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RESULTS OF SWITCHING TERAZOSIN AND DOXAZOSIN IN THE TREATMENT OF BPH

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ABSTRACT: Objective: Medical treatment of the BPH is one of the alternatives among a variety of therapeutic options. Doxazosin and terazosin are the most widely used molecules in the treatment of BPH. We compared the effectivity of these molecules by switching the drug in those who did not benefit from the first drug.

Methods: This was a prospective randomized study. Patients in the study were similar in age, prostatic weight, International Prostatic Symptom Score (I-PSS), uroflow parameters and PSA levels. Fifty men (mean age 59.4 years, SD 7.6, range 48-78) received either doxazosin (25 men), or terazosin (25 men), once daily at night. Patients were evaluated at one, 2 and 3 months. Improvement in I-PSS and the maximal flow rate (Qmax) by minimum 20% was accepted as improvement. Patients who showed improvement in none of the parameters have switched the drug and these patients were followed in the next 3 months.

Results: Of the 25 men using doxazosin, 11 (44%) showed improvement both in I-PSS and Qmax at 3 months. Of the 25 men using terazosin, 10 (40%) showed improvement both in I-PSS and Qmax at 3 months ($p>0.05$). After 3 months of treatment, the peak urinary flow rate increased significantly ($p< 0.001$) for both doxazosin (+4.5 mL/s) and terazosin (+3.1 mL/s) groups. The International Prostatic Symptom Score improved significantly ($p< 0.01$) with both alpha-blockers after 3 months of treatment in these groups. Nineteen patients, who did not show improvement in any of the parameters, switched the drug. Of the patients who switched the drug, 2 (4%) showed improvement both in I-PSS and in the peak urinary flow rate, 2 (4%) showed improvement only in I-PSS but not in the peak urinary flow rate and 15 (30%) did not show improvement in any of the parameters.

Conclusion: These results suggest that alpha blockade with either doxazosin or terazosin is effective in men with symptomatic BPH. Two of the alpha-blocking molecules showed equal effectivity in the treatment of BPH. If one of the molecules is ineffective in the treatment of BPH, then the other molecule will probably be ineffective.

[Key Words: terazosin, doxazosin, benign prostatic hyperplasia, drug switch]

INTRODUCTION

Men over the age of 50 will probable have benign prostatic hyperplasia (BPH) at a rate of about 85%. Also 50% of the men will require treatment at their eighties [1]. Medical treatment of the BPH is one of the alternatives among a variety of therapeutic options. Various types of surgery, medical treatment with alpha-1-adrenergic antagonists or 5-alpha-reductase inhibitors are included in the options of treatment.

In the 1970s, the pioneering work of Caine led to the discovery of alpha-1-adrenoceptor predominance in the prostatic stroma and capsule. This finding triggered the search for a-receptor blocking agents in patients with lower urinary tract symptoms suggestive of bladder outflow obstruction [2]. The initial agents were derived from antihypertensive drugs because of the a-receptor blocking capability [3]. Recently, several investigations have detected significantly more alpha-1-adrenergic receptors

in hypertrophic prostatic tissue than in normal tissue [4, 5, 6] and that blocking urethral alpha-1-adrenoceptors causes the prostatic urethra to relax [7]. More recently, several prostate specific drugs have been introduced. During the last 2 decades, the therapeutic efficacy of these drugs has been clearly demonstrated in several clinical trials, and today alpha-1-adrenoceptor blockers are the first line medical treatment for lower urinary tract symptoms suggestive of bladder outlet obstruction [8]. The alpha-1-blockers are valued for rapid onset of action, effectiveness independent of prostate size, minimal influence on sexual function and good therapeutic profile [9].

We searched the literature for doxazosin and terazosin switch or conversion protocols. One of the 2 studies we found in the literature that investigated both drugs looked at which dosage of each agent control blood pressure [10]. This study also did not provide an appropriate conversion dosage for patients with benign prostatic hyperplasia. The other study in the literature reported the conversion of doxazosin to terazosin to determine whether the switch would lead to differences in BPH symptoms, blood pressure or adverse effects [11].

In this study, we planned to investigate whether different types of alpha-1-blockers may have different clinical responses. However the molecular structures of the alpha-1-blocker agents are similar, this may not prove the effectiveness of the agents are similar. We investigated whether one of the alpha-1-blockers is not effective; is it rational to expect some improvement with another alpha-1-blocker.

