Prospective Comparison of Two Treatment Modalities in Benign Prostate Hyperplasia: Alpha-Blocker Alone vs. Alpha-Blocker Plus Anticholinergic Combination

Benign Prostat Hiperplazisi Olgularında İki Tedavi Modalitesinin Prospektif Karşılaştırılması: Tek Başına Alfa Bloker ile Alfa Bloker ve Antikolinerjik Kombinasyon Tedavisi

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ABSTRACT Objective: We investigated the efficiency and reliability of treatments with alfuzosin alone and in combination with tolterodine in patients with benign prostate hyperplasia accompanied by lower urinary system symptoms. **Material and Methods:** Forty-five males, ages over forty that applied to the clinic between April 2007 and July 2007 were included in the evaluation. As the initial examinations, international prostate symptom score, peak floq rate in uroflowmentry and post-voiding measurement of the residual urine were performed. Treatment of the patients who were included in the study was started with 10 mg alfuzosin (Group 1). At the end of the third month, tolterodine 2 mg taken twice a day was added to the treatment (Group 2). **Results:** Thirty-seven patients (82%) out of 45 patients were able to complete the six-month study. Average age of these patients was 59.2 ± 7.2 years. The average prostate specific antigen value of the patients was found as 1.4 ± 1.0 (ng/mL), and the average prostate volume as 34.8 ± 13.1 ml. Four patients left the study after tolterodine was added because of intensive dryness in the mouth. According to the statistical data, at the end of the study, significant improvement was found in both groups when compared to baseline. **Conclusion:** When the two treatments were compared, no statistical differences were noted between the two groups.

Key Words: Prostatic hyperplasia; drug therapy

ÖZET Amaç: Bu çalışmada benign prostat hiperplazisi ile alt üriner sistem semptomları birlikte bulunan hastalarda tek başına alfuzosin ve alfuzosin ile birlikte tolterodin tedavisinin etkinlik ve güvenilirliğini araştırdık. **Gereç ve Yöntemler:** Nisan ile Temmuz 2007 tarihleri arasında poliklinliğe başvuran 40 yaş üstü erkek hastalar değerlendirmeye alındı. Başlangıç tetkikleri olarak uluslararası prostat semptom skoru sorgulaması, üroflovmetri ile tepe akım hızı olçümü, transrektal ultrasonografi ile prostat boyutu ölçümü, ultrason ile işeme sonrası rezidü ölçümü yapıldı. Bunlara ilave olarak prostatın parmakla rektal muayenesi, prostat spesifik antijen (PSA) ölçümü yapıldı. PSA değeri 4 ng/mL'den yukarı olanlar ile muayenesi şüpheli olanlar çalışma dışı bırakıldı. Çalışmaya dahil edilen hastalara 10 mg alfuzosin ile tedaviye başlandı (Grup 1). Üçüncü ayın sonunda tedaviye günde iki kez alınan 2 mg tolterodin eklendi (Grup 2). **Bulgular:** Çalışmaya dahil edilen 45 hastanın 37 (%82)'si altı aylık çalışmayı tamamlayabildi. Bunların ortalama yaşı 59.2 ± 7.2 idi. Hastaların ortalama PSA değeri 1.4 ± 1.0 (ng/mL), ortalama prostat volümü 34.8 ± 13.1 ml olarak saptandı. Tolterodin eklendikten sonra 4 hasta yoğun ağız kuruluğu nedeniyle çalışmayı bıraktı. Sonuçlarımıza göre, her iki tedavi ile başlangıca göre tüm parametrelerde anlamlı iyileşme saptandı. Ancak iki grup kendi arasında karşılaştırıldığında ise anlamlı bir fark saptanmadı (Tablo 1). **Sonuç:** Sonuç olarak, tek başına alfuzosin ile elde edilen değerler ile alfuzosin+tolterodin kombinasyon tedavisi ile elde edilen değerler arasında istatistiksel olarak anlamlı bir fark saptanamamıştır.

Anahtar Kelimeler: Prostat hiperplazisi; ilaç tedavisi

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Benign prostatic hyperplasia (BPH) is a common condition in elderly men, occurring in up to 70% of men older than 60 years.[1] BPH often causes bladder outlet obstruction (BOO) and it commonly results in lower urinary tract symptoms (LUTS).[2] LUTS include overactive bladder (OAB) symptoms, e.g. frequency, urgency and incontinence, and voiding symptoms, e.g. dribbling, hesitancy, a weak flow and incomplete emptying. Although voiding symptoms are more prevalent in men with BPH and BOO, OAB symptoms are generally more bothersome and, thus, they represent an important target in the management of BPH and BOO.[3] Frequency, urgency and urgency incontinence have been attributed to detrusor over activity (DO), which reportedly occurs in 40% to 70% of patients with BOO.[4,5] BOO induced DO may result from ischemia, cholinergic detrusor denervation, increased detrusor collagen content or changes in the electrical properties of detrusor smooth muscle cells.[6-9]

