Additive Role of Trospium Chloride in the Management of Men with Voiding and Storage Symptoms

İşeme ve Depolama Semptomları Olan Erkeklerde Trospium Klorid Eklenmesinin Rolü

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ABSTRACT Objective: In patients who suffer from Lower Urinary Tract Symptom (LUTS) and overactive bladder (OAB), the quality of life is affected negatively. The aim of this study was to assess the efficacy and safety of trospium chloride, which is here used for the first time in an alpha-blocker and anticholinergic combination therapy for older men who suffer from benign prostate hypertrophy (BPH)-related LUTS with OAB. **Material and Methods:** This prospective, randomized, placebo controlled, double-blind trial included men aged ≥45 years with LUTS and OAB. Subjects were randomized into trospium chloride 45 mg with terazosin 5 mg or placebo with terazosin 5mg for 12 weeks. At baseline and week 12, subjects were evaluated using total prostate serum antigen, uroflowmetry, and post voiding residual urine (PVRU) and completed the International Prostate Symptom Score (IPSS), Overactive Bladder Questionnaire (OAB-q), 3-day bladder diaries, BPH impact index, and Urolife quality of life questionnaire form. The patients were monitored for side effects and safety at 4, 8 and 12 weeks. **Results:** While the improvement in maximum and average urination streams, PVRU, bladder capacity, IPSS, OAB, BPH impact index scores was not significant, ther was significant improvement in Urolife quality of life questionnaire score and voiding frequency in favour of the trospium chloride group (0.0009 and 0.0216 respectively). There was no statistically significant difference in side effect profile between the groups. **Conclusion:** In men with BPH-related OAB trospium chloride and alpha-blocker combination treatment is effective and safe. The improvement in quality of life is remarkable.

Key Words: Prostatic hyperplasia; lower urinary tract symptoms; urinary bladder, overactive; cholinergic antagonists; male

ÖZET Amaç: Benign prostat hipertrofisi (BPH) ve aşırı aktif mesane (AAM) birlikteliğinin görüldüğü hastalarda yaşam kalitesi olumsuz yönde etkilenmektedir. Bu çalışmanın amacı, BPH ve buna bağlı alt üriner sistem yakınmaları olan ileri yaştaki erkeklerin tedavisinde kullanılan alfa bloker ve antikolinerjik kombinasyonunda daha önce hiç denenmemiş olan trospiyum klorürün etkinliğinin ve güvenilirliğinin araştırılmasıdır. **Gereç ve Yöntemler:** İleri dönük, randomize, plasebo kontrollü ve çift kör olarak planlanan çalışma, alt üriner sistem yakınmaları ve aşırı aktif mesanesi olan 45 yaşından büyük hastaları kapsamaktadır. Hastalar 12 hafta boyunca 45 mg trospiyum klorür ile 5 mg terazosin veya plasebo ve 5 mg terazosin almak üzere randomize edilmiştir. Çalışmanın başlangıcında ve 12. haftada hastalar total prostat serum antijeni, üroflovmetri, işeme sonrası üriner kalıntı, enternasyonel prostat semptom skoru, AAM sorgulama formu, 3 günlük işeme günlüğü, BPH etki indeksi ve Urolife yaşam kalitesi sorgu formu kullanılarak değerlendirilmiştir. Hastalar 4., 8. ve 12. haftalarda yan etki ve güvenlilik açısından değerlendirilmiştir. **Bulgular:** İyileşme düzeyleri açısından iki grup karşılaştırıldığında maksimum ve ortalama idrar akım hızları, işeme sonrası üriner kalıntı, mesane kapasitesi, enternasyonel prostat semptom skoru, AAM ve BPH etki indeksi skorlarındaki değişimler anlamlı değilken, Urolife yaşam kalitesi skoru ve işeme sıklığı trospiyum klorür grubu lehine istatistiksel olarak anlamlı bulundu (sırasıyla 0,0009 ve 0,216). Yan etki açısından değerlendirildiğinde iki grup arasında anlamlı bir fark bulunamadı. **Sonuç:** BPH'ye bağlı AAM'si olan erkeklerin tedavisinde trospiyum klorür ve alfa bloker kombinasyonu etkili ve güvenli bir tedavi yöntemidir. Yaşam kalitesindeki iyileşme dikkat çekicidir.