MATERIAL AND METHODS

This is a two-armed, randomized study and lasted about 1,5 year. The pretrial assessment and establishing a baseline to evaluate the effect of treatment required each patient to undergo a history and symptom assessment, digital rectal examination (DRE), transrectal ultrasound (TRUS), and uroflowmetric analysis. The severity of symptoms was assessed subjectively using the International Prostatic Symptom Score (I-PSS) (maximum 35 points). Objective symptoms of BPH were evaluated by uroflowmetry [12]. Inclusion criteria of the study can be seen in Table (1). Parameters of the patients enrolled in the study are listed in Table (2). Patients were excluded if they had urinary tract infection (>10 white blood cell/high power field), prostate cancer, had any other medication that would interfere with doxazosin and terazosin or underwent prostatic surgery. I-PSS and quality of life scores (QOL score) were evaluated by the same physician.

Table 1. Inclusion criteria

Parameter	Value
Qmax	<15 mL/s
I-PSS score	≥8
PSA	<4.0 ng/mL
DRE	No sign of malignancy
TRUS	Any volume of prostate

Table 2. General parameters of the patients

	Age (years)	Prostate Vol. (mL)	I-PSS score	QOL score	Qmax	Average flow rate
mean±S.D.	59,4±7,6	49,1±16,5	14,1±5,4	3,7±1,1	11,1±2,4	5,3±2,2
min-max	48-78	14-83	8-28	2-6	5-14	2-9

Fifty patients with symptomatic BPH randomly assigned to terazosin (n = 25) or doxazosin (n = 25). Terazosin 10 mg and doxazosin 8 mg once daily was administered for 12 weeks. Symptoms were evaluated using the International Prostate Symptom Score (I-PSS), and quality of life score (QOL) was assessed subjectively before treatment, and again after four, 8 and 12 weeks of treatment. Objective measurement taken before and after the treatment period was the maximum urinary flow rates (Qmax). Improvement was defined as a 20% decrease from baseline in I-PSS and 20% increase from baseline in Qmax. Increasing QOL score by 1 point was detected, but it was not accepted as one of the improvement criteria (Table 3). Adverse reactions potentially related to the study drugs were recorded throughout the treatment period.

Table 3. The criteria for evaluating treatment efficacy

Parameter	favorable	unfavorable
I-PSS score; after treatment to baseline [(before treatment)-(after treatment)]/[before treatment]	≥ 20%	< 20%
Qmax (mL/sec) ; after treatment to baseline [(after treatment)-(before treatment)]/[before treatment]	≥ 20%	< 20%

The following protocol was used in drug dose regimen; in the doxazosin group, patients started from 1mg and increased to 8mg, and in the terazosin group, patients started from 1mg and increased to 10mg. Patients switched doxazosin to terazosin or terazosin to doxazosin with the following protocol; doxazosin 8 mg to 10 mg terazosin, and 10 mg terazosin to 8 mg doxazosin.

Treatment and follow-up flowchart was represented in Fig. (1). Twenty-five patients in each arm of the treatment scheme were randomized for the each drug. Patients were evaluated every 4 weeks and reassessment was employed with I-PSS, uroflowmetry and PSA measurements. At the end of the 12 weeks of treatment Qmax, I-PSS score were assessed whether to continue the drug or switch the drug with the other one. Ten patients on terazosin arm and nine patients on doxazosin arm did not show improvement in I-PSS score and Qmax, so they had their drug switched with the other one after 2 weeks of washout period. These patients were followed-up for more 3 months to evaluate effectiveness of the switched drug.