In medical treatment of lower urinary tract symptoms suggestive of bladder outlet obstruction α-adrenoceptor antagonists remain the most widely used pharmacological agents in the first line therapy aimed at the dynamic component of benign prostatic obstruction.[10] These agents promote relaxation of the bladder neck and prostate smooth muscle, thus, they decrease bladder outlet resistance.[11] However, the low density of detrusor α-receptors may preclude the direct effects of α-blockers on detrusor contractility, and α-blockers have demonstrated limited success for OAB symptoms.[12,13] Muscarinic reseptor antagonists such as tolterodine are widely used to treat OAB symptoms but the potential role of antimuscarinics for LUTS secondary to BPH has not been explored extensively. In this study we prospectively evaluated the effectiveness and safety of therapy with an alpha-adrenoceptor antagonist alone and combined with an anticholinergic for LUTS in men with BPH.

MATERIALS AND METHODS

Male patients over 40 years of age who applied to the outpatient clinic with lower urinary system complaints were evaluated. Of these, those without and urinary system infections, with international prostate symptom score (IPSS) ≥ 8, with peak flow rate (Qmax) < 15 ml/sec, and those with prostate specific antigen (PSA) < 4 ng/ml were included in the study. Initially, all the patients were examined with rectal digital examination, transrectal ultrasound, and prostate volume measurements. Patients diagnosed with prostate pathologies were excluded from the study.

Those with post voiding residual urine (PVR) > 200 ml, with Qmax < 5ml, or PSA values > 4 ng/ml were excluded from the study. In addition, those with postural hypotension or syncope anamnesis in their medical history, with serious liver or kidney diseases, with neurological diseases like Parkinson's disease or multiple sclerosis, past spinal cord injury, prostate cancer, past prostate surgeries, past acute urine retention, urine retention history other than BPH, and those who have used alpha-blockers, antispasmodics, 5-alpha-reductase inhibitors and other phytotherapeuticals were also excluded from the study.

Treatment started by administering 10 mg alfuzosin daily (Xatral-XL 10 mg tablet p.o. Sanofi Aventis) in one single dose to all the patients (Group 1). Quality of life scores (QoL) were recorded three months later according to IPSS, Qmax, PVR amount and IPSS-urinary symptoms. PVR amount was measured by ultrasonography and Qmax was measured with uroflowmetry. Treatment of the same patients was continued with adding tolterodine 2mg (Detrusitol 2 mg tablet p.o. Pfizer) twice daily to alfuzosin for the next three months (Group 2). Following this three-month combination therapy, IPSS, Qmax, PVR amount and QoL query of the patients were recorded again. In addition, adverse effects seen during the use of the drugs were recorded.

Paired-samples *t* test was used in the comparison of values recorded for Groups 1 and 2. SPSS for Windows software (version 11.5) program was used for the evaluation of all the statistical data. $P<0.05$ value was accepted as the value of significance.

RESULTS

Thirty-seven patients (82%) out of total 45 patients were able to complete the six-month study. Ave-

rage age of the patients was calculated as 59.2 ± 7.2 (43 – 76) years. Average basal PSA value was found as 1.4 ± 1.0 ng/ml and average prostate volume as 34.8 ± 13.1 ml. Four patients were excluded from the study immediately after the commencement of alfuzosin treatment because of urinary infection and PVR amount exceeding 200 ml. Four patients left the study after the addition of tolterodine because of intensive dryness in the mouth. Apart from these, no serious side effects that caused patients to leave the study were seen. Transurethral resection (TUR) operation was performed in four patients with excessive amounts of residual urine. We summarized all the results of our study in Table 1.

DISCUSSION

The main objective in the treatment of BPH is to eliminate effectively the obstruction it causes as soon as possible, and to ensure relief in lower urinary symptoms.[14] It has been shown that lower urinary symptoms have negative effects on the individual's quality of life.[3] Insufficiency in the depositing function of the bladder is seen in patients with BPH accompanied by detrusor instability. Hypertrophy and collagen accumulation throughout the bladder wall has been found in these cases. It has been shown in the that together with obstruction, ageing, changes in the central nervous system, detrusor innervation changes and conditions like local ischemia also play a role in detrusor instability.[15-17]

There are many studies on the combination of alpha-blockers and anticholinergics for the treatment of patients BPH together with LUTS.[18-21] However, to the best of our knowledge, alfuzosin was used in none of these studies as the alpha-blocker. The reason for our choice of alfuzosin 10 mg tablet was that it did not require initial dosage adjustment, was well tolerated with regard to the cardiovascular system, it is uro-selective, and ensures effectiveness on the same level throughout the day due to its controlled release.[22]

It has been shown in a study that treatment with tolterodine ER reduced the over-active bladder and voiding symptoms in patients with lower urinary symptoms together with BPH in whom alpha-blocker treatment has been unsuccessful.[18] Extended release (ER) form of tolterodine was used in this study, and it was emphasized that tolterodine taken twice daily was more effective than tolterodine 2mg. In another study, tolterodine 2 mg tablet was used twice daily, and it was seen that this treatment caused no change in the deposition of urine and urine flow rate.[18]

In still another study, terazosin 2mg alone and terazosin 2 mg + tolterodine 2 mg combination were compared in BPH patients with lower urinary system findings. Increased in bladder capacity together with significant decrease in IPSS was found in the group taking combination therapy. In addition, it was seen that there were more side effects in the group taking the combination therapy.[20] A comparison was performed between two distinct groups in that study. In our study however, efficiency and reliability of two different therapies we-

TABLE 1: The results of patients in the baseline, Group 1 and Group 2.

