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Comparison of Use of Propiverine at 45 mg and Combined Treatment of Propiverine 30 mg and Mirabegron in Patients with Overactive Bladder Who did not Benefit from Propiverine 30 mg Treatment

Propiverin 30 mg Tedavisinden Fayda Görmeyen Aşırı Aktif Mesaneli Hastalarda Propiverin 45 mg Kullanımı ile Propiverin 30 mg ve Mirabegron Kombine Tedavisinin Karşılaştırılması

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ABSTRACT

Objective: There are many anti-cholinergic drugs that are used to treat overactive bladder. Mirabegron was created to lessen the many side effects of these drugs, especially acute urinary retention. The use of mirabegron along with anti-cholinergic is a safe and effective treatment method. In addition, anti-cholinergic therapies have been developed that reduce bladder overactivity with side effects similar to those of lower dose approaches and with higher efficacy.

Methods: In this study, data were collected for 35 male patients (group 1) in whom propiverine 45 mg was administered instead of propiverine 30 mg treatment; the other 31 patients (group 2) were given mirabegron 50 mg on propiverine 30 mg treatment. Patients were called for control at 1 and 6 months; adherence and persistence were determined; residual urine volumes were measured by ultrasonography; and complaints were evaluated using the Overactive Bladder Assessment Form (OAB-V8).

Results: When the ages and chronic diseases of the patients in groups 1 and 2 were compared, there was no significant difference between the groups. Similar rates of adherence and persistence were observed between the groups. There were no statistically significant differences between the groups in terms of daily micturition and weekly incontinence frequencies, post-voiding residual urine volumes, side effects (especially dry mouth), and responses and scores on the OAB-V8 forms.

Conclusion: Propiverine 45 mg monotherapy or propiverine 30 mg and mirabegron combined treatment can be safely administered with similar efficacy and limitations.

ÖZ

Amaç: Mesane aşırı aktivitesinin yaşam tarzı değişikliği ve davranışların düzenlenmesi gibi birinci basamak tedavilerinden fayda görmeyen hastalarda kullanılan medikal tedavi için birçok antikolinerjik ilaç geliştirilmiş olmasına rağmen, mirabegron antikolinerjik ilaçlara bağlı birçok yan etkiyi özellikle akut üriner retansiyonu azaltmak için kullanılmaya başlanmıştır. Mirabegronun antikolinerjiklerle kombinasyon tedavisinde kullanılmasının güvenli ve etkili bir tedavi yöntemi olduğu gösterilmiştir. Antikolinerjik ilaçlardan propiverin de düşük doz antikolinerjik ilaçlardan kısıtlı fayda gören hastalarda kullanılması amacıyla 45 mg uzatılmış salınımlı formunun kullanımının da etkin ve güvenli olduğu gösterilmiştir.

Yöntemler: Bu çalışmada propiverin 30 mg tedavisi yerine propiverin 45 mg propiverin uygulanan 35 erkek hastanın (grup 1) ve 30 mg propiverin tedavisine ek olarak mirabegron 50 mg tedavisi uygulanan 31 erkek hastanın (grup 2) verileri toplandı. Hastalara ilk başvurularında üroflowmetri yapıldı, semptomları ve işeme günlükleri incelendi. Hastalar 1. ve 6. ayda kontrole çağırıldı. Tedavi uyumu ve memnuniyet belirlendi. Ultrasonografi ile rezidü idrar hacimleri ölçüldü ve Aşırı Aktif Mesane Değerlendirme Formu (OAB-V8) ile şikayetler değerlendirildi.

Bulgular: Her iki gruptaki hastaların yaşları ve kronik hastalıkları karşılaştırıldığında gruplar arasında anlamlı fark yoktu. Gruplar arasında günlük işeme ve haftalık inkontinans sıklıkları, işeme sonrası rezidüel idrar hacimleri, yan etkiler (özellikle ağız kuruluğu) ve OAB-V8 formlarındaki yanıtlar ve puanlar açısından istatistiksel olarak anlamlı fark yoktu.