Anahtar Kelimeler: Prostat hiperplazisi; alt üriner sistem semptomları; mesane, aşırı aktif; kolinerjik antagonistler; erkek

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Benign prostate hypertrophy (BPH) is the most frequent benign tumor developing in men. Its incidence increases with age.[1] Depending on the urinary outflow obstruction, BPH can cause obstructive and irritative symptoms. Even overactive bladder (OAB) symptoms such as urgency, frequency and urinary incontinence may develop in BPH patients.[2,3] OAB syndrome is a chronic condition that impairs health-related quality of life.[4]

The treatment concept adopted for these patients was "the treatment with anticholinergic agents for detrusor instability related to obstruction is not appropriate and often increases urinary retention" until recent years.[5] The anticholinergic agent was considered to cause difficulty in voiding, increase postvoid residual urine or acute urinary retention.

Recently there are many randomized controlled studies concerning alpha-adrenergic blockers with antimuscarinic drugs and this combination is very effective and safe in patients who have BPH with OAB. In those studies, tolterodine, oxybutynin, propiverin and solifenacin were combined with alpha-adrenergic blockers.[6-8] Major adverse events associated with those drugs are dry mouth, inability to urinate, increase in the amount of residual urine and sexual dysfunction.[9-12]

Trospium chloride, a quarternary amine is an antimuscarinic agent, lacking central nervous system effect because of low lipophilicity and limited transition from blood-brain barrier.[13] In this study, for the first time we used trospium chloride in addition to alpha blockers as an antimuscarinic and investigated the efficacy and safety of the combination of alpha adrenergic blockers with trospium chloride in patients who have LUTS and OAB due to BPH.

MATERIAL AND METHODS

The study was run in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines and the Declaration of Helsinki. The protocol was approved by the Ethics Committees in Numune State Hospital (protocol no: 07-32, date: 18.10.2007). All subjects provided written informed consent. This was a prospective, randomized, placebo controlled and double blind study. Subjects who presented to the Urology Department of Gülhane Medical Military Hospital with LUTS and OAB between November 2008 and April 2010 were included in this study.

Eligible subjects were men aged 45 years with OAB symptoms (urgency and mean urinary frequency ≥8 times per 24 hours with or without urinary incontinence in 3-day bladder diaries at baseline). Exclusion criteria for the study were neurologic diseases, previous use of an anticholinergic or alpha adrenergic blocker, post voiding urinary residue (PVRU) ≥100 mL, prostate volume >50 mL, history of acute urinary retention (AUR) requiring catheterization, prostatic surgery, history of prostate cancer or prostate specific antigen (PSA) level >4 ng/mL, urinary tract infection (UTI) and diabetes.

All subjects underwent digital rectal examination, total PSA determination, uroflowmetry, PVRU and transabdominal ultrasonography (USG). Uroflowmetry and PVRU were repeated at week 12. In addition, subjects were asked to complete the International Prostate Symptom Score (IPSS), OAB questionnaire, 3-day bladder diaries, BPH impact index, and Urolife quality of life questionnaire form at baseline and week 12. Eligible subjects were randomized to receive trospium chloride 45 mg (morning 30 mg, evening 15 mg) with terazosin 5 mg (first 10 days 2.5 mg) or placebo with terazosin 5 mg for 12 weeks. The patients were assessed for side effects and safety at 4, 8 and 12 weeks.

Inability to urinate, dry mouth, headache, hypotension, dizziness, constipation, and drug related side effects such as nasal obstruction were recorded. Patients who had severe side effects were excluded.

Uroflowmetry was performed two times and average values were used. In addition, PVRU was assessed by ultrasound.

STATISTICAL ANALYSIS

Sample size was calculated by the Power and Sample Size Calculations Version 2.1.31 program. Sample size was calculated using assumptions about the

alterations in Urolife Quality of Life Scale. We planned to include one control subject per case. In the preliminary study the standard deviation was 135; the true difference between the subject group and the control group was 135. The need was calculated as 17 experimental subjects and 17 control subjects for this study to be able to reject the null hypothesis that the population means of the cases and control groups are equal with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

Statistical analysis was performed using MedCalc version 10.2.0.0. Wilcoxon test was used for the comparison of values obtained from groups after treatment. Mann-Whitney U test was performed for the comparison of changes in the criteria for both groups.

While hypotension and dizziness were considered terazosin related side effects, trospium chloride related side effects were dry mouth and constipation. The frequency of side effects was calculated using the chi-square test. In all statistical studies, p-value less than 0.05 was considered significant.

