# Aşırı Aktif Mesane hastalarında semptomları gidermede hangisi daha etkili: Trospium 30 mg 2x1 ya da solifenasin 5 mg 1x1

## *Which one is more effective for symptom relief in overactive bladder patients: Trospium 30 mg 2x1 or solifenacin 5 mg 1x1*

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**Özet**

**Amaç:** Aşırı Aktif Mesane (AAM) hastalarında trospium ve solifenasinin işeme sayısı, nokturi ve urge inkontinans üzerine etkilerini araştırmak.

**Gereç ve Yöntem:** Prospektif bir çalışma planlandı. Hastalar tedaviye başlamadan önce AAM farkındalık anketini (AAM-V8) doldurdular. Hastaların 3 günlük işeme günlüğünden günlük işeme, nokturi ve urge inkontinans sayıları belirlendikten sonra trospium 30 mg 2x1 veya solifenasin 5 mg 1x1 den birisi başlandı. Hastalar kontrolde işeme günlüğü ve AAM-V8 formu ile tekrar değerlendirildi. Ayrıca yan etkiler sorgulandı.

**Bulgular:** Bu çalışma yaş ortalaması 47.8±12.2(18-75 yaş) olan toplam 225 hasta içermektedir. Hastaların 173(76.9%)'sı kadın, 52(23.1%)'si erkektir. Trospium grubunda(n=104, M/F:24/80) yaş ortalaması 47.4±12.7 ve solifenasin grubunda(n=121, M/F:28/93) yaş ortalaması 48.1±11.8 olup gruplar arasında istatistiksel farklılık izlenmedi (p=0.657). Validasyon ölçeği anketinde azalmada iki molekül arasında istatistiksel farklılık izlenmedi. Hem 4.hafta hemde 12.haftada işeme sayısı trospium molekülünde solifenasin den daha fazla azalmıştır ve bu azalmalar istatistiksel olarak anlamlıdır (sırasıyla p<0.027, p<0.045 ). Nokturi ve urge inkontinans sayıları azaldı fakat trospium ve solifenasin molekülleri arasında farklılık izlenmedi. En sık izlenen yan etkiler ağız kuruluğu, kabızlık ve bulanık görmedir.

**Sonuç:** Her iki molekülde AAM hastalarında 4.hafta ve 12.haftalarda validasyon ölçeğini, işeme sayısı, nokturi ve urge inkontinans sayılarını azaltır. İşeme sayısını trospium molekülü solifenasin den daha fazla azaltmıştır ve bu azalma istatistiksel olarak anlamlıdır. Özellikle işeme sayısı fazlalığından yakınan AAM hastalarında trospium molekülü solifenasinden daha etkili olabilir.

**Anahtar Kelimeler:** Overactive Bladder, Validation Scale, Voiding Diary, Trospium, Solifenacin

**Absract**

**Aim:** To investigate the effect of trospium and solifenacin on the micturition, nocturia and urge incontinence numbers in overactive bladder (OAB).

**Material and Method:** A prospective study was planned. The patients completed the OAB awareness survey (OAB-V8) before starting the treatment. The patient's daily micturition, nocturia and urge incontinence numbers were recorded from the 3-day voiding diaries and one of trospium 30 mg bd or solifenacin 5 mg od was started. The patients were evaluated again at follow-up using the voiding diary and the OAB-V8 form.

**Results:** The study included a total of 225 subjects aged 18-75 years with a mean age of 47.8±12.2 years. There were 173 (76.9%) females and 52 (23.1%) males. The mean age was 47.4±12.7 in the trospium (n=104, M/F:24/80) and 48.1±11.8 years in the solifenacin (n=121, M/F:28/93) with no statistically significant difference (p=0.657). No statistically significant difference was found between the two molecules regarding the decrease in the validation scale. The micturition number at both the 4th and 12th weeks decreased more markedly with trospium then solifenacin and the difference was statistically significant (p<0.027 and p<0.045 respectively). The nocturia and urge incontinence numbers decreased as well but without a statistically significant difference between the trospium and solifenacin. The most common side effects were dry mouth, constipation and blurred vision.

**Conclusions:** Both molecules decreased the micturition, nocturia and urge incontinence numbers in addition to the validation scale values at the 4th and 12th weeks in OAB patients. There was no difference between the two molecules as regards decreasing the nocturia and urge incontinence numbers and validation scale values. The trospium decreased micturition numbers more than the solifenacin and this difference was statistically significant. Trospium could be more effective than solifenacin in the treatment of OAB patients, especially those complaining of increased micturition numbers.

