A Comparison of Tamsulosin and Combination Therapy with Tamsulosin and Dutasteride in Patients with Benign Prostate Hyperplasia-Related Acute Urinary Retention

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Abstract

Objective: To investigate whether combination therapy is more effective than either monotherapy in reducing the relative risk for benign prostate hyperplasia (BPH)-related surgery in patients with acute urinary retention (AUR).

Methods: We retrospectively reviewed recorded data of patients who were randomized into two groups according to medical treatment as tamsulosin monotherapy and tamsulosin with dutasteride combination therapy between June 2002 and February 2008. A total of 150 patients who were initially admitted to the emergency department for BPH-associated AUR were selected. The urethral catheters were removed at the end of 3 days, and 96 patients who had a post-void residual urine volume of <150 mL were included in the study. Patients were followed up in an interval of 3 months; the primary endpoint was time to BPH-related surgery. Logistic regression was used to determine factors that contribute to BPH-related surgery. Furthermore, we compared the groups in terms of post-treatment variables.

Results: Of the patients, 26 (27%) were diagnosed with prostate cancer and excluded from the study. A total of 70 patients, 38 in the monotherapy and 32 in the combination groups, participated in the study and were followed up for 1 year. The comparison of the monotherapy group and the combination group showed that the BPH-related surgery ratio (p=0.005) and serum total prostate-specific antigen (PSA) level (p=0.013) were lower in the combination group. By multivariate logistic regression analysis, we found that older age, higher serum PSA level, and higher prostate volume were independently associated with BPH-related surgery.

Conclusion: Of all the factors analyzed, prostate volume, age, and serum PSA level were the most accurate predictors of BPH-related surgery. Moreover, combination treatment was found to be more effective treatment choice for prevention of BPH-related surgery.

Keywords: Benign prostate hyperplasia, alpha blockers, acute urinary retention

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a benign enlargement of the prostate tissue, which is histologically detected in 80% of men over 80 years of age, and which most commonly leads to the lower urinary tract symptoms (1). Until the age of 80, 25% of men receive medical treatment or undergo surgery due to BPH (2). The clinical course of BPH is usually proportional to the com-

plaints of the lower urinary tract at the time of diagnosis. Acute urinary retention (AUR) caused by BPH is seen in 10% of men aged over 70 years, and it is the most common cause of admissions to the emergency services in BPH patients (3). In the United States and Great Britain, AUR constitutes 25%-40% of the indications for prostate surgery (4). The United States National Association of Prostatectomy has reported increased morbidity and mortality after early surgical operations performed due to AUR (5, 6). In the literature, there are studies showing that 25%-75% of patients with BPH-induced AUR are successful in spontaneous miction after the removal of catheter (7).

The mechanism of the BPH-induced acute urinary retention is explained by the prostatic flat muscle infarction, increased activity of the alpha-adrenergic system, detrusor failure, and neurotransmitter modulation (8). Alpha-1 receptors are known to exist in the bladder neck and prostate smooth muscle tissue, and they have been successfully used for years in the treatment of BPH. In the literature, the rate of prostate smooth muscles was found to have increased after AUR and transrectal prostate biopsy, and the maximum urine flow rates of these patients increased after alpha-1 blocker therapy. It has also been shown that the use of alpha-1 blockers after AUR may also recover the miction (9). However, there are still no clear clinical data to explain the mechanisms of action of alpha-1 blockers after AUR.

Another group of drugs currently being used in the treatment of BPH is 5-alpha reductase inhibitors (5-ARI). 5-ARI stops the growth of the prostate by decreasing the serum levels of serum 5-alpha dihydrotestosterone. While finasteride reduced serum dihydrotestosterone by 70% (10, 11), it was found to be reduced by 90% with dutasteride treatment (12). After 6 months of treatment with dutasteride or finasteride, prostate glandular tissue enters atrophy, and the prostate volume is reduced by 20%-30% (13). The decrease in prostate volume in patients reduces the risk of the development of acute urinary retention, which is one of the long-term outcomes of BPH.

In this study, in patients with BPH-induced AUR, we compared the treatment efficacy of Tamsulosin monotherapy, and the combined therapy of tamsulosin and dutasteride used for the treatment of BPH in terms of BPH-induced surgery after 1-year follow-up. In addition, multiple factors that could lead to surgical intervention due to BPH after acute urinary retention were investigated.

