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Efficacy and safety of propiverine and terazosine combination for one year in male patients with luts and detrusor overactivity

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ABSTRACT

Purpose: To evaluate the long term efficacy and safety of the use of propiverine and terazosine combination in patients with LUTS and DO by a placebo controlled study.
Materials and Methods: One hundred patients were enrolled in the study. They were randomized into two groups (each group consisted of 50 patients). Terazosine and placebo were administered to the patients in Group 1 and terazosine plus propiverine HCL was administered to Group 2. The patients were evaluated by international prostate symptom score (IPSS), the first four questions of IPSS (IPSS4), the 8th question of IPSS (quality of life-QoL), overactive bladder symptom score questionnaire (OAB-q V8), PSA test, urodynamic studies, post voiding residue (PVR). All patients were followed for one year and were reassessed for comparison.
Results: IPSS, IPSS4, OAB symptoms, QoL score, PVR, and Qmax scores of the groups did not differ. After one year treatment, there was significant improvement in IPSS, IPSS4, OAB symptoms, QoL and Qmax values in Group 2. No significant improvement was noted for the same parameters in Group 1.
Conclusion: This is the first study to show long term safety and efficacy of anticholinergic therapy for patients with LUTS. In patients with OAB or DO, long term anticholinergic treatment may be regarded as a treatment option.

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Lower Urinary Tract Symptoms; Prostatic Hyperplasia; Urinary Bladder, Overactive; propiverine [Supplementary Concept]

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INTRODUCTION

For many years lower urinary tract symptoms (LUTS) in elderly men were considered to be caused by benign prostatic obstruction (BPO). However, after the studies conducted in the 1990's, it was described that LUTS of men were not always caused by benign prostatic hyperplasia (BPH) or BPO (1-3). Nowadays, it is known that some pathologies concerning men bladder can cause these symptoms. One of these issues is detrusor over activity (DO), which incidence increases with age, causing symptoms such as frequency and urgency. It is thought that DO is present in 47-66% of cases with BPO and LUTS (4,5). These patients, however, are usually treated with agents for BPO. Nowa-

days, in cases with BPH and DO, anticholinergic agents are successfully used in addition to standard therapies (6,7). However, the long term data for this treatment is lacking in literature.

We aimed to show the long term efficacy and safety of the use of anticholinergic agents in patients with LUTS and DO (proven by urodynamic studies) by a placebo controlled study.

MATERIALS AND METHODS

The study was designed as a double blind, placebo controlled, randomized trial conducted at our hospital, between May 2009 and November 2012. The study was conducted in accordance with the Declaration of Helsinki. The local ethics committee approved our protocol. All subjects provided written informed consent.

Patient selection

Patients suffering from LUTS who applied to our clinic had been enrolled in the study. Patients were evaluated by international prostate symptom score (IPSS), the first four questions of IPSS (IPSS4), the 8th question of IPSS (quality of life-QoL), overactive bladder symptom score questionnaire (OABSS; OAB-q V8), PSA test, urodynamic studies, post voiding residue (PVR) assessment via ultrasound and uroflowmetry. Selection criteria for patients were as follows: over 40 years old, having IPSS over 12, having PSA scores below 2.5, having OAB symptoms (> 8 cycles of urination/24h, > 3 with urgency (or urge incontinence)/24h) and having documented detrusor pressure > 10 cm H2O in urodynamic studies.

Patients having PVR > 200 cc with USG or Qmax < 5 mL/s were excluded due to severe bladder outlet obstruction symptoms. Patients suspected to have prostate cancer were excluded. Other exclusion criteria were: previous treatment with an anticholinergic agent; surgical treatment of BPH or a history of surgical intervention in the bladder or urethra; history of acute urinary retention (AUR); chronic urinary retention; acute urinary tract infection (UTI); chronic UTI; prostatitis caused by bacteria or history of recurrent UTIs; history of interstitial cystitis; concomitant medication that may cause urinary retention (e.g., tricyclic antidepressants, neuroleptic agents, antihistamine drugs, anti-Parkinson drugs); indwelling catheter or intermittent use of self-catheterization.

From the patients applied to our clinic suffering from LUTS, 100 patients were enrolled in the study. They were randomized into two groups (both groups consisted of 50 patients). Terazosin 2 mg/day and placebo was administered to patients in Group 1 and terazosin 2 mg/day plus propiverine HCL 15 mg/day was administered to Group 2.

Assessed endpoints were: change in IPSS, IPSS4, QoL, OAB symptoms, PVR and Qmax. Patient demographics are summarized in Table-1. All patients were followed for 1 year, and were reassessed for comparison.

Statistical analysis

Statistical comparisons of the mean values before and after treatment were done using parametric paired t-test. For comparison between placebo and propiverine, unpaired t test was used. $P < 0.05$ was considered statistically significant.