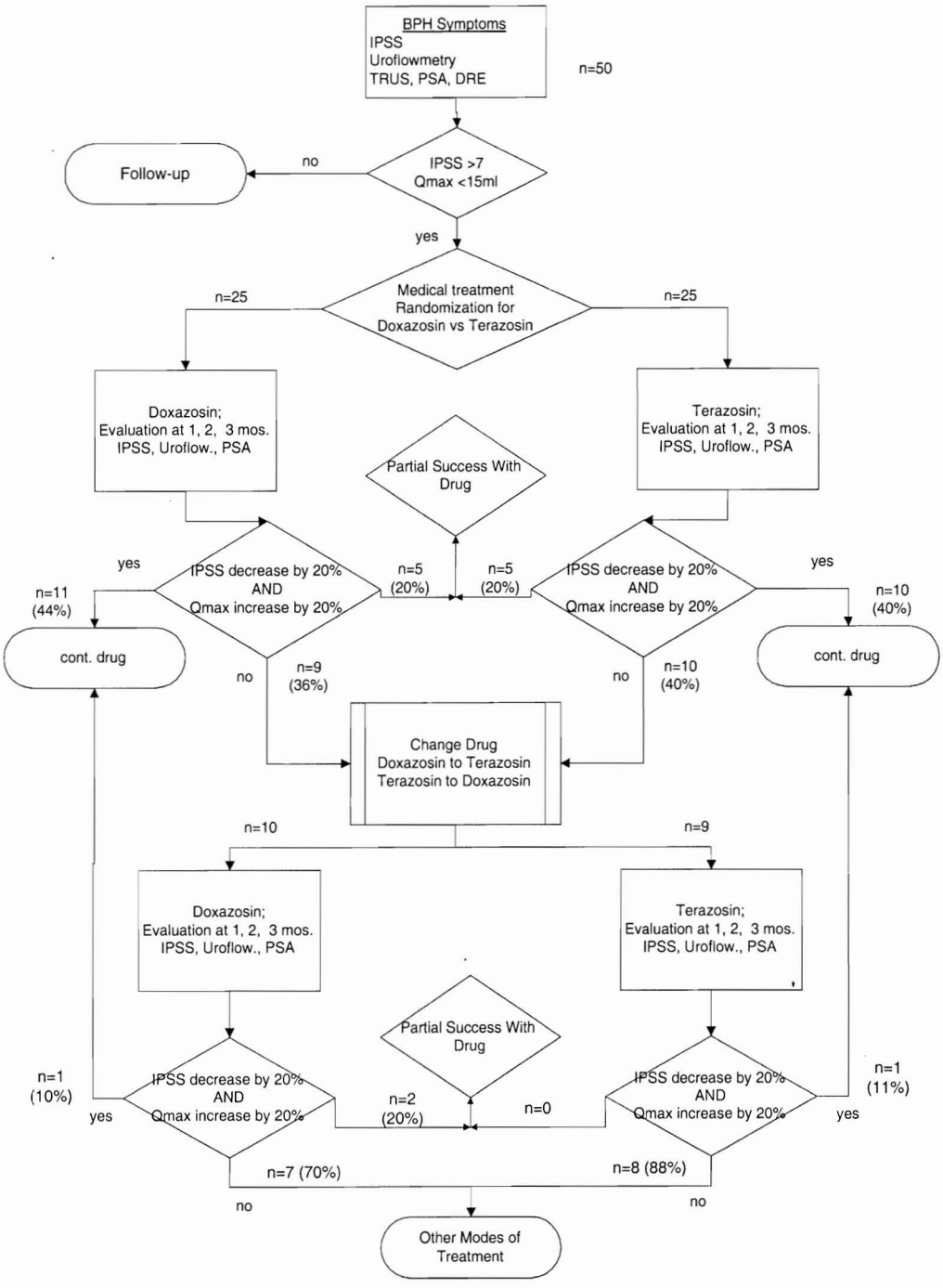

Fig. 1. Treatment and follow-up scheme

Statistical Analysis

Changes in urodynamic parameters, I-PSS and QOL scores between baseline and, 3- and 6-month follow-up were determined, and p values were calculated with the Wilcoxon signed-rank test. Chi-square test with Yates' correction for continuity is applied to analyze the percentages on the treatment scheme. Friedman test for several related samples was used to analyze the values of a parameter, measured during the study at different times. Improvements with drugs were evaluated with Kolmogorov-Smirnov test.

RESULTS

Patients characteristics at baseline are presented in Table (4). Patients in the both arm of the treatment were homogenous. There was no statistical difference between the ages of the patients, prostate volume, I-PSS score, QOL score, Qmax values and PSA levels of the groups.

Fig. (1) represents the treatment and follow-up of the patients. There were twenty-five patients on each arm of the treatment program. Of these 11 (44%) patients on the doxazosin arm and 10 (40%) patients on the terazosin arm showed improvement in both Qmax value and I-PSS score. Five patients on each of the treatment arms showed either improvement in Qmax value or I-PSS score (4 showed improvement in I-PSS and 1 in Qmax value in the doxazosin arm, and 3 showed improvement in I-PSS and 2 in Qmax value in the terazosin arm). These patients were not included in the switching the drug program. Nine patients (36%) using doxazosin and 10 patients (40%) using terazosin did not show any improvement in those parameters. These patients had their drug switched; nine patients began to use terazosin instead of doxazosin and 10 patients began to use doxazosin instead of terazosin. These patients were in follow-up for more 3 months duration. The results of the patients who switched the drug were as follows; out of 10 patients who switched terazosin-to-doxazosin; 1 (10%) showed improvement in both parameters, 7 (70%) did not show improvement in any of the parameters and 2 (20%) showed improvement only in I-PSS score. On the other hand, out of nine patients who switched doxazosin-to-terazosin; one (11%) showed improvement in both parameters and 8 (88%) did not show improvement in any of the parameters. None of the patients showed improvement in Qmax and in I-PSS score. Statistical analyses of the percents on each branch of the treatment arms were statistically insignificant (Chi-square test with Yates' correction for continuity is applied; $p>0.05$).