METHODS

We retrospectively evaluated the prospective data recorded at the Istanbul Training and Research Hospital between June 2002 and February 2008. Written informed consent was received from all patients, and the Institutional Review Board of Istanbul Training and Research Hospital approved the study (10.04.2007-17.4). The study was performed with patients who were admitted to Emergency Urology Department and were diagnosed with acute urinary retention, which clinically developed due to BPH. The patients older than 50 years who were admitted to the emergency urology polyclinic with the complaint of BPH-induced AUR, were literate, and who could come to the control examinations were included in the study. The diagnosis of AUR, which was caused by BPH, was made

through the anamnesis of the patients and the International Prostate Symptom Score (IPSS) questionnaire that the patients filled out. The patients who were prohibited from using alpha-blockers due to cardiac disease; who received other medical treatments due to BPH; who had bladder stone, prostate cancer, renal failure, urethral stricture, urinary infection, and neurogenic bladder dysfunction; and who previously underwent surgery for bladder tumor or prostate cancer were excluded from the study. A permanent urethral catheter was applied in patients who met the study criteria, and an appointment was made to remove the catheter on the 3rd day.

The Formation of Treatment Groups
A single dose of daily tamsulosin 0.4 mg or the combination of tamsulosin 0.4 mg and dutasteride 0.5 mg tablets was started in patients after the insertion of a permanent urethral catheter. Three days later, patients' catheters were removed. The study was continued with the patients who were found to have residual urine below 150 mL in the examination performed with transabdominal ultrasound. The serum prostate-specific antigen (PSA) levels were examined on the 10th day, and patients with PSA levels higher than 4 ng/dL were referred to transrectal prostate biopsy. The patients in whom prostate cancer was detected as a result of the pathology were excluded from the study. Every patient in the study was examined once every 3 months for 1 year. The patients who had more than 150 mL of residual urine in the transabdominal ultrasound examination, bacterial reproduction in urine culture, macroscopic hematuria, an increased IPSS, or re-emergence of AUR were directed to surgical operation. During the follow-up; serum IPSSs, serum PSA values, maximum urinary flow rates, post-mictional residual urine through transabdominal method, and prostate volumes were measured, and serum biochemicals were followed up.

Statistical Analysis
The mean, standard deviation, minimum and maximum median, and frequency and ratio values were used in the descriptive statistics of the data. The distribution of the variables was measured by the Kolmogorov-Simirnov test. An independent sample t-test and Mann-Whitney U test were used to compare the quantitative independent data of monotherapy and combination treatment groups. A paired sample t-test and Wilcoxon test were used for the analysis of dependent quantitative data. A chi-squared test was used for the analysis of qualitative independent data, and Fischer's test was used when the Chi-squared test conditions were not met. Simple linear and multiple regression analyses were performed to investigate the multiple factors affecting the patients' referrals to surgery due to BPH. The Statistical Package for the Social Sciences 22.0 (IBM SPSS Corp.; Armonk, NY, USA) was used in the analyses.

RESULTS

A total of 150 patients were included in the study, and 16 patients could not continue with the study for different reasons. Tamsulosin monotherapy was started in 66 patients and combination therapy in 68 patients. One hundred and thirty-four patients were called for catheter withdrawal and for the micturition follow-up on the 3rd day. Post-miction residual urine volumes were found to be below 150 mL in 96 (71%) of 134 patients in the measurements performed after the removal of

catheter, and they were observed to have spontaneous micturition. In the controls on the 10th day, the patients with serum total PSA level above 4 ng/dL were directed to transrectal prostate biopsy. Twenty-six patients (27%) were excluded from the study upon the detection of prostate adenocarcinoma. Thirty-eight patients in the monotherapy group and 32 patients in the combination group were followed up. The mean age of the patients was 72.4 (52-81), the mean total PSA levels measured 10 days after the catheter removal were 4.3 ng/dL (2.19-15.97), the mean maximum voiding velocities were 11 mL/sec (9-14), and the mean prostate volumes were 40 cc 24-122). The demographic and clinical information of all the patients included in the study are shown in Table 1.

Ninety-six (71%) of 134 patients were successful in spontaneous micturition after the urethral catheter removal. Table 2. shows the comparison of the data of the patients who were successful in spontaneous micturition after the end of the 3rd day following the removal of catheter. In the comparison of the two groups, it was observed that age (p=0.001) and total serum PSA values (p=0.003) were significantly different, and other clinical and demographic factors did not show any significant difference between the two groups.

Table 3 shows the clinical and demographic data, as well as the comparison of the referral rates to surgery due to BPH in patients receiving tamsulosin monotherapy and combination therapy at the end of the first year. The comparisons between the two groups revealed that the total serum PSA levels in the patients of combination group were significantly lower than in the patients of monotherapy group (p=0.013). When comparing the number of patients who were directed to surgery due to BPH, it was observed that statistically fewer patients were directed to surgery in the combination group (p=0.005).

Table 4. demonstrates simple linear and multiple regression analyses of the factors affecting the referrals of the patients to surgery due to BPH. Age (OR=4.037, p<0.001), only tamsulosin monotherapy treatment (OR=2.132, p=0.016), prostate volume (OR=5.243, p<0.001), and serum total PSA elevation (OR=5.787, p<0.001) were found to be the factors affecting surgery due to BPH. In the multiple regression analysis, age (OR=3.123, p<0.001), the prostate volume (OR=6.186, p<0.001), and the serum total PSA level (OR=4.186, p<0.001) were found to be the factors affecting the referrals to surgery due to BPH.