RESULTS

A total of 58 patients among 1436 BPH patients were included in the study. Seven patients in the trospium group and five patients in the placebo group were later excluded from the initial study group of 58 patients. The reasons for exclusion are listed below:

- Five patients did not accept longer drug use (4 trospium group and 1 placebo group)
- One patient was diagnosed with glaucoma during the study (trospium group)
- Two patients had hypotension (1 trospium group and 1 placebo group)
- Three patients had dizziness (placebo group)
- One patient had dry mouth (trospium group)

After the exclusion of patients, 22 patients in the placebo group and 24 patients in the trospium group completed the study. The power of the study was 89.5 %. Baseline data of both groups were summarized in Table 1.

While there was no difference between the two groups in terms of age, t-PSA, prostate volume, Qmax, PVRU, voiding frequency, total IPSS, total OAB-q score, BPH impact index, and total Urolife quality of life questionnaire score, the difference in terms of average voiding flow and functional bladder capacity was significant after randomization. Mean urinary flow and functional bladder capacity were lower in the placebo group compared to the patient group.

When pre- and post-treatment values (Table 2) of the trospium group were compared, improvements in all parameters except PVRU were statistically significant.

Pre- and post-treatment values (Table 2) of the placebo group showed significant improvements in all parameters except PVRU and Urolife quality of life questionnaire score, which were not significant.

THE COMPARISON OF IMPROVEMENT LEVEL

The differences between the two groups in terms of improvement of Qmax, Qave, PVRU, bladder capacity, total IPSS, OAB-q score, and BPH impact

TABLE 1: Comparison of the two groups in terms of baseline demographic data and other parameters.

	Placebo Group**	Treatment Group**	p
Age	57 (45-72)	58 (53-75)	0.264
PSA (ng/mL)	1.6 (0.2-4)	1.04 (0.4-4)	0.293
Prostate volume (mL)	27.5 (20-60)	29 (20-50)	0.810
Q max. (mL/sec)	15 (6-37)	17.5 (8-29)	0.100
Q ave. (mL/sec)	6.5 (3-22)	9.5 (4-16)	**0.034***
PVRU (mL)	25 (0-100)	20 (0-100)	0.660
Total IPSS score	15 (3-28)	15.5 (3-35)	0.911
Total BPH-II score	6.5 (0-12)	6.5 (1-12)	0.300
Total OAB Questionnaire score	13 (9-39)	16 (3-38)	0.920
Total Urolife QoL score	660 (110-860)	510 (170-840)	0.061
Voiding frequency (day)	8 (7-17)	8 (4-19)	0.400
Functional bladder capacity (mL)	193 (73-800)	258 (167-558)	**0.003***
n	22	24	

*Statistically significant; **median (range); PSA: Prostate specific antigen; Qmax: Maximal urine flow rate; Qave: Average urine flow rate; PVRU: Post-Voided Residual Urine; IPSS: International Prostate Symptom Score; BPH-II: Benign Prostatic Hyperplasia Impact Index; OAB: Overactive Bladder; QoL: Quality of Life.

TABLE 2: Comparison of the two groups in terms of pre- and post- treatment parameters.

	Trospium Group			Placebo Group		
	**Pre-treatment	**Post-treatment	p	**Pre-treatment	**Post-treatment	p
Q max. (ml/sec)	17.5 (8-29)	21 (7-42)	**0.019***	15 (6-37)	17 (7-37)	**0.006***
Q ave. (ml/sec)	9.5 (4-16)	12 (3-20)	**0.012***	6.5 (3-22)	8.5 (3-25)	**0.0009***
PVRU (ml)	20 (0-100)	0 (0-200)	0.854	25 (0-100)	0 (0-300)	0.733
Total IPSS score	15.5 (3-35)	8.5 (2-19)	**0.0001***	15 (3-28)	7 (1-22)	**0.0001***
Total BPH-II score	6.5 (1-12)	3 (1-11)	**0.0001***	6.5 (0-12)	3 (0-21)	**0.003***
Total OAB Questionnaire score	16 (3-38)	10 (1-38)	**0.0004***	13 (9-39)	12 (5-31)	**0.001***
Total Urolife QoL score	510 (170-840)	690 (250-900)	**0.0001***	660 (110-860)	687 (260-856)	0.800
Voiding frequency (day)	8 (4-19)	6 (4-14)	**0.0007***	8 (7-17)	7.5 (6-12)	**0.008***
Functional bladder capacity (ml)	258 (167-558)	321 (200-917)	**0.014***	193 (73-800)	236 (117-967)	**0.002***
n	24			22		

* Statistically significant; **Median (range); Qmax: Maximal urine flow rate; Qave: Average urine flow rate; PVRU: Post-Voided Residual Urine; IPSS: International Prostate Symptom Score; BPH-II: Benign Prostatic Hyperplasia Impact Index; OAB: Overactive Bladder; QoL: Quality of Life.

index were not statistically significant (Table 3). The quality of life scores with regard to Urolife and voiding frequency were significantly better in the trospium group (0.0009 and 0.0216 respectively). Urolife quality of life questionnaire median score was 0.29 [(-0.07)-1.03] in the trospium group, while it was 0.02 [(-0.3)-1.7] in the placebo group (Table 3 and Figure 1).

