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Original Research Article

Effectiveness of tolterodine in relief of postoperative symptoms related to urethral catheter in transurethral prostate resection patients: a prospective randomized trial

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ABSTRACT

Background: Urethral catheterisation following surgery causes significant discomfort postoperatively. Use of muscarinic receptor antagonists for relief of these symptoms in transurethral prostate resection (TURP) patients has been studied previously. In this study it is aimed to identify efficacy of toltoredine for relief of bladder overactivity symptoms in the post-operative period following TURP.
Methods: In this randomized, prospective, controlled study, results of 95 patients evaluated. Group 1(n=49) received tolterodine 4 mg/day and group 2 (n=45) received no medication. Presence and severity of symptoms together with visual pain scale (VPS) scores were recorded and compared in very early and late postoperative period (0, 4, 8, 12, 24 hours and every 24 hours thereafter). Additional analgesic requirement was also compared and adverse events were recorded.
Results: Tolerodine treatment was shown to be associated with low incidence and less severity of symptoms. Symptoms were shown to be present especially in the early postoperative period. VPS scores were also shown to be less in group 1. Treatment was not cessated in any of the patients due to adverse events.
Conclusions: Tolterodine 4 mg/day was shown to be effective in relief of symptoms related to urethral catheterisation in the postoperative period following TURP. Treatment was not cessated in any of the patients due to adverse events. Further prospective placebo-controlled studies are needed with tolterodine and other muscarinic receptor antagonists.

Keywords: Bladder overactivity, Muscarinic receptor antagonists, Tolterodine, Transurethral resection of prostate

INTRODUCTION

Urinary bladder is frequently catheterized following surgery for bladder drainage. The catheter is remained in bladder in some cases postoperatively and this is associated with complaints, such as urge to void, suprapubic discomfort, pain through the urethra and sometimes passage of urine through the urethra besides the catheter. These symptoms are parallel to those of bladder overactivity that refers to the common and bothersome group of storage lower urinary tract symptoms.

Muscarinic receptor activity is responsible from involuntary contractions of muscle layer of bladder wall and these contractions result in bladder overactivity.[1] Antimuscarinic agents are the first-line pharmacotherapy for bladder overactivity treatment.[2] These symptoms are especially prominent in cases of transurethral prostate resection (TURP), due to the fact that usually catheter with greater size is used with an inflated balloon of greater volume. Therefore, relief of these symptoms is especially important following TURP. Prescription of muscarinic receptor antagonist for relief of catheter related symptoms has been studied previously in a

population of patients following percutaneous nephrolithotomy and oxybutinin and tolterodine were found to be more effective compared to placebo.[3]

However, to our knowledge the current literature lacks trials on efficacy muscarinic receptor antagonists in TURP patients. In this study it is aimed to identify efficacy of toltoredine for relief of bladder overactivity symptoms in the post-operative period following TURP.

METHODS

This randomized, prospective, controlled study was conducted in Ankara University School of Medicine department of urology between September 2012 and September 2013. Patient groups were planned to be group 1, receiving tolterodine and group 2, control group receiving no medication. Sample size was estimated to 90 (45 patient each group) based on an effect size of 50% and results to be statistically significant with a=0.05 and b=0.80. Effect size was estimated by bladder overactivity symptom rate to be 60% and treatment would reduce this rate to 30%.

Inclusion criteria

Inclusion criteria were patients underwent TURP with spinal anesthesia, prostate volume of 30-100 ml, no contraindication for use of tolterodine and age, 40-70.

Exclusion criteria

Exclusion criteria were 1) patients with a history of bladder overactivity (frequency>3 times in the night or>8 times in 24 h) 2) end-stage renal disease (urine output <500 ml/24 h) 3) patients diagnosed with neurogenic bladder

Computer generated table of random numbers were used for randomization and evaluation of the symptoms in the postoperative period was performed by a single blinded physician. with the help of an into two groups. Surgery was performed under spinal anesthesia. TURP was performed with a monopolar 26 Fr vaporcut system (Karl Storz inc.) and at the end of the procedure 20 Fr Foley's catheter was inserted with a lubricant gelly and its balloon was inflated with 50 ml distilled water. Gentle traction of the catheter was performed to maintain homeostasis in the early postoperative period. After surgery the patients were transferred to the inpatient clinics and symptoms were assessed by one of the phsicans (FA) at 0, 4, 8, 12, 24 hours and every 24 hours thereafter. Symptom (urge to void, suprapubic discomfort, pain through the urethra) severity was recorded as mild (reported by the patient only on questioning), moderate (reported by the patient without questioning; not accompanied by any behavioral responses) and severe (reported by the patient without questioning and accompanied by behavioral responses) as it was previously described by Agarwal et al.[3] Additionally visual pain scale (VPS) from 0 to 10 (0: no distress and 10: unbearable distress) was also performed. Tolterodine 4 mg prolonged release was administered 24 hours prior to surgery and continued 4 mg/day till 24 hours prior to catheter extraction. Treatment related adverse events were also recorded. Additional pain medication was performed by administration of diclofenac sodium and need for analgesics was also recorded.