DISCUSSION

The pathophysiology of acute urinary retention is complex and multifactorial. Overactivity of the alpha-adrenergic system, detrusor decompensation, and modulation of neurotransmitters are considered to be responsible for the development of AUR in many hypotheses (8). AUR may be a consequence of benign prostatic hyperplasia or, in some cases, it may be seen due to the infarction of prostate epithelial cells in patients without a severe bladder neck obstruction (14). Clinicians usually direct patients with AUR to operation for early surgical intervention. In a study conducted by Taube and Gajraj (7) in 60 patients admitted to emergency service due to the BPH-induced AUR, permanent catheters were removed 2 days later. Seventeen of the patients (28.3%) were successful in spontaneous miction despite not receiving any medical treatment. In addition, in this study, the residual urine volume after micturition was found to be the only significant difference in the comparison of the successful and non-successful groups in terms of spontaneous micturition. In our study, 71% of our patients (96) successfully discharged their bladders after the removal of a permanent urethral catheter. It was observed in the group comparison that patients with high serum PSA levels and elderly patients (<70) failed to have spontaneous miction.

Table 1. Demographic and clinical data of the patients

	Min-Max	Median	Mean±SD
Age	52.0-81.0	72.4	65.7±9.8
BMI (kg/m^2)	21.0-35.0	2.0	26.3±3.4
Qmax	9-14.17	11.00	10.33±1.43
PSA (ng/dL)	2.19-15.97	4.30	4.15±0.85
Creatinine (mg/dL)	0.53-1.56	0.89	0.89±0.17
Prostate volume (mL)	24.0-112.0	42.0	45.2±11.4
IPSS	18-30	21	22±4.5
Glucose (mg/dL)	70.0-122.0	89.5	93.3±11.6

BMI: body mass index; IPSS: International Prostate Symptom Score; PSA: prostate specific antigen; Qmax: maximum voiding rate; SD: standard deviation

Table 2. Comparison of the patients who had successful and unsuccessful voiding after the removal of permanent urethral catheter

	Sucessful (n=96)		Unsucessful (n=38)		p
	Mean±SD/n-%	Median	Mean±SD/n-%	Median	
Age	70.8±4.8	69.0	62.2±3.7	58.0	0.001[t]
BMI (kg/m^2)	26.6±3.9	26.0	26.0±3.0	26.0	0.592[m]
PSA (ng/dL)	7.24±1.05	6.00	3.07±0.65	3.2	0.003[m]
Creatinine (mg/dL)	0.88±0.14	0.90	0.89±0.19	0.87	0.587[m]
Glucose (mg/dL)	92.5±11.7	89.0	93.9±11.6	90.0	0.786[m]
PMR (mL)	334.5±81.6	355.0	485.4±92.4	505.0	0.134[m]
IPSS	19.0±2.6	17.0	16.3±12	16.0	0.765[m]

[t]t-test; [m]Mann-Whitney U test; BMI: body mass index; IPSS: International Prostate Symptom Score; PMR: post-mictional residue; PSA: prostate-specific antigen; Qmax: maximum voiding rate

Table 3. Comparison of treatment groups at the end of the first year

	Tamsulosin (n=38)		Combination (n=32		p
	Mean±SD/%-n	Median	Mean±SD/%-n	Median	
Age	69.8±9.8	71.3	68.8±9.7	5.0	0.129^t
BMI (kg/m^2)	27.6±3.9	26.0	28.0±3.0	26.0	0.592^m
Number of patients for whom surgery was recommended	17	44%	8	2%	0.005^{x2}
PMR	80±24	70±21	0.496		
PSA (ng/dL)	5.24±1.05	4.20	2.07±0.65	1.89	0.013^m
Creatinine (mg/dL)	0.88±0.14	0.90	0.89±0.19	0.87	0.587^m
Glucose (mg/dL)	92.5±11.7	89.0	93.9±11.6	90.0	0.786^m
Q max (mL/sec)	4.5±1.6	5.0	5.4±2.4	5.0	0.134^m
IPSS	17.1±2.6	17.0	16.3±1.2	6.0	0.678^m

^{t}t-test; ^{m}Mann-Whitney U test; ^{x2}Chi-squared test; BMI: body mass index; IPSS: International Prostate Symptom Score; PSA: prostate-specific antigen; Qmax: maximum voiding rate