Parameters	Baseline	Group 1	p* (n:37)	Group 2	P** (n: 37)	p***(n:37)
IPSS	21.6 ± 6.0	15.3 ± 5.7	<0.01	14.7 ± 4.6	<0.01	ns
Qmax (ml/s)	12.4 ± 4.3	14.1 ± 4.5	=0.19	13.9 ± 4.4	=0.03	ns
Residual volume (ml)	58.0 ± 46.5	38.3 ± 37.8	<0.01	41.9 ± 42.0	<0.01	ns
QoL score	4.5 ± 1.1	3.6 ± 1.1	<0.01	3.8 ± 1.0	<0.01	ns

Baseline. Parameters of patients before treatment (± standart deviation).
Group 1. Results of after alone alfuzosin XL treatment (± standart deviation).
Group 2. Results of after alfuzosin XL plus tolterodine treatment (± standart deviation).
P*: Baseline vs Group1
P**: Baseline vs Group2
P***: Group1 vs Group2
ns. not significant
IPSS: International prostate symptom scare; Qmax: Peak flow rate; QoL: Quality of life.

re compared on the same patients in sequential fashion. In addition, terazosin dose was low in this study, only 2 mg was used. Although there was decrease in IPSS in both groups in our study, the difference between the two groups was not found as statistically significant.

It is known that Qmax improves with the use of alpha-blockers in patients with BPH. However, the same effect was found in recent studies with tolterodine.[18,20,21] There were significant increases in both groups in Qmax as compared to basal values. It was seen that the increase in Qmax was greater in the group using alfuzosin alone. Since it is theoretically known that tolterodine inhibits the contraction of detrusor, it was thought that this could cause this difference in Qmax. However, it was seen that this difference between the two groups was not statistically significant.

Voiding function is affected from the urethral resistance including the prostate, bladder neck and the contraction of the detrusor. For normal voiding, a prostate and bladder neck muscle capable of simultaneous relaxation is required together with a detrusor contracting normally. In a study on this subject, patients with mild and medium bladder outlet obstruction determined with urodynamic studies together with detrusor instability were divided into two groups. The group taking 0.4 mg tamsulosin daily and the group taking tamsulosin 0.4 mg + tolterodin 2 mg twice daily were compared. Interestingly, increase in the bladder capacity was found in the group taking tamsulosin, together with an increase in Qmax. In the group taking combination therapy, however, significant increase in urinary flow, decrease in the maximum unstable contraction pressure, and increase in bladder capacity were found. Decrease in PVR was found in both groups; however, this decrease was not found as tatistically significant. Acute urinary retention was seen in none of the groups.[21] We did not perform bladder capacity measurements in our patients; instead, we performed IPSS, Qmax and PVR measurements for a better evaluation of the function and response of the bladder to treatment. Although there was decrease in PVR as compared to the baseline, urinary retention was seen in none of the patients. Using alfuzosin only within the first three months to create relaxation in the bladder neck and smooth muscles of the prostate and using tolterodine after this may have caused this lack of retention. Since performing urodynamic studies routinely in BPH patients is impractical and also it is an invasive procedure, we did not feel any urge to perform it. However, it is known that anticholinergic drugs can suppress the involuntary detrusor contractions that can be created by the basal release of neuronal and urothelial acetylcholine during the filling of the bladder.[23]

Quality of life was determined in the patients included in the study before and after both therapies according to IPSS-urinary symptoms. Although there was improvement in both groups according to the baseline, the difference between the two groups were not found to be statistically significant.

The most frequent side effect seen in patients taking tolterodine is dryness in the mouth.[18,20] Intense dryness in the mouth was seen in four patients in our study after tolterodine was added, and, for this reason, these patients did not continue with the study and were excluded. Apart from this, no adverse effects were seen with severity enough to cause the patients to leave the study.

Since the results in our study are different from those performed previously, we suppose that, randomized studies with placebo controls with longer periods of time and including greater numbers of patients are required. Additionally, performing urodynamic studies will be beneficial in uncovering the underlying potential bladder pathologies.

CONCLUSION

Although our study involved a small number of patients and although it was not a placebo-controlled study, our results indicated that alfuzosin+tolterodine treatment did not have a significant superiority to treatment with alfuzosin alone. When compared with the baseline, it was seen that there was significant improvement in the parameters of IPSS, Qmax, PVR and quality of life after both treatments.

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