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ABSTRACT

Keywords: Anti-cholinergic, beta 3 receptor agonist, propiverine, sustained release, high dose, combination therapy, bladder overactivity, post-micturition residual urine, acute urinary retention, OAB-V8 Overactive Bladder Questionnaire, adherence, persistance

ÖZ

Sonuç: Propiverin 45 mg monoterapisi veya propiverin 30 mg ve mirabegron kombine tedavisi benzer etkinlik ve sınırlamalarla güvenle uygulanabilir.

Anahtar Sözcükler: Antikolinerjik, beta 3 reseptör agonisti, propiverin, sürekli salım, yüksek doz, kombinasyon terapisi, mesane aşırı aktivitesi, işeme sonrası kalan idrar, akut idrar retansiyonu, OAB-V8 Aşırı Aktif Mesane Anketi, bağlılık, kalıcılık

INTRODUCTION

Overactive bladder is a clinical disorder with urgency with or without urinary incontinence, and it is often accompanied by frequency and nocturi without any detectable pathology, such as urinary tract infection (1). Studies on its frequency have shown that it occurs in 12-17% of the population, and its frequency is known to increase with age (2,3). In cases of bladder overactivity, the main treatment has been accepted as anti-cholinergic drugs, and although many have been developed for this purpose, side effects often limit their use, especially acute urinary retention; this has led to the search for different drugs (1,4,5). As a result, the beta-3 adrenergic receptor agonist drug mirabegron, which is in a different drug group from anti-cholinergic therapy, was developed to reduce the use of anti-cholinergic drugs and avoid their side effects, especially acute urinary retention (6).

Acute urinary retention is caused by the inability to empty the bladder due to different pathologies, and it is an important health problem that can cause serious complications if not treated (7). This condition is sudden and manifests as severe pain and discomfort caused by urgency (8). It usually occurs in elderly male patients with benign prostatic hypertrophy due to infection or drug use. Spinal trauma and operations such as pelvic surgery that may impair the neurological coordination of voiding can also cause acute urinary retention. Acute urinary retention is seen at a rate of 0.45-0.68% in men over the age of 40 years, with a corresponding rate of 0.007% in women (9-11). While the risk increases from the age of 40 years, it is especially common at older ages (8). Similar to complaints related to bladder storage phases and bladder overactivity, the risk of urinary retention increases with age (12).

The measurement of residual urine volume by ultrasound imaging or catheterization is recommended in patients with risk factors for acute urinary retention, such as residual urinary symptoms, incontinence, or a history of neurological diseases and previous pelvic surgery (1). Although a residual urine volume of up to 100 mL can be monitored without intervention, a residual urine volume above 200 mL is considered pathological. Although there is no absolute standardization of these numbers, if there is a residual urine volume above 500 mL, the patient is considered to have acute urinary retention (11,13).

In patients with acute urinary retention risk, care should be taken in dose and drug selection because anti-cholinergic drugs, especially when used in overactive bladder treatment, relax the bladder muscle and reduce contractions. Bladder muscle contractility decreases over time, especially in elderly patients. In addition, polypharmacy and comorbidities increase with age and reduce bladder muscle contraction, and the amount of residual urine in these patients increases with obstruction (11,14).

Studies that have investigated propiverine treatment in patients who had not benefited from anti-cholinergic therapy have shown a decrease in complaints due to its calcium antagonistic effect. There are also studies showing that propiverine 45 mg sustained release high doses reduce complaints due to bladder overactivity with similar side effects and higher efficiency when compared with propiverine 30 mg (15). As a beta 3 receptor agonist, mirabegron, unlike anti-cholinergic drugs, relaxes bladder smooth muscles in the storage phase without decreasing contractility in the voiding phase; therefore, some studies have shown that side effects in the voiding phase are less common. The use of mirabegron in combination therapy with anti-cholinergics has also been shown to be safe and preferential because it increases the success rate of the treatment. However, although high-dose (45 mg) propiverine and mirabegron combined with anti-cholinergic therapy are the preferred methods for treating patients who do not benefit from low-dose anti-cholinergic therapy, no study has compared these two treatment options (16).

MATERIALS AND METHODS

This prospective study follows the rules of the Declaration of Helsinki regarding patients' rights and ethical guidelines and was approved by the Ethics Committee of Van Training and Research Hospital (approval number: 2021/06). All patients involved in this study provided written informed consent.