**Keywords:** Overactive Bladder, Validation Scale, Voiding Diary, Trospium, Solifenacin

## INTRODUCTION

Overactive Bladder (OAB) has been described as urgency with or without urinary incontinence accompanied by frequent urination and nocturia (1). The prevalence of OAB was reported to be 13.3% in men and 21.6% in women in our country (2). The disorder has a significant effect on the quality of life. It especially causes problems during work. Anticholinergics are commonly used for the medical treatment of OAB (3). Anticholinergic drugs block muscarinic receptors and decrease bladder contractions (4).

The trospium has a quaternary amide structure with a half-life of 15-20 hours. It's important features are lack of metabolism with the cytochrome P450 system in the liver and the excretion of 60% of the absorbed amount unchanged (5). The solifenacin has a tertiary amide structure. It is absorbed in the gastrointestinal system and metabolized in the liver with the cytochrome P450 system. Its half-life is 60 hours (6).

Many current studies report that anticholinergic drugs decrease OAB symptoms but the side effects seen with almost all anticholinergics to a certain degree should be considered. There are many unanswered questions regarding antimuscarinics. For example, despite several studies showing their effectiveness compared to placebo, only a few studies have compared different molecules with each other. There is little information on the effectiveness and side effects during long-term use. Despite all these questions, antimuscarinics have proven safety and effectiveness in selected patient groups and have become our most important molecule in OAB treatment.

We studied the effectiveness of the trospium and solifenacin molecules in decreasing the micturition, nocturia and urge incontinence numbers in OAB patients in this study. We also documented the side effects observed during treatment.

## MATERIAL AND METHOD

This was a prospective study conducted at the Urology Clinic between October 2014 and April 2016 and patients' informed consents were obtained. Approval of the ethics committee for the study was taken from the xxxx. Patients between 18 and 75 years of age with bladder outlet obstruction and BPH for male patients who were diagnosed with AAM and who did not have previous anticholinergic treatment with uroflowmetry and prostate specific antigen screening for uroflowmeter in male patients, urine examination, routine hemogram and biochemistry, ultrasonography, they were included in the study. We excluded patients with a systemic disease, previous incontinence surgery, those who previously used anticholinergic drugs due to AAM, urinary retention, intestinal obstruction, and glaucoma, in addition to pregnant or nursing women. The OAB-V8 validation survey was administered to patients before treatment was started and the daily micturition, nocturia and urge incontinence numbers were determined from the 3-day voiding diary. Solifenacin 5 mg od or trospium 30 mg bd was started and the patient called for follow-up 4 weeks later. At the end of the 4 weeks, the OAB-V8 form and the micturition, nocturia and urge incontinence numbers from the 3-day voiding diary were recorded and the side effects documented. The medication was continued if it was effective and with minimal side effects that did not require drug discontinuation. All the procedures were repeated at the 12th week follow-up. The patients were evaluated for drug effectiveness and side effects. The dose was used in our country since only 30 mg of short-acting, 2x1 form of trospium is available.

### *Statistical Analysis*

The Cronbach alpha value showing the internal validity of the scale was 0.83 for the first administration (week 0), 0.86 for the second administration (week 4) and 0.87 for the third administration (week 12), indicating "good" internal validity. Cronbach's alpha is a measure of internal consistency, that is, how closely related a set of items are as a group. Test-retest consistency evaluation showed a strong relationship ($r=0.77$; $p<0.001$) between week 0 and week 4 total scores, a moderate relationship ($r=0.69$; $p<0.001$) between week 0 and week 12 scores and a strong relationship ($r=0.87$; $p<0.001$) between week 4 and week 12 scores. Shapiro Wilk test was used for assessing whether the variables follow normal distribution or not. Variables were reported as mean ± standard deviation or median(Inter Quartile Range-IQR) values. According to normality test result independent samples t test or Mann Whitney U test were used for between group comparisons. For the measurement obtained from

**Table 1:** Comparison of the age, gender, BMI and validation total scale scores of the trospium and solifenacin molecule groups

| | Trospium (n=104) | Solifenasin (n=121) | p value |
|---|---|---|---|
| Gender (M/F) | 24/80 | 28/93 | 0.991 |
| Age | 47.4±12.7 | 48.1±11.8 | 0.657 |
| BMI | 28.87 (7) | 28.71 (7.25) | 0.709 |
| Validation total (week 0) | 17(11) | 18(9) | 0.973 |
| Validation total (week 4→0) | 11(8) -38.46% | 11(8) -32.15% | 0.114 |
| Validation total (week 12→0) | 10(9) -41.67% | 10(8) -43.75% | 0.547 |