RESULTS

IPSS, IPSS4, OAB symptoms, QoL score, PVR and Qmax scores did not differ between groups (Table-1). After 1 year of therapy, there were significant improvement in group 2 in IPSS, IPSS4, OAB symptoms, QoL and Qmax (Table-1). The same significant improvement was not present in group 1. The results are summarized in Table-1. Patients in Group 2 mildly suffered from dry mouth (18%) and constipation (6%). No patient left the study because of side effects. No patient suffered from acute urinary retention (AUR) after one year of treatment.

DISCUSSION

The term “lower urinary tract symptoms”, was first used by Abrams to imply that LUTS can be caused not only by prostatic symptoms (3). Recent studies show that pathologies concerning bladder issues can cause LUTS and storage symptoms are the main problem in this subset of patients (2,8).

Table 1 - Age and clinical characteristics of the patients.

	Group 1 (n = 50)		Group 2 (n = 50)		P*
	Day 0	After 1 Year	Day 0	After 1 Year	
Age ± SD	54.1 ± 5.1 (43-64)		54.7 ± 6.0 (41-64)		0.45
IPSS ± SD	29.2 ± 1.6 (25-33)	24.2 ± 1.1 (22-30)	28.8±2.4 (23-33)	16.0±1.2 (14-21)	P < 0.05
IPSS4 ± SD	17.6 ± 1.0 (15-19)	16.1 ± 1.0 (13-18)	17.1 ± 1.1 (15-19)	9.7 ± 1.9 (8-12)	P < 0.05
Q8(QoL) ± SD	5.0 ± 0.7 (4-6)	5.2 ± 0.9 (3-6)	5.0 ± 0.7 (4-6)	2.1 ± 0.8 (1-4)	P < 0.05
Qmax ± SD	8.0 ± 0.9 (9-12)	9.5 ± 1.1 (8-11)	8.9 ± 1.1 (7-11)	10.7 ± 1.3 (9-12)	P = 0.32
OABSS ± SD	28.7 ± 1.5 (26-32)	26.4 ± 1.2 (23-31)	28.2 ± 2.4 (24-32)	12.9 ± 1.9 (11-19)	P < 0.05
PVR ± SD	70.5 ± 5.5 (65-76)	51.5 ± 2.4 (49-60)	68 ± 4 (64-72)	50 ± 2 (45-54)	P = 0.41

P*: Between groups 1 and 2 at one year.

Treatments with such agents as alpha-blockers, 5-alpha reductase inhibitors (5-ARI) or prostate surgery are applied to this group and a significant amount of patients does not improve.

Incidence of detrusor over activity increases with age and accompany a significant amount of patients having LUTS. Knutson et al. showed DO accompany 55% of patients with LUTS by urodynamic studies (9). Hyman et al. stated 46% of patients having LUTS also suffer from DO in 109 patients with LUTS or bladder outlet obstruction (BOO) (10). Similar studies showed this combination can be seen up to 75% of cases (2,11-13).

Studies conducted on animal models described major alterations of bladder wall morphology and detrusor biochemistry induced by partial outlet obstruction that can interfere with bladder contractility and emptying. These include: 1) increased mass; 2) reduced cholinergic nerve density; 3) reduced mitochondrial substrate (e.g., glucose) utilization and associated reduction in oxidative energy generation; 4) concomitant deregulation of intracellular Ca2+ homeostasis; and 5) increased and redistributed connective tissue (14). An abnormal increase in the amount of collagen and elastic fibers leads to loss of strength and elasticity of the bladder wall (15).

Anti-muscarinic drugs bind to muscarinic receptors on detrusor muscle cells, thereby blocking the action of acetylcholine, which is released from activated cholinergic (parasympathetic) nerves and diminish bladder contractions (16).

In current literature, patients suffering from storage symptoms, which can be caused by a pathology such as OAB or DO, there are reports using different treatment modalities using agents such as Oxybutynin, Tolterodine, Propiverine, Solifenacin and Fosfoterodine (17).

Initially, Saito suggested the use of alpha blocker-antimuscarinic combination instead of

alpha-blocker alone to a better control of daytime frequency, urge incontinence and urgency rates (18). Athanasopoulos et al. compared tamsulosine--tolterodine combination with tamsulosine alone in mild or moderate BOO and urodynamically proven concomitant DO and reported improvement in quality of life index scores, significant decrease in maximum detrusor pressure and the magnitude of maximum bladder contraction after therapy in the combination arm (19). Lee et al. enrolled 211 men with urodynamic evidence of BPH and OAB symptoms and randomized them into two groups to receive doxazosin 4 mg either alone or in combination with propiverine 20 mg daily. The combination arm showed statistically significant improvement in urinary frequency (25% vs. 14.3%), average micturition volume (32.3% vs. 19.2%) and IPSS storage symptoms (41.3% vs. 32.6%). No patients suffered AUR (20). In another study, patients suffering from BOO (proven by pressure-flow urodynamic study) and BOO+OAB received doxazosin for 3 months. After 3 months, Tolterodine was added to the therapy in both groups to patients that did not respond to treatment. The authors concluded that combining Tolterodine with doxazosin was effective in three--quarters of men with BOO+OAB (21).