Age, prostate volume, duration of surgery, duration of catheterization and side effects were recorded. Primary end point of the study was difference in symptom severity and VPS scores. Differences in the age, prostate volume and VAS score between the groups were compared by one-way ANOVA test, differences in severity of bladder discomfort (mild, moderate and severe) was analysed by Fisher's exact test. SPSS 16.0 (SPSS Inc., Chicago, IL) was used for the statistical analysis. P<0.05 was considered as significant.

RESULTS

Totally 108 patients were randomized for the trial. Four patients were excluded due to previous use of another muscarinic receptor antagonist during the last month and 8 patients were excluded due to the unsuccessful spinal anesthesia. One patient required reinervention due to severe bleeding at 36 hours postoperatively and therefore excluded from the study. There were 49 patients in group 1 and 46 patients in group 2. Mean age of the whole population was 65.2±6.3, mean prostate volume 45.2±9.5 ml, mean operation duration was 58.1±11.4 minutes and mean duration of catheterization was 3.4±0.9 days. Two groups were similar with respect to mean age, prostate volume, operation duration and duration of catheterization and the results are summarized in Table 1.

Overall symptoms were observed more frequently in the group 2 (30 of 46 patients (65.2%)) compared to group 1 (16 of 49 patients (32.6%)) and the difference was statistically significant (p=0.001). Symptoms were not prominent in the very early postoperative period (0 hour) and becomes prominent after 4th hour. Incidence and severity of symptoms together with VPS score tended to increase up to 24 hours and decrease thereafter at 48 and 72 hours. Incidence and severity of symptoms were significantly lower in group 1 compared to group 2 at 4th, 8th, 12th and 24th hours, however no significant difference was observed at 48th and 72 nd hours.

The results are summarized in Table 2. When VPS scores were compared there was significant difference at all time intervals except 72 nd hours, and results are presented in Figure 1. With respect to adverse events, tolterodine withdrawal was not needed in any of the patients.

Dry mouth was the most prevelant side effect and it was observed 29 patients (59.1%). Nausea was observed in 5 and 6 patients in group 1 and group 2 respectively.

Additional analgesics was required in 5 (10.2%) and 15 (32,6%) patients in group 1 and group 2 respectively (p=0.01). Urinary retention following catheter extraction was not observed in any of the patients.

Table 1: Baseline and postoperative characteristics of the patients.

	Group 1 (n=49)	Group2 (n=46)	P value
Age, years (Mean±SD)	66.1±6.2	64.2±6.0	0.374
Prostate volume, ml (Mean±SD)	44.9±8.9	45.5±9.3	0.452
Duration of operation, minutes (Mean±SD)	60.6±12.3	55.4±11.1	0.09
Duration of catheterisation, days (Mean±SD)	3.5±0.9	3.3±0.9	.114

Values are expressed as median (interquartile range) and number. A p value<0.05 was considered significant.

Table 2: Presence and severity of symptoms in certain time intervals of the two groups.

	Group 1 (n=49) (Number of patients)				Group 2 (n=46) (Number of patients)				P value
	No symptom	Mild symptom	Moderate symptom	Severe symptom	No symptom	Mild symptom	Moderate symptom	Severe symptom	
Hour 0	46	2	1	0	42	2	2	0	0.393
Hour 4	43	3	1	2	25	12	6	3	0.001
Hour 8	41	2	4	2	21	9	6	10	0.001
Hour 12	41	3	2	3	23	10	5	8	0.00
Hour 24	43	4	1	1	24	14	6	2	0.002
Hour 48	45	4	0	0	42	3	1	0	0.375
Hour 72	47	2	0	0	44	2	0	0	0.480

A P value <.05 was considered significant.