*The data were expressed as median (IQR); mean±standard deviation; week 4→0 indicates the change in the week 4 measurement compared with the week 0 measurement; week 12→0 indicates the change in the week 12 measurement compared with the week 0 measurement.*

**Table 2:** Comparison of micturition, nocturia and urge incontinence numbers between the trospium and solifenacin molecule groups

| | Trospium (n=104) | Solifenacin (n=121) | p value |
|---|---|---|---|
| Micturition number (Week 0) | 11 (4) | 10 (4) | 0.045 |
| Micturition number (Week 4→0) | 8(2) (¯33.33%) | 8(2) ¯-27.27% | 0.027 |
| Micturition number (Week 12→0) | 7(2) (¯36.84%) | 7(2) (¯33.33%) | 0.045 |
| Urge incontinence (Week 0) | 1 (3) | 1 (3) | 0.518 |
| Urge incontinence (Week 4→0) | 0 (1) | 0 (1) | 0.123 |
| Urge incontinence (Week 12→0) | 0 (2) | 0 (1) | 0.269 |
| Nocturia number (Week 0) | 2(1) | 2(1) | 0.678 |
| Nocturia number (Week 4→0) | 1(1) (¯33.33%) | 1(1) (¯33.33%) | 0.415 |
| Nocturia number (Week 12→0) | 1(1) (¯-50% ) | 1(1) (¯50%) | 0.217 |

*The data were expressed as median (IQR); week 4→0 indicates the change in the week 4 measurement compared with the week 0 measurement; week 12→0 indicates the change in the week 12 measurement compared with the week 0 measurement.*

different time points, score difference or percent change values were computed and between group comparisons were performed by using Mann Whitney U test. Categorical variables were compared by Chi square test. Internal consistency of the scale was examined by Cronbach alpha coefficient where test-retest reliability was examined by correlation analysis with Pearson correlation coefficient. SPPS (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) software was used for performing statistical analysis and $p<0.05$ was set at statistical significance.

## RESULTS

The study included a total of 225 subjects aged 18-75 years with a mean age of 47.8±12.2 years. There were 173 (76.9%) females and 52 (23.1%) males (Table 1). The mean age was 47.4±12.7 in the trospium (n=104) and 48.1±11.8 years in the solifenacin (n=121) with no statistically significant difference (p=0.657). The Male/Female gender distribution was 24/80 in the trospium and 28/93 in the solifenacin with no statistically significant difference (p=0.991). The median body mass index (BMI) value was 28.9 (IQR=7) in the trospium and 28.7 (IQR=7.24) in the solifenacin, again with no statistically significant difference (p=0.709).

Evaluation of the validation scale total scores showed a median scale score (Table 1) of 17 (IQR=11) for the trospium and 18 (IQR=9) for the solifenacin with no difference between the two groups for total scale scores (p=0.973). The median scale scores at the 4th week administration were 11 (IQR=8.25) and 11 (IQR=8) for the trospium and solifenacin scores with a 38.46% decrease in the trospium group and a 32.15% decrease in the solifenacin group with no statistically significant difference (p=0.114). The median scale scores for the 12th week administration were 10 (IQR=9) and 10 (IQR=8) for the trospium and solifenacin groups with a decrease of 41.67% and 43.75% respectively, again with no statistically significant difference (p=0.547).