Table 4. Predrug assessment of the patients in each group.

	Pts. Age (years)	Prostate vol (mL)	I-PSS score	QOL score	PSA (ng/mL)	Qmax (mL/sec)
Doxazosin						
Mean±S.D.	58,7±8,7	47,4±15,2	14,4±6,2	3,7±1,2	2,5±2,1	10,8±2,7
Min.-max.	48-78	14-83	8-28	2-6	0,60-1,1	5-14
Terazosin						
Mean±S.D.	60±6,3	50,8±17,9	13,8±4,4	3,8±1,1	2,3±1,1	11,5±1,9
Min.-max.	49-71	21-83	8-21	2-6	0,43-3,9	8-14

Mann Whitney-U test; $p>0.05$ for all parameters.

Table (5) shows that the effectiveness of the drugs was equal in patients who respond favorably to the treatment. Graphic presentation on Fig (2) is an alternative method for evaluating the improvement of alpha-1-blockers advocated by The International Consultation on BPH (ICBPH) [13]. It is easy to evaluate the percent of patients who achieved some change in the I-PSS score. As an example, if change in the I-PSS score (–3) was accepted as a reference then as it could be seen on the graph, more than 60% of patients showed improvement. No statistical difference between the efficacies of the drugs was detected (Kolmogorov-Smirnov test; p=0.99)

Table (6) represents the outcome of the patients after 6 months of treatment who did not improve after 3 months of treatment of one drug and switched to the other drug. Friedman test for several related samples was applied to analyze the difference between baseline, three and 6 months' values of I-PSS score, QOL score and Qmax value for the each treatment arms. However, statistical differences were detected between baseline and at 3 and 6 month values, improvement of the parameters were not equal or more than 20%, so the patients were accepted as unresponsive to the treatment. Moreover, no statistical difference was detected between QOL score and Qmax value in the terazosin arm.

Table (7) shows the changes in the PSA value of the patients during 6-month follow-up. However a decrease in the level of PSA could be seen, the difference was not statistically significant (Friedman test for several related samples, p>0.05).

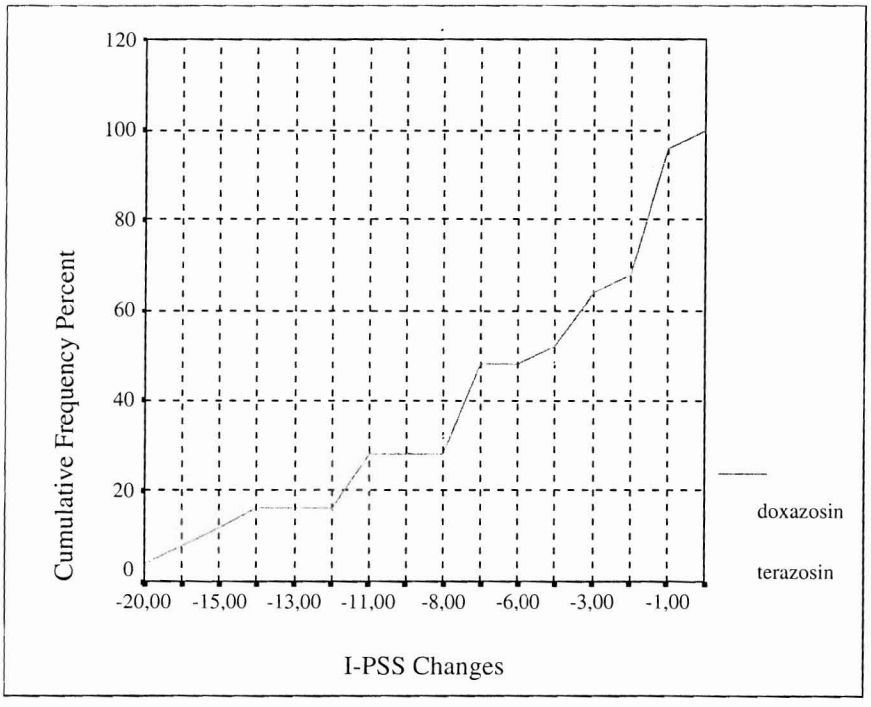

Fig. 2. Cumulative frequency distribution of improvement for doxazosin and terazosin for patients after 3 months of treatment.
Kolmogorov-Smirnov test; p=0.99