EVALUATION OF SIDE EFFECTS

All side effects developed at week 4. No side effects were detected at week 8 and 12. Comparison in terms of the side effect frequency showed no statistical difference between the two groups (p=0.443). Hypotension and dizziness developed in 6 patients (%25) in the trospium group and in 5 patients (%22.7) in the placebo group. While dry mouth developed in 3 (%12.5) patients only in the trospium group, constipation was not present in any patient.

TABLE 3: Comparison of the two groups in terms of changes in parameters after treatment.

	Placebo Group**	Trospium Group**	p
Q max. (ml/sec)	0.14 [(-0.3)-1.06]	0.14 [(-0.4)-1.9]	0.991
Q ave. (ml/sec)	0.22 [(-0.2)-0.88]	0.16 [(-0.4)-2.2]	0.582
PVRU (ml)	0 [(-0.9)-3]	0 [(-0.9)-29]	0.605
Total IPSS score	0.32 [(-0,8)-0]	0.41 [(-0,8)-0]	0.435
Total BPH-II score	-0.46 [(-1)-9.5]	-0.41 [(-0.8)-0.2]	0.775
Total OAB Questionnaire score	-0.25 [(-0.7)-0.2]	-0.3 [(-0.6)-0.4]	0.134
Total Urolife QoL score	0.02 [(-0.3)-1.7]	0.29 [(-0.07)-1.03]	**0.0009***
Voiding frequency (day)	-0.15 [(-0.4)-0.2]	-0.29 [(-0.5)-1]	**0.0216***
Functional bladder capacity (ml)	0.22 [(-0.2)-1.5]	0.16 [(-0.4)-1.7]	0.791
n	22	24	

*Statistically significant; **Median (range); Qmax: Maximal urine flow rate; Qave: Average urine flow rate; PVRU: Post-Voided Residual Urine; IPSS: International Prostate Symptom Score; BPH-II: Benign Prostatic Hyperplasia Impact Index; OAB: Overactive Bladder; QoL: Quality of Life.

DISCUSSION

BPH-originated lower urinary tract symptoms detoriorate the quality of life. When OAB symptoms are added to this condition the discomfort is further increased and the combination of those two situations are common.[14] A study on this topic according to urodynamic tests points out that 40% to 70% of older men with LUTS have also detrusor overactivity.[15]

When OAB symptoms develop in patients with LUTS accompanied by BPH, the condition becomes more complicated. Thus, monitoring the response to treatment also becomes more important. This is the reason why we used commonly ratified questionnaires such as IPSS, Overactive Bladder Questionnaire, BPH impact index, and Urolife quality of life questionnaire in addition to objective measurements.

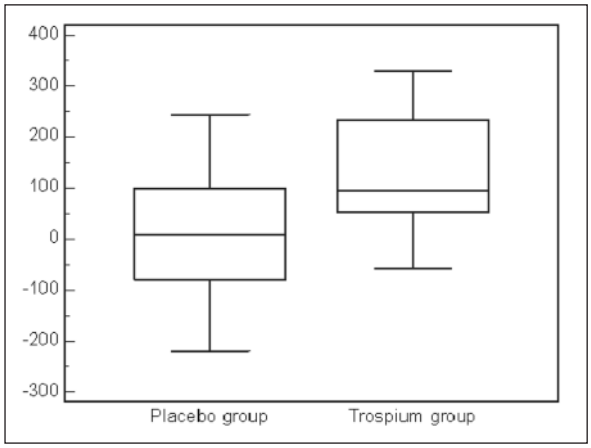

FIGURE 1: Comparison of the two groups in terms of improvement in quality of life score.