Table 4. Simple linear and multiple regression analyses

	Univariate Model			Multivariate Model		
	OR	95% CI	p	OR	95% CI	p
Age	4.037	3.989-7.088	0.011	3.123	3.234 - 5.002	0.000
BMI (kg/m^2)	0.949	0.831-1.083	0.438			
Tamsulosin treatment	2.132	1.498-2.396	0.016			
Combination treatment	0.274	1.091-1.026	0.311			
PSA (ng/dL)	5.787	2.453-5.366	0.001	4.186	3.765 - 8.231	0.000
Creatinine (mg/dL)	1.338	0.090-1.816	0.832			
Prostate volume (mL)	5.243	3.867-9.471	0.000	6.176	4.765 - 12.231	0.000
Glucose (mg/dL)	1.010	0.972-1.051	0.602			
Qmax (cm/sn)	0.833	0.759-0.915	0.052			

BMI: body mass index; CI: confidence interval; IPSS: International Prostate Symptom Score; OR: odds ratio; PSA: prostate-specific antigen; Qmax: maximum voiding rate

Researchers tried to predict patients in whom AUR could develop. Parameters used for prediction are complaints of lower urinary symptoms, age, maximum flow rates, and prostate volumes of the patients (15). In a study conducted by Jacobsen et al. (3) a total of 2115 patients aged between 40 and 79 years were followed for 4 years with regard to IPSS, maximum urinary flow rates, serum PSA values, and prostate volumes. As a result, they found an advanced age, miction with low urinary flow rates, and the severity of lower urinary symptoms to be the risk factors for the development of acute urinary retention. It was also observed in our study that high PSA levels and an advanced age were the risk factors for acute urinary retention.

In the Olmstead County study, 477 patients who were over 45 years of age and were randomly selected were included in the study; their serum PSA values, prostate volumes, maximum urinary flow rates, IPSS, and post-void residual urine volumes were followed for 4 years (16). As a result of the study, the risk factors leading to acute urinary retention were found as a large prostate volume (>40 cc) and a residual urine volume greater than 50 cc after the miction. During our follow-up period, 80% of the patients had a prostate volume higher than 40 cc, and the mean post-void residual urine volume was over 70 mL, although they received medical treatment. These results show that AUR will develop again within 4 years in the majority of followed-up patients. However, the aim of medical treatment (especially combination therapy) is to prolong the duration to the relapse of AUR and to provide an improved preoperative evaluation of the patients, and to reduce mobility by turning the emergency surgical procedure into elective surgery.

Perioperative and postoperative morbidity and mortality were found to be increased in patients undergoing surgery with urethral catheterization. In their study, which they conducted on 1236 patients to investigate the complications of prostatectomy performed due to BPH-induced AUR indications, Pickard et al. (4) reported that the probability of complications during perioperative and postoperative first 30 days was 26 times higher than in planned operations. In addition, in this study, surgery was able to be performed within 1 month only in 45% of the patients after AUR because of patient density, and the remaining patients used permanent catheter for 2 months or more. A prolonged duration of permanent catheter use leads to increased postoperative mortality and morbidity of the patients, and it

Eur Arch Med Res 2018; 34 (3): 191-5

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decreases the quality of life. In our country, it seems appropriate to try a medical treatment (in combination with monotherapy alpha-blocker, or alpha-reductase inhibitors) in selected patients (young patients and patients with a prostate volume less than 40 cc), because the period with catheter may be prolonged due to patient density.

In the MTOPS study, 5-ARI have been shown to cause a significant reduction in the risk of AUR in elderly patients and in patients with a prostate volume above 40 cc. In addition, in this study, it was found that combination therapy (alpha-blocker and 5-ARI) was not superior to 5-ARI monotherapy (17). Roehborn et al. (18) compared dutasteride and finasteride treatments in terms of the risk of BPH-induced AUR in the study that was randomized, controlled, and conducted in 2455 patients, and they found no statistically significant difference in the rates of BPH-induced AUR between the groups at the end of a 2-year follow-up. In our study, the patients who received a combined medical treatment (tamsulosin and dutasteride) had significantly fewer BPH-induced AURs than those receiving only an alpha-blocker monotherapy at the end of the 1st year.

This study showed that a large proportion (71%) of patients with a BPH-induced acute urinary retention were successful in miction and that at the end of follow-ups, a combination of tamsulosin and dutasderide was more effective in reducing the number of patients referred to the BPH-induced surgery. In addition, it was found in our study that age, increased serum total PSA levels, and a large prostate volume were the factors that could cause a BPH-induced surgical intervention. The retrospective design of the study, a low number of patients, and the absence of a control group in the study are the study limitations. However, we believe that a longer follow-up period and the effort to find a solution to preventing the BPH-induced acute urinary retention, which is currently being discussed in the literature, are the positive features of the study.

CONCLUSION

Of all the factors analyzed, prostate volume, age, and serum PSA level were the most accurate predictors of BPH-related surgery. Moreover, combination treatment was found to be more effective treatment choice for prevention of BPH-related surgery.

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