Table 5. Clinical and urodynamic outcomes of patients who showed favorable results after 3 months of treatment with one of the alpha1-blockers

	Doxazosin	Terazosin	p*
Qmax	13.1±3.1	12.9±2.3	>0.05
I-PSS	8.2±3.7	8.3±4.2	>0.05
QOL	2.7±0.97	2.8±0.95	>0.05

*Mann Whitney-U test

Table 6. Clinical and urodynamic outcomes of patients who had their drug switched

	I-PSS Baseline	I-PSS At 3 mo	I-PSS At 6 mo	p*	QOL Baseline	QOL At 3 mo	QOL At 6 mo	p*	Qmax Baseline	Qmax At 3 mo	Qmax At 6 mo	p*
Doxazosin arm												
Mean±S.D	13.3±4,3	11.5±3.7	10.3±3.4	<0.05	3.6±0.8	3.3±0.8	2.9±0.7	<0.05	12.1±1.6	11.4±1.3	13.3±1.6	<0.05
Terazosin arm												
Mean±S.D	10.±3.9	9.7±3.2	8.9±2.7	<0.05	3.2±0.6	3.2±0.6	2.5±1.2	>0.05	11.5±2	11.3±2.2	12.4±2.4	>0.05

*Friedman Test for several related samples

Table 7. PSA changes of the patients shows the changes in the PSA value of the patients during 6 month follow-up.

	PSA baseline	PSA at 3th month	PSA at 6th month	p*
Doxazosin arm				
Mean±S.D.	2.5±2.1	1.9±0.6	1.3±0.8	>0.05
Terazosin arm				
Mean±S.D.	2.3±1	1.7±0.7	1.6±0.9	>0.05

*Friedman Test for several related samples

In our group of patients, one patient in the doxazosin arm complained of dizziness, but did not caused him to give up taking the drug. The other patient on the terazosin arm complained of erectile dysfunction and caused him to give up taking the drug. This patient showed only improvement in the I-PSS score.

Fifteen patients did not benefit from both of the alpha-1-blockers. Transurethral endoscopic surgery was planned for these patients. Endoscopic evaluation of these patients revealed minimal urethral stricture in 2 patients and bladder neck contracture in 3 patients. Ten out of 15 patients did not show additional pathology for unresponsiveness to both of the alpha-1-blockers. Transurethral resection of the prostatic tissue was applied to these patients.

DISCUSSION

Multiple methods of minimally invasive surgical therapies have been introduced in the last decade. These methods include balloon dilatation, temporary and permanent urethral stents, various laser techniques, microwave thermotherapy, transurethral needle ablation, electrovaporization, and high-intensity focused ultrasound. Alpha-1-receptor blockers to reduce the sympathetic tone of the prostate are considered as first-line therapy to relieve the symptoms of benign prostatic hyperplasia [14]. The rationale for selective alpha-1-blockade in benign prostatic hyperplasia (BPH) is based upon the observations that the prostate

adenoma contains between 20% and 40% smooth muscle and the contractile properties of prostatic smooth muscle are mediated by the alpha-1-adrenoceptor [15]. Selective alpha-1-receptor blockers relax prostatic smooth muscle, relieve bladder outlet obstruction, and enhance urine flow with fewer side effects.

Several alpha-blockers are available for treatment of benign prostatic hyperplasia, including alfuzosin, tamsulosin, terazosin, and doxazosin. Different meta-analyses have shown these agents to be comparable in terms of efficacy in improving symptom score and increasing urinary flow rates [16].

In this study, we planned to compare the efficacy of doxazosin and terazosin by switching the drug on the same patient who did not show improvement with the previous drug. Patients were selected randomly to prescribe one of the drug and followed during the first 3 months' duration. The drug was switched if the evaluation of the patient showed unfavorable results at the end of the 3rd month. Patients who switched the drug were also followed for more 3 months' duration and evaluated whether they show improvement in the same parameters.

