |
| Dry mouth | 11 (33.3) | 5 (16.2) | 0.112 ^b |
| Constipation | 6 (18.2) | 4 (12.9) | 0.561 ^b |
| Headache | 4 (12.2) | 1 (3.2) | 0.185 ^b |
| No. of analgesic | 10.09±2.67 | 15.10±5.31 | 0.0001 ^a |

Values are presented as mean±standard deviation or number (%). IPSS, International Prostate Symptom Score; TURP, transurethral resection of the prostate.

^a:Mann-Whitney U test. ^b:Chi-square test.

ciation suggests that we should consider other strategies for treating these conditions. The lack of efficacy of α -blockers and 5- α -reductase inhibitors in improving such urinary symptoms contrary to the efficacious effect of anticholinergics is a main rationale for considering the likely affected function of the bladder to control storage symptoms after TURP or prostatectomy [14].

Iselin et al. [5] have shown that oxybutynin improved early storage symptoms except nocturia in patients who underwent TURP owing to BPH during a 1-week study period. In the present study, the results demonstrated that tolterodine compared with placebo significantly improved the total IPSS, frequency, urgency, and QoL but not nocturia. Our findings are similar to those reported by Iselin et al. [5]; however, those findings were associated with the apparent occurrence of dry mouth in the oxybutynin group, in contrast with the current investigation (65% vs. 33%, respectively).

We think that alleviation of urinary symptoms resulted in less bothersome symptoms and consequent improvement in QoL and total IPSS and also decreased analgesic consumption. Moreover, the low number of adverse events in the patients who were given tolterodine may be another alleviating factor. However, nocturia was the sole index that was not improved by medication.

Researchers in one study [15] showed that despite a high rate of nocturia in patients with BPH, among the seven symptoms included in the IPSS questionnaire improve-

ment in nocturia symptoms was lowest in the patients after undergoing medical and surgical treatment for BPH. Additionally, some investigators concluded that nocturia is the least specific symptom in benign prostatic obstruction associated with the lowest sensitivity to treatment [16,17].

In a study by Chapple et al. [18] that was designed to ascertain the effect of anticholinergics in overactive bladder symptoms, it was noted that oxybutynin was the only anticholinergic agent that contributed to risk of discontinuing the study. Those authors concluded that anticholinergics are efficacious, safe, and well-tolerated agents for improving storage symptoms and health-related QoL. In contrast, Sexton et al. [19] concluded that rates of discontinuing anticholinergic consumption were higher and increased over time. They also reported that we need to enhance patients' adherence levels through the use of new agents or alternative options.

Kuo [12] demonstrated that more than half of patients who had a small PV and low resected prostate weight during TURP would experience persistent LUTS. At this point, tolterodine-treated patients had higher PV than did the placebo group (52.8 mL vs. 48.6 mL, respectively); however, there was no statistically significant difference. We think that the impact of tolterodine on storage symptoms might be augmented by the effect of preoperative PV; thus, the improvement of storage symptoms may not be solely a medication effect.

To the best of our knowledge, this investigation is the first to elucidate whether tolterodine can alleviate storage symptoms after TURP. This study had some limitations owing its nature. First, we did not use urodynamic studies, which suggests that we cannot conclude which types of impaired bladder function might have caused the storage symptoms. Second, the small sample size and short-term follow-up may have unintentionally influenced our results. Third, given that urge incontinence is an overactive bladder symptom that could be evaluated in this setting, the fact that we did not consider it because we used the IPSS as an outcome evaluating tool may be regarded as a limitation.

CONCLUSIONS

Administration of 2 mg of tolterodine twice daily in patients who underwent TURP improved early storage symptoms, QoL, and amount of analgesics used during a 1-month follow-up period. Although tolterodine does not impact nocturia, it is a safe, effective, and well-tolerated medication that we recommend administering after catheter removal to alleviate early storage symptoms following TURP. Large-scale, multicenter and prospective studies will be helpful to confirm the proper effect of tolterodine on storage symptoms, especially for patients who undergo TURP.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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