Comparison of the two groups for daily micturition

**Table 3:** Adverse effect rates by week in the trospium and solifenacin molecule groups, respectively

| | Week4 | | Week12 | |
|---|---|---|---|---|
| | Trospium | Solifenacin | Trospium | Solifenacin |
| Dry mouth | 17 (21.20%) | 19 (20.40%) | 17 (21.50%) | 18 (19.80%) |
| Constipation | 12 (15%) | 20 (21.50%) | 12 (15.20%) | 18 (19.80%) |
| Blurred vision | 6 (7.50%) | 8 (8.60%) | 6 (7.60%) | 8 (8.80%) |
| Weakness | 4 (5%) | 5 (5.40%) | 4 (5.10%) | 4 (4.40%) |
| Dyspepsia | 3 (3.80%) | 4 (4.30%) | 3 (3.80%) | 4 (4.40%) |
| Headache | 2 (2.50%) | 3 (3.20%) | 1 (1.30%) | 2 (2.20%) |
| Insomnia | 1 (1.20%) | 4 (4.30%) | 1 (1.30%) | 4 (4.40%) |
| Sleepiness | 1 (1.20%) | 3 (3.20%) | 1 (1.30%) | 2 (2.20%) |
| Palpitations | 1 (1.20%) | 3 (3.20%) | 0 | 3 (3.30%) |
| Dry eye | 0 | 1 (0.82%) | 1 (0.96%) | 0 |

*Data were expressed as n (%).*

number (Table 2) revealed a baseline number of 11 (4) in the trospium group and 10 (4) in the solifenacin group. The 4th week median micturition numbers in the trospium and solifenacin molecule groups were 8 (IQR=3) and 8 (IQR=3) respectively with a decrease of 33.33% and 27.27% respectively and there was a statistically significant difference in the decrease compared to the baseline measurement (p=0.027). The 12th week median micturition numbers were 7 (IQR=2) and 7 (IQR=2) in the trospium and solifenacin groups with a decrease compared to baseline of 36.84% and 33.33% respectively. There was a statistically significant difference between the two groups (p=0.045).

Comparison of the two groups for the number of nocturia (Table 2) revealed that the baseline median nocturia numbers were 2 (IQR=1) and 2 (IQR=1) in the trospium and solifenacin groups with no statistically significant difference (p=0.678). The median nocturia numbers at the 4th week measurements were 1 (IQR=1) and 1 (IQR=1) in the trospium and solifenacin groups with a 33.33% decrease compared to baseline in both groups with no statistically significant difference between the groups (p=0.415). The median nocturia numbers at the 12th week measurements were 1 (IQR=1) and 1 (IQR=1) in the trospium and solifenacin groups respectively with a 50% decrease compared to the baseline measurements in both groups and no statistically significant difference between the groups (p=0.217).

Comparison of the urge incontinence number between the two groups (Table 2) revealed a baseline median urge incontinence number of 1 (IQR=3) in both groups with no statistically significant difference between the groups (p=0.518). The 4th week measurements for median urge incontinence were 0 (IQR=1) and 0 (IQR=2) while the 12th week measurements were 0 (IQR=1) and 0 (IQR=1) respectively with no difference compared to the baseline measurement in either group and no statistically significant difference between the two groups (p=0.123 and p=0.269 respectively).

Adverse effect rates were similar at the 4th and 12th weeks. The medication was discontinued in 5 patients due to adverse effects during the study. The most common side effects were dry mouth, constipation and blurred vision.

## DISCUSSION

Overactive bladder is characterized by lower urinary system symptoms originating from the storage period in the bladder. The urge incontinence seriously affect the quality of life and the work life (12,13). It is commonly thought that none of the OAB treatments are superior to each other (14). All medical treatments aim to decrease symptoms and not to cure the patient. Antimuscarinic drugs can show various levels of effectiveness and side effects due to their muscarinic receptor affinity, lipid solubility, half-life and pharmacological form (early or late release or transdermal). All muscarinic receptors lead to effective blockage but their administration route, metabolism and side effect profiles vary. Anticholinergics are recommended at the 1A level in guidelines (15).

The OAB-V8 validation results showed a decrease of 38.46% and of 32.15% in the trospium and solifenacin molecules respectively from baseline to the 4th week with no statistically significant difference between the two molecules. The decrease from baseline to the 12th week was of 41.67% and of 43.75% in the trospium and solifenacin molecules respectively, again with no statistically significant difference between the two molecules. Treatment with the trospium or solifenacin molecule decreased the OAB-V8 validation scale values but we did not find a statistically significant difference between the two.

The systematic review by Chapple in 2008 included 73 studies (16). These studies were evaluated for criteria such as the changes in the continence rate, the mean change in daily incontinence and voiding numbers, and change in ml in the daily numbers of urge episodes and the urinary volume at each micturition so that the treatment effectiveness could be assessed. In conclusion, antimuscarinics are statistically significantly more effective than placebo but the data on their comparative effects are not adequate (16).

OAB is a complex disorder with many symptoms. Frequent urination is one of the commonly encountered symptoms. Many studies have shown that anticholinergics decrease the frequency of urination. A study on tolterodine tartrate, trospium and placebo effects has shown that both molecules decrease urination frequency but the decrease compared to placebo is statistically significantly more prominent with the trospium molecule (17).