In the literature, a dose of 8 mg. doxazosin was found to be more efficacious than 4 mg. and the side effects associated with both dosages appeared to be similar. MacDiarmid et al concluded that the 8 mg. dose should be tried in patients who have not achieved an adequate therapeutic response to 4 mg. and are tolerating the medication [17]. Kaplan reported that 10mg of terazosin and 8mg of doxazosin result in superior subjective and objective results versus the lower doses [18]. Fawzy et al showed in a multicenter study that steady-state peak and trough plasma doxazosin concentrations were achieved by 6 weeks of therapy [19]. As symptom relief is the primary goal of therapy in BPH, doxazosin's effects are rapid in onset [8, 20]. On the other hand, the effect of terazosin on the peak urinary flow rate was apparent in studies as short as 8 weeks [20, 21]. Improvements were included both in symptom score and in the peak flow rate. These data were also remarkably consistent among the various alpha-1-blocking agents.

Another published data by Kaplan et al suggested that efficacy of terazosin and doxazosin was not affected by the dosing schedule. Adverse events were also significantly decreased by dosing in the evening period [21, 22].

Literature about the side effect of these drugs reports dizziness, headache, postural hypotension, and retrograde ejaculation [16]. The most common adverse events of terazosin and doxazosin resulting in premature termination were dizziness (6.7-10.7%), asthenia (3.8-7.5%), peripheral edema (4.0%) and somnolence (2.0%) [22, 23, 24]. However, publications proposed the alpha-blockers has not been associated with an increased incidence of erectile dysfunction as a side effect [25], some authors published erectile dysfunction (3-7%) as an adverse drug reaction of alpha-1-blocking drugs. [26, 27]

Under the light of these studies, patients in the doxazosin arm received 8 mg and in the terazosin arm received 10 mg daily at night and the follow-up period was limited to 3 months duration to evaluate the efficacy of the drug. Patients on the both treatment arm consumed the drug in a titrated way from 1 mg to 8 mg in the doxazosin arm and 1 mg to 10 mg in the terazosin arm within a week period. Patients who consumed their drug in this schedule were not affected seriously by side effects. Only one patient in the doxazosin arm reported dizziness (4%) and another patient in the terazosin arm reported erectile dysfunction (4%).

The efficacy of the alpha-1-blocker agent in the treatment of benign prostatic hyperplasia were represented between 15% and 30% change from baseline after 3 months of treatment [22, 23, 28, 29]. Djavan et al reported improvement in total symptom score by 30-40% and Qmax by 16-25% [8].

We accepted favorable response to therapy, defined as any reduction in symptom score and maximum flow rate by 20%. If the patient did not respond to the therapy by 20% on both parameters than it was accepted as partial response to the therapy. These patients were dropped from follow-up.

Most importantly, the effect of terazosin on symptoms and peak urinary flow rate was

independent of the baseline prostate size for the range of prostate volumes reported [30]. However literature reported the efficacy of the alpha-1-blocker therapy was not influenced with prostate volume, our patients were homogenous on prostate volumes with addition to other parameters.

In our group of patients improvement was achieved on doxazosin and terazosin arm of the treatment group by 44% and 40% respectively. Twenty percent of patients on each treatment arm showed partial improvement. Thirty-six percent of the patients on the doxazosin arm and 40% of the patients on the terazosin did not show improvement in any of the parameters. The efficacy of the doxazosin and terazosin in our group of patients agreed with the literature. Since quality of life score (QOL score) was a relative parameter so it was not accepted as the parameter of improvement in the treatment arms.

Patients who did not respond to the first line medical treatment had their drug switched with the other one. Nine patients (36%) in the doxazosin arm and 10 patients (40%) in the terazosin arm did not show improvement. Furthermore, 7 out of 10 patients (70%) in the terazosin-to-doxazosin arm and 8 out of 9 patients (88%) in the doxazosin-to-terazosin arm did not also represent further improvement. However, change in I-PSS score and in the flow rate was statistically significant, none of these patients achieved improvement by 20% or more. Change in the PSA values of these patients did not show statistical difference during 6-month follow-up.

CONCLUSION

Subjective and objective improvements could be achieved with the use of alpha-1-blocker therapy in BPH symptoms. If the patient does not improve in I-PSS score and in the flow rate with the use of one alpha-1-blocker, changing the molecule does not show further improvement.

If one type of molecule is ineffective to BPH symptoms then it will be better not to test another alpha-1-blocking molecule. It is preferable to search other options of treatment for the patient.

However, the number of the patients included in this study is low and the result can be suggested, it is one of the rare studies in the literature documenting the subject.

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