In our clinic, 178 adult male patients, whose complaints continued despite propiverine 30 mg treatment for a month, presented with bladder storage phase complaints between September 2019 and January 2021. Patients under the age of 18 years were excluded from the study. Patients with fewer bladder storage phase complaints, more voiding phase complaints, alfa broker treatment with a pre-diagnosis of benign prostatic hyperplasia, and known neurological pathology were not included in the study.

A total of 66 patients met the study criteria, and their maximum urinary flow rate was above 15 mL/min and post-voiding residue urine volume was below 100 mL in uroflowmetry analysis. In 35 of the 66 patients (group 1), propiverine 45 mg was started instead of 30 mg propiverine treatment; mirabegron 50 mg was added to the 30 mg propiverine treatment of the other 31 patients (group 2). Patients were called for control 1 and 6 months after the treatment began; at this time, adherence and persistence were determined. Post-voiding residual volumes were evaluated by ultrasonography, and complaints were assessed using the Overactive Bladder Assessment Form (OAB-V8). Patient information and results were retrospectively

analyzed. Patients with a post-voiding residual volume above 500 mL were evaluated as having acute urinary retention.

Statistical Analysis

For statistical analysis, Mann-Whitney U, chi-square, and McNemar tests were performed to evaluate numerical variables and categorical data between groups, respectively. P-values less than 0.05 were considered significant.

RESULTS

In our study, the ages of 35 patients who received propiverine 45 mg in group 1 and 31 patients who received propiverine 30 mg and mirabegron combination therapies in group 2 (48.26±19.45 vs. 45.74±18.36; p=0.592) and their comorbid chronic diseases were compared (p=0.229); no significant differences were found between the groups. Furthermore, there were no significant differences between the daily micturition counts (7.70±1.59 vs. 7.40±1.59; p=0.488) and weekly incontinence counts (2.57±2.67 vs. 2.00±1.65; p=0.307) of the patients in the groups. Although there was no significant difference between the groups in terms of post-voiding residual volumes, one patient in group 1 developed acute urinary retention two weeks after using propiverine 45 mg treatment. This caused us to determine the standard deviation rate, which was high in group 1 (65.00±117.44 vs. 64.69±39.17; p=0.323). When dry mouth developed after treatment, its advent was not statistically significant, although 12 patients (34.29%) in group 1 had new reports of dry mouth, and five patients (16.13%) reported the condition in group 2 (p=0.092) (Table 1).

It was observed that there was no significant difference between the two groups in persistence during the first month (45.71% vs. 32.26%; p=0.267) and the sixth month after treatment (25.71% vs. 22.58%; p=0.875), as well as adherence during the first month (62.86% vs. 64.52%; p=0.889) and the sixth month after the treatment (40.00% vs. 41.94%; p=0.891). It was found that the patients who were not satisfied with the treatment after one month of use were not satisfied after six months of use. Similarly, it

Table 1. Comparison of demographic characteristics, micturations, post-voiding residual volumes, incontinence, and dry mouth between the groups

	Group 1; (n=35)	Group 2; (n=31)	p
Age	48.26±19.45	45.74±18.36	0.592
Comorbidity			
Positive	10 (28.57%)	5 (16.13%)	0.229
Negative	25 (71.43%)	26 (83.87%)	
Micturations/d	7.70±1.59	7.40±1.59	0.488
Post-voidingresidual volumes	65.00±117.44	64.69±39.17	0.323
Incontinence/w	2.57±2.67	2.00±1.65	0.307
Dry mouth			
Positive	12 (34.29%)	5 (16.13%)	0.092
Negative	23 (65.71%)	26 (83.87%)	

Group 1: Patients using propiverine (45 mg). Group 2: Patients using propiverine (30 mg) and mirabegron combination treatment. Mann-Whitney U and chi-square tests were utilized for statistical analyses.