Studies comparing trospium with the oxybutynin and tolterodine tartrate have shown decreased urination, nocturia and urge incontinence numbers (17). Trospium and oxybutynin have been similarly reported to decrease the frequency of urination and urge incontinence (18).

We observed a decrease of 33.33% with the trospium and of 27.27% with the solifenacin from the baseline to the 4th week in this study. The decrease with the trospium was less than with the solifenacin and this difference was statistically significant. There was of 36.84% and of 33.33% decrease with the trospium and solifenacin respectively from the baseline to the 12th week and this difference was statistically significant. OAB can lead to a wide range of symptoms such as frequent urination, nocturia, feeling of fullness and urge incontinence. The trospium may be primarily considered as medical treatment to decrease the micturition number in OAB patients who especially complain of this problem.

Nocturia is a problematic OAB symptom. It is common in both genders. Nocturia indicates getting up for urination at least once a night. Nocturia-related sleep problems have been reported to significantly disturb the quality of life (19). The frequency of waking up at least twice a night for urination has been reported as 53% in males and 60% in females (20). We found that both the trospium and solifenacin decreased the number of nocturia episodes from the baseline to the 4th week and from the baseline to the 12th week but there was no statistically significant difference when the two molecules were compared. The two molecules have a similar effect in OAB treatment.

Urge incontinence is quite important in OAB patients as it decreases the quality of life with its social, psychological, occupational and sexual effects. Approximately 62% of OAB patients have dry OAB (without urge incontinence) and 38% have wet OAB (with urge incontinence) (21). This urge incontinence limits their daily living activities. The elderly can especially become dependent on others. The patients become isolated and suffer increased anxiety (22). Studies comparing Trospium and placebo have reported a significant decrease in the daily urge incontinence numbers at the end of the 12th week with decrease rates of 59% and 44% respectively (23).

We observed a decrease from the baseline to the 4th week and from the baseline to the 12th week in urge incontinence numbers with both the trospium and solifenacin molecules and we did not find a statistically significant difference between the two molecules. The trospium and solifenacin molecules have similar effectiveness in decreasing urge incontinence symptoms in OAB patients.

OAB increases with age together with other accompanying disorders. The medication side effects therefore become more important because of the multiple drug use in OAB patients. Muscarinic receptors are found in the salivary glands, parotid gland, gastrointestinal system, brain, the eye and the heart in addition to the bladder. Muscarinic drugs do not have effects specific to any organ and therefore to the bladder, and lead to adverse effects

by blocking muscarinic receptors outside the bladder as well. The main side effects are mouth dryness, constipation and blurred vision, due respectively to blockage of the M3 receptors in the salivary glands, intestines and ocular ciliary muscles. Patients occasionally need to discontinue the drug due to unwanted effects. The most common of these side effects are dry mouth and constipation with a negative effect on the quality of life (24).

Trospium side effects reported in clinical studies include dry mouth in 20%, constipation in 10%, headache in 4%, weakness in 2% and dyspepsia in 1% in general (25). Garely et al. have reported the side effects of OAB treatment with Solifenacin as dry mouth in 21.4%, constipation in 13.3%, headache in 3.4%, blurred vision in 2.6%, nausea in 1.8%, dyspepsia in 2.5%, and dry eye in 1.3% (26). We did not find a difference between the side effect rates of trospium and solifenacin at the 4th and 12th weeks. The most common side effects were constipation and dry mouth, followed by blurred vision, weakness, dyspepsia, insomnia, palpitation, headache, sleepiness and dry eye at various rates. Our results were consistent with the rates reported in the literature. Future studies on muscarinic receptors and their subtypes can enable the development of more effective treatments with a better side effect profile.

The disadvantage of our study was that this form was used because only 30 mg of the trospium molecule in our country exists in 2x1 form and is not a different dose or long acting trospium molecule. The comparative efficacy and side effect rates could be different when different doses and posologies were used.Conclusion

It is important to treat OAB as it has a negative effect on the quality of life. Trospium and solifenacin decrease the validation scale values and nocturia and the urge incontinence numbers but there is no statistically significant difference between these two molecules. The decrease in the micturition number was significantly better with the trospium than the solifenacin and we therefore believe trospium is more effective in the treatment of patients complaining of increased micturition than solifenacin.

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