In our study, there was no significant difference between groups in initial IPSS; after one year, significant improvement was present in combination group. When comparing the rates in both groups, improvement could be detected. Only combination group, however, had statistically significant improvement. The problem to cause this result is the underlying 50-75% OAB in patients referring to urology clinics. When placebo group is compared, there is no difference present in IPSS between day 0 and final outcome.

First four questions of IPSS were named as IPSS4 and can be used to interpret the storage symptoms. In conducted studies, patients having high IPSS4 tend to suffer from OAB. We, like previous authors, evaluated the IPSS4 with OAB symptom score. Initially, the groups did not differ in scores, but after 12 weeks, there was statistically significant difference between groups and the same difference was present at one year. As anticipated, the antimuscarinic arm had significantly improved OAB scores and IPSS4. As observed in current literature, quality of life decreases in patients having OAB accompanying LUTS (22). In antimuscarinic arm, quality of life improves with decrease of OAB symptoms; but in placebo group, none of these scores differed.

After 12 weeks of treatment, Qmax in both groups improved but there was no significant difference between groups. Results similar to our study can be found in literature. After one year of treatment, the same effect could still be demonstrated. In one study, tamsulosine and combination of tamsulosine and tolterodine were compared; Qmax improved in both groups but no significant difference was reported (19). In another study with 211 men, combination of doxazosin and propiverine was compared with doxazosin alone; after treatment, both groups were reported to have improved Qmax but there was no statistical difference between groups (20). One of the remarkable outcomes of our study was the statistically significant improvement of quality of life symptom scores. In placebo group, there was an improvement of Qmax values but not for other symptoms, therefore patient satisfaction and quality of life symptoms were not improved.

Formerly, for men with LUTS, the use of antimuscarinics was believed to aggravate the mixing symptoms, increase PVR and might precipitate AUR and therefore there was a consensus to avoid these agents (23-25). Risk factors for AUR are age, prostatic enlargement, increased LUTS severity, low peak flow rate and high PVR (26). With recent studies however, there is a tendency to alter this belief. In a recent retrospective study, the incidence rate of AUR among men treated with antimuscarinics increased with age, ranging from 0.1 per 1000 person-years in men aged 20-49 years to 6.9 per 1000 persons--years in men aged 80-84 (27). After 12 weeks of treatment, AUR was not observed in both groups. Layton's analysis in 2001 (28) concluded that the incidence of AUR in patients on Tolterodine was 0.5% in 6 months. In a placebo-controlled study, that rate was 0.4% (29). In current literature, that incidence is 1-2% (29,30). Our study shows that the use of antimuscarinics is safe in selected patient groups. None of our patients suffered from AUR in a one-year follow-up. We came to similar outcomes to current literature as efficacy and safety in antimuscarinic therapy in patients suffering from LUTS

and DO. To our knowledge, however, no study in current literature compared antimuscarinic treatment to placebo for one year.

Nishizawa et al. (31) conducted a similar study using tamsulosine and propiverine, however their groups received either 10 or 20 mg of propiverine. They found out that adding 10 mg of propiverine to tamsulosine, patients suffer less from DO and LUTS. They also found out adding 10 mg of propiverine does not show a positive effect on tamsulosine neither on efficacy nor on safety. Our results suggest adding 15 mg of propiverine is an efficient and safe method to treat LUTS and DO.

There are many studies on antimuscarinic treatment for patients with LUTS and OAB. However, there are only very little and uncontrolled data of long term studies (32). Our study, however, shows excellent safety and efficacy of anticholinergic treatment in combination with alpha receptor blockage. However, because most of the studies designed for antimuscarinic treatment on BPO patients concern only limited duration, the safety of the treatment is not well known. Even though our study reveals the safety of antimuscarinic treatment on PVR increase, on long term, patients should be carefully monitored to avoid further complications.

As a conclusion with this study, the outcomes presented in urology literature clearly states BOO is not the only cause of LUTS; there are other causes such as OAB in a significant amount of patients. It is believed that this arm causes symptoms decreasing QoL more. Patients not responding to medical treatment are set as benign prostate enlargement and undergo surgical treatment. Various studies demonstrate that antimuscarinics can be used for this group of patients safely. In this study, we tried to show that in a long term placebo controlled study these agents may be used with same safety and efficacy. Patients having OAB or DO, a long term anticholinergic treatment option should be kept in mind.

CONFLICT OF INTEREST

Placebo was supplied (by Dr. Frik, Istanbul, Turkey) for academic purposes only. The hospital or investigators were not charged for materials.

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