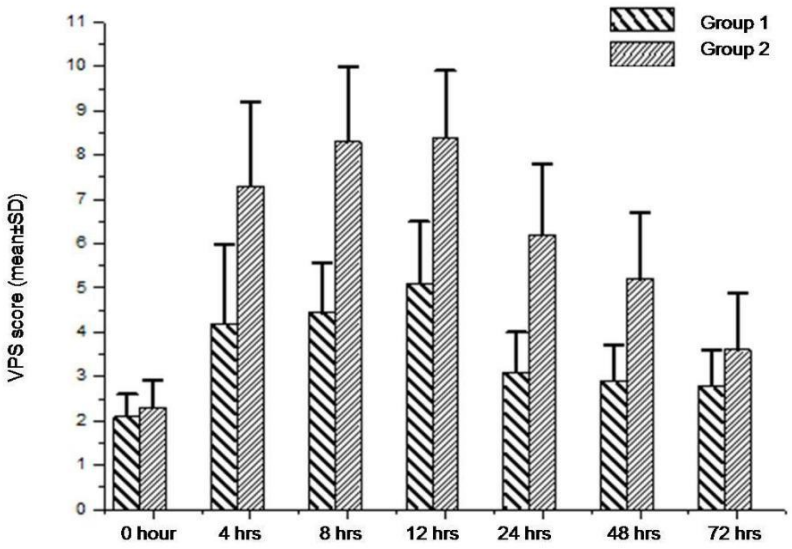

Figure 1: VPS scores of the two groups in certain time interval.

DISCUSSION

Stimulation of muscarinic receptors in the detrusor muscle mediates bladder contractions in humans. Muscarinic receptors are responsible for the signal transduction between parasympathetic nerves and smooth muscle of the detrusor.[4] Symptoms of bladder overactivity such as urge to void, suprapubic discomfort, pain through the urethra are often assumed to be caused by detrusor overactivity.[5,6] These symptoms are generally prominent following urethral catheterization and were shown to respond to muscarinic receptor antagonists previously.[3,7] TURP is one of the most common procedures in the era of urological surgery and symptoms of bladder overactivity are frequently seen in the early postoperative period. The symptoms effect the quality of life and mainly tought to be due to detrusor overactivity caused by mass effect of balloon of the catheter. Following TURP generally balloon of the urethral catheter is inflated for a greater volume and traction is applied for homeostasis.

This results in contact of balloon of the catheter with trigone of the bladder and detrusor overactivity occurs. To overcome such symptoms, use of muscarinic receptor antagonists may be of great importance. In the previous study of Agarwal et al symptoms related to urethral catheter were seen in 55% of the patients. In that study the study population consisted of patients underwent percutaneous nephrolithotomy and catheter of 16 Fr with balloon inflated with 10 ml.[3]

In our study bladder overactivity symptoms were observed more frequently (65.2%) in the control group. This higher incidence is tought to be due to use of catheter with greater dimension and balloon inflation of greater volume. Agarwal et al, also found that tolterodine 2 mg administered 1h before surgery reduced the incidence of catheter related bladder discomfort by 19%.[3] They used tolterodine with a short half-life and administered the drug just 1 hour earlier than surgery. In our study tolterodine 4 mg prolonged release capsules were used and began 24 hours prior to surgery and cessated 24 hours prior to extraction of the catheter. Also, in our population all of the patients underwent spinal anesthesia and symptoms started 4 hours following surgery when the effect of spinal anesthesia ceases. With use of tolterodine incidence and severity of symptoms decreased significantly. VPS was also used and in correlation with symptom presence, increase of VPS scores began after 4 hours, increased thereafter until 24 hours and began to decrease thereafter. VPS of group 1 was significantly lower compared to that of group 2 except in the evaluation of 72 hours postoperatively. This finding proves that symptoms are especially prominent in the early postoperative period until 72 hours and this interval seems to be optimal for use of muscarinic receptor antagonists. Need for additional anesthesia was another efficacy point and muscarinic receptor antagonists were shown to decrease the need for additional analgesics by almost 3-fold. Also, patients with bladder overactivity symptoms prior to surgery were excluded from the study.

However, this special population might benefit from the treatment more extesively and further trials in this special population should also be conducted. In the previous study of Agarwal et al tolterodine and oxybuinine were compared and similar efficacy results were observed.[3] However, in our study tolterodine was the only muscarinic receptor antagonist to be used, therefore effectiveness of other muscarinic receptor agonists should also be verified in relief of symptoms following TURP. This treatment seems to be safe, in terms of treatment related adverse events.

None of the patients were withdrawn from the study related to adverse events. Dry mouth was found to be the most common side effect. Urinary retention following catheter extraction was not observed in any of the patients. Most important drawback of the present study is the lack of placebo. Placebo capsules could not be maintained therefore the control group received no medication, except diclofenac sodium for pain relief when needed.

CONCLUSION

Symptoms related to bladder overactivity following TURP is an important problem. Muscarinic receptor antagonists aid relief of symptoms with high efficacy and safety. Further prospective trials with placebo control are needed for verification of this treatment.

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