Table 2. Comparison of adherence and persistence between the groups

	Group 1; (n=35)	Group 2; (n=31)	p
Adherence (first month)			
Positive	22 (62.86%)	20 (64.52%)	0.889
Negative	13 (37.14%)	11 (35.48%)	
Persistence (first month)			
Positive	16 (45.71%)	10 (32.26%)	0.267
Negative	19 (54.29%)	21 (67.74%)	
Adherence (sixth month)			
Positive	14 (40.00%)	13 (41.94%)	0.891
Negative	21 (60.00%)	18 (58.06%)	
Persistence (sixth month)			
Positive	9 (25.71%)	7 (22.58%)	0.875
Negative	26 (74.29%)	24 (77.42%)	

Group 1: Patients using propiverine (45 mg), Group 2: Patients using propiverine (30 mg) and mirabegron combination treatment. Chi-square test.

was observed that the adherence and persistence rates decreased from the first-month control to the sixth-month control (Table 2). In the group using propiverine 45 mg treatment, the adherence (62.86% vs. 42.86%; p=0.008) and persistence (45.71% vs. 25.71%; p=0.016) rates decreased significantly in the sixth month of the treatment compared with the first month of the treatment. In the group using combined propiverine 30 mg and mirabegron treatment, the adherence rate (64.52% vs. 38.71%; p=0.016) decreased significantly in the sixth month of the treatment compared with the first month, whereas the decrease in the persistence rate (32.26% vs. 22.58%; p=0.250) was not statistically significant (Table 3).

The complaints of the patients after treatment in both groups were evaluated using the OAB-V8 form; the average scores for each of the questions and the total scores on the OAB-V8 forms were compared between the two groups. Both groups were similar in their reports of frequent urination during the daytime hours (4.64±0.59 vs. 4.43±0.90; p=0.288), an uncomfortable urge to urinate (4.36±0.80 vs. 4.17±0.91; p=0.359), a sudden urge to urinate with little or no warning (4.31±0.95 vs. 4.13±0.86; p=0.447), accidental loss of small amounts of urine (2.22±1.90 vs. 2.20±1.60; p=0.960), night-time urination (3.22±1.25 vs. 3.00±1.53; p=0.518), waking up at night tourinate (2.72±1.49 vs. 2.40±1.73; p=0.419), an uncontrollable urge to urinate (3.89±1.09 vs. 3.63±1.10; p=0.348) and urine loss associated with a strong desire to urinate (2.22±1.90 vs. 2.17±1.60; p=0.899). There was no statistically significant difference between the mean values (29.58±7.06 vs. 28.13±7.13; p=0.411) of the total OAB-V8 scores of both groups (Table 4).

DISCUSSION

Although beta 3 receptor agonists and anti-cholinergic drugs are the most important treatment modalities for overactive bladder, their success is limited. For this reason, sustained release forms of medication administered in higher doses and combination therapies, which have a synergistic effect on the bladder through different receptors, can be given to increase the effectiveness of anti-cholinergic drugs used for this purpose while keeping the side effects at tolerable levels (6,15,16). In the study of Sussman et al. (17), in which the 12-month treatment adherence and persistence levels of 71,980 patients who received anti-cholinergic and mirabegron treatment were examined, the adherence rate was 44% for those receiving mirabegron treatment and 31% for those receiving anti-cholinergic treatment. A persistence rate of 19% was reported for patients using mirabegron and 12% for those receiving anti-cholinergic treatment. Although the adherence rates in our study were much higher after one month of treatment, they appeared to be similar after six months of treatment. In the study by Sussman et al. (17), adherence was observed to be much higher in patients using anti-cholinergics because there were patients who received combination therapy and mirabegron alone in the group using mirabegron. However, in our study, all patients in the group using mirabegron received combination therapy; therefore,

Table 3. Comparison of the adherence and persistence of the groups in the first and sixth months

	Group 1; (n=35)	p	Group 2; (n=31)	p
Adherence				
First month	22 (62.86%)	**0.008**	20 (64.52%)	**0.016**
Sixth month	14 (42.86%)		13 (38.71%)	
Persistence				
First month	16 (45.71%)	**0.016**	10 (32.26%)	0.250
Sixth month	9 (25.71%)		7 (22.58%)	

Group 1: Patients using propiverine (45 mg), Group 2: Patients using propiverine (30 mg) and mirabegron combination treatment, McNemartest.