Studies investigating the efficacy of alpha blockers with anticholinergics have shown greater improvements in the combination group compared to the control group.[16-19] In a randomized, prospective study including patients with low or medium bladder obstruction, tamsulosin 0.4 mg was given for 1 week and afterwards treatment was continued using tamsulosin alone in one group, and tamsulosin with tolterodin 2 mg (twice a day) in the other group. The quality of life scores improved significantly in the combination group.[17] In another double blind, randomized, placebo controlled study, patients with concurrent OAB and BPH, tolterodine 4 mg, tamsulosin 0.4 mg, tolterodine with tamsulosin or placebo were administered for 12 weeks. Eighty percent of the patients receiving tolterodine with tamsulosin, 62% receiving placebo, 71% receiving tamsulosin and 65% receiving tolterodine benefited from treatment. In addition, the quality of life scores improved significantly in the combination group.[18] Similarly in our study, the improvement in questionnaire scores was greater in the combination group even though the differences were not significant for any parameter except the urolife quality of life questionnaire and voiding frequency. The reason of Urolife questionnaire being statistically significant might be because other forms question the disease rather than quality of life. Interestingly, even though the improvement in the OAB questionnaire for the trospium group seemed to be greater, the difference in total scores between the two groups was not statistically significant. This could depend on the effect of terazosin on the bladder. Our findings support that some alpha- blockers could be effective on bladder smooth muscle and need to be further investigated.

Comparison of two groups in terms of maximum flow velocity and PVRU as in the study by Ji Young Lee et al., revealed an insignificant difference.[9] Adding trospium to the alpha-blocker treatment of OAB patients with LUTS accompanied by BPH does not cause any negative effects on the bladder functions.

No patient had urinary retention in our study. In contrast, in the study conducted by Ji Young Lee et al., 3.3% of patients had urinary retention. In addition, comparison of pre-and post-treatment PVRU revealed no significant difference, whereas Kyu Sung Lee et al. reported a significant increase in PVRU.[6] Furthermore, the European Association of Urology 2010 guidelines stated that 0.9-3.3% of patients using anticholinergics with alpha-blockers had high amounts of PVRU.[20] We think that this depends on the inclusion of patients with medium-grade LUTS and low total PSA levels in the study; because acute urine retention risk is higher when total PSA level and IPSS score are high.[20]

Our study revealed no significant difference between the two groups in terms of side effects. Dry mouth developed in 3 patients in the trospium group. In the study conducted by Ji Young Lee et al., 27% of patients using the combination treatment had dry mouth, and European Association of Urology (EAU) 2010 guidelines state that dry mouth is the most commonly reported side effect.[20] The lower percentage of dry mouth in our study could be due to the pharmacokinetics of trospium. Trospium chloride is reported to be the combination passing into the central nervous system at the lowest level.[13]

In our study, alpha-blockers were used in both groups. Even if the question 'Would the study be more significant if a group using only anticholinergics was included?' seems to be unacknowledged, in the literature there is a consensus that bladder

output resistance should be reduced with alpha blocker treatment before anticholinergics are added in men with LUTS.[21] Actual findings lack the power to prove the reverse. In a review made by Chapple underlines that in patients with LUTS with OAB, the use of antimuscarinics alone could be disappointing. The same review states that clinically significant healing may be ensured by the addition of an alpha-blocker to antimuscarinics.[22]

Our study has a prospective, placebo controlled, randomized and double blind design. Only one study in the literature has a placebo arm, and all the other studies compare the combination therapy efficacy with the efficacy of an alpha-blocker monotherapy.[22] The recent studies on this topic have follow-up periods of 4 to 12 weeks.[7,20] Our follow up period was long enough (12 weeks) to make accurate judgements.

Tolterodine, oxybutynin, propiverin and solifenacin were used in similar studies but our study is the first one assessing the effect of trospium chloride (a quarternary amine) in the combination therapy for patients with LUTS and OAB symptoms.[22] Transition of trospium chloride through biological membranes including the blood-brain barrier is difficult because its lipophilic characteristic is low and it is ionized in neutral pH.Less frequent side effects related to the central nervous system compared with other antimuscarinic agents in patients receiving trospium chloride was explained with this property of the molecule.[13] Dry mouth complaint in three out of 24 patients (12.5%) in the present study also supports this argument.

CONCLUSION

To our knowledge, our study is the first study evaluating the safety and efficacy of trospium chloride; a quaternary amine used as an anticholinergic agent with an alpha blocker in BPH and OAB patients which also is low lipophilic, so transition through biological membranes including the blood-brain barrier is not possible.

This study showed that the use of trospium chloride, in addition to the alpha-blocker for 12 weeks, reduced voiding frequency significantly and improved the quality of life significantly compared to placebo. No significant side effects were detected in terazosin-trospium combination, and there was no significant increase in PVRU levels. In conclusion, trospium chloride can be safely used in the combination treatment in BPH patients with LUTS and OAB.

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