Table 4. OAB-V8 Overactive Bladder Questionnaire for patients

	Group 1; (n=35)	Group 2; (n=35)	p
Frequent urination during daytime hours	4.64±0.59	4.43±0.90	0.288
Uncomfortable urge to urinate	4.36±0.80	4.17±0.91	0.359
Sudden urge to urinate with little or no warning	4.31±0.95	4.13±0.86	0.447
Accidental loss of small amounts of urine	2.22±1.90	2.20±1.60	0.960
Night-time urination	3.22±1.25	3.00±1.53	0.518
Waking up at night because you had to urinate	2.72±1.49	2.40±1.73	0.419
Uncontrollable urge to urinate	3.89±1.09	3.63±1.10	0.348
Urine loss associated with a strong desire to urinate	2.22±1.90	2.17±1.60	0.899
OAB-V8 score	29.58±7.06	28.13±7.13	0.411

Group 1: Patients using propiverine (45 mg), Group 2: Patients using propiverine (30 mg) and mirabegron combination treatment, Mann-Whitney U test, OAB-V8: Overactive Bladder Assessment Form.

we found that the use of multidrugs reduced patient compliance, but because of fewer anti-cholinergic side effects, adherence was similar between the two groups. When we called for control after one month in our study, we found that the patients in our study had higher persistence rates, but after six months of treatment, the rates were similar. Sussman et al. (17) showed that persistence rates decreased after an average of three months, and many patients discontinued the treatment. In our study, it was observed that the adherence and persistence rates decreased between 1 and 6 months.

In a study conducted by Stöhrer et al. (16), 66 patients with neurogenic detrusor hyperactivity who were administered sustained release propiverine (45 mg) were called as controls to determine the efficacy and side effects after 21 days, and they found a persistence rate of 39%. In addition, 36% of the patients had side effects such as dry mouth, which is similar to our study (16). In a review article evaluating 64 studies and 46,666 patients in total to examine the efficacy and effects of anti-cholinergic drug therapy after mirabegron treatment, it was shown that, similar to our study, mirabegron and anti-cholinergic treatment can be safely used with high efficiency and a similar side effect profile in patients who do not benefit from anti-cholinergic monotherapy (18). In their studies with patients using anti-cholinergic monotherapy such as solifenacin or tolterodine, Drake et al. (19) investigated the effects of mirabegron and solifenacin or mirabegron and tolterodine combination therapies on residual urine volume and the risk of acute urinary retention. As with our study, they showed that it can be safely used without increasing post-voiding residual volumes and the risks of acute urinary retention, especially in patients without obstructive pathologies such as benign prostatic hypertophy (19).

In all studies that evaluated mirabegron combination therapy, combination therapy was compared with mirabegron combined with the same dose of anti-cholinergic monotherapy. Similarly, all studies that evaluated high-dose sustained release propiverine 45 mg treatment were compared with low-dose propiverine treatment (15-19). Although there are different studies evaluating mirabegron combination therapy and high-dose sustained release anti-cholinergic treatment in patients who do not benefit from anti-cholinergic therapy, there is no study comparing the two treatments in patients who do not benefit from low-dose anti-cholinergic therapy to determine which of the mirabegron combination and high-dose anti-cholinergic therapies should be preferred. In our study, we compared the effectiveness and limitations of these two treatment modalities.

Study Limitations

The limitations of our study were the insufficient number of patients and the fact that it was not possible to completely exclude patients who had obstructive diseases, especially older male patients, because the study was conducted with male patients.

CONCLUSION

According to the findings we obtained in our study, in male patients with bladder overactivity without obstructive pathologies who did not benefit from low-dose anti-cholinergic treatment, propiverine 45 mg monotherapy or propiverine 30 mg and mirabegron combined treatment can be safely preferred with similar efficacy and limitations.

Ethics

Ethics Committee Approval: This study was reviewed and approved by the Medical Ethics Committee of Van Training and Research Hospital (approval number: 2021/06).

Informed Consent: All patients involved in this study provided written informed consent.

Authorship Contributions

Surgical and Medical Practices: İ.Ş.B., S.D., Concept: İ.Ş.B., S.D., Design: İ.Ş.B., S.D., Data Collection or Processing: İ.Ş.B., S.D., Analysis or Interpretation: İ.Ş.B., S.D., Literature Search: İ.Ş.B., S.D., Writing: İ.Ş.B., S.D.

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