The use of primary and secondary doxazosin XL (8 mg) in the treatment of benign prostate hyperplasia: Is there a new approach in the event of alpha-blocker failure?

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ABSTRACT

Objective: Lower urinary tract symptoms (LUTS), which are related to benign prostate hyperplasia (BPH), are the most commonly encountered diseases in urological practice. In our study, we compared responses to (doxazosin mesylate extended release tablets) treatment.

Material and methods: In our study, we included one hundred patients with LUTS who did not receive any medical treatment, and one hundred patients with LUTS who did not respond to alpha-blocker drugs other than doxazosin XL (8 mg). The inclusion criteria for the study were as follows: international prostate symptom score (IPSS)>7, prostate volume >20 cc, Q-max <15 mL/sn, lack of any previous pelvic or prostatic surgery, and/or urethral catheterization.

Results: The mean age of the patients was 62.2±7.9 years. No statistically significant differences were detected between the groups with respect to age, prostate volume, and total prostate-specific antigen (PSA) levels. The duration of the follow-up period was calculated as 3-26 (mean 11) months. Significant differences were detected in post-voiding residual urine, IPSS, quality of life and Qmax between pre- and post-treatment values. Similar decreases in the IPSS scores, and increases in Qmax values were detected in both groups.

Conclusion: Doxazosin XL (8 mg) treatment was found to be efficient and reliable in primary patients and in patients with severe LUTS who did not respond to medical treatment. Trial of doxazosin XL (8 mg) therapy, before surgery in patients who respond inadequately to other alpha-blocker drugs is a rational approach.

Key words: Alpha-blocker; benign prostate hyperplasia; doxazosin.

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Introduction

Benign prostatic hyperplasia (BPH) is a pathology seen in men which increases in frequency with age, and with its symptoms affects quality of life unfavourably.^[1] Surveillance, medical, and surgical treatment alternatives are available.^[2] In the treatment various medical agents were brought into agenda, and surgical treatment rates decreased gradually. Still, in the whole world, as a first-line treatment a consensus favouring medical therapy has gained dominance provided that BPH-related complications do not develop.^[3]

One of the pathogenetic mechanisms of lower urinary tract symptoms (LUTS) of benign prostatic hyperplasia is increased resistance produced by stimulation of

α-adrenergic receptors intensely localized in the bladder outlet, hyperplastic prostatic tissue, and capsule, and prostatic urethra.^[4] This phenomenon renders medical treatment alternative as a rational choice for the management of complaints. Nowadays, alpha-blocker treatment has become the fundamental medical therapy of BPH. As a quinazoline derivative doxazosin has been used to this end for a long time.^[5] Double-blind, randomized, multicentered, placebo-controlled studies have demonstrated efficacy, reliability, and safety of 8 mg doxazosin in the treatment of BPH.^[6]

In our study, we compared responses to 8 mg doxazosin XL therapy given by the treatment-naïve patients, and those with moderate and advanced LUTS/BPH symptoms previously treated patients alpha-blocker therapy.

Material and methods

A total of 203 patient with LUTS who consulted to our outpatient clinics between January 2010, and December 2012 were evaluated within the context of the study. Three patients who did not attend follow up were excluded from the study. The patients who didn't receive any treatment previously (n=100 patients; primary group), and 100 patients who were still using alpha-blockers routinely (secondary group) without any response to treatment were included in the study. The alpha-blockers used consisted of tamsulosin 0.4 mg, alfuzosin 10 mg, terazosin 5 mg, and doxazosin 4 mg. After approval of the ethics committee of Haydarpaşa Exemplary Training and Research Hospital, and informed consent forms from patients were obtained. Patients' medical history was recorded, and their physical examinations were performed. Subsequently, the patients were requested to complete International Prostate Symptom Score (IPSS) forms. All patients underwent prostate specific antigen (PSA) (ng/mL), creatinine (mg/mL) tests, digital rectal (DRE), uroflowmetric, and urinary system sonographic examinations. Based on IPSS scores, symptoms were evaluated as mild (0-7 pts), moderate (8-19 pts), and severe (20-35 pts). Use of any drug effective on BPH for 4-6 weeks was not permitted.

Inclusion criteria were as follows: IPSS >7, prostate volume >20 cc, peak urinary flow rate (Q-max) <15 mL/sec, absence of any previous evidence of pelvic or prostatic surgery, and urethral catheterization. Patients with higher PSA values or DRE findings suggestive of prostate cancer were not included in the study, and they were referred to prostate biopsy. BPH patients with absolute indication for surgery, and those using 5-alfa-reductase inhibitors were excluded from the study.

In both groups, patients were started on once daily doses of 8 mg doxazosin XL. All patients were called for a control visit

3 months after the initiation of the treatment for the evaluation of IPSS, uroflowmetry, and PMR results. During subsequent 3-monthly follow-ups, maintenance of doxazosin XL 8 mg therapy, and medication-related side effects were interrogated. Patients who didn't benefit from the drug therapy or cases who couldn't tolerate the drug were directed to different treatment modalities.

Statistical Analysis

For statistical analysis, Statistical Package for the Social Sciences (SPSS) 15.0 for Windows program was used. For intergroup comparisons Student's t-test, and Mann-Whitney U test were employed and. For the comparison of intragroup pre-, and post-treatment values, analysis of repeated measurements, and Wilcoxon Signed Rank Test were used. Level of statistical significance was accepted as *p* values lower than 0.05.

Results

Two hundred patients out of 203 cases included in the investigation completed the study. Mean age of the patients was 62.2±7.9 years. Both groups were similar as for age, prostate volume, and PSA levels (Table 1). Mean duration of previous drug usage was 22.66±25.84 months in the secondary group. These patients had used tamsulosin (n=42), alfuzosin (n=25), terazosin (n=23), doxazosin (n=2), and more than one alpha-blocker.

Patients both in the primary, and secondary groups, IPSS, Qmax, quality of life (QoL), and PMR results before, and after doxazosin XL 8 mg therapy were found to be statistically significantly different (Table 2). In both groups, amount of decrease in the posttreatment IPSS, QoL, and PMR values, and increase in Qmax were found to be similar (*p*>0.05).

Mean follow-up period was 10.7±6.3 months (3-26 mos). During this period, surgical intervention for BPH was applied in 33 (16.5%) patients. Surgical interventions were documented as TURP (n=29; 14.5%), TVP (n=2; 1%), KTP-Laser prostatectomy (n=2; 1%). A total of 33 patients were included in the study (primary group, n=12, and secondary group, n=21) (*p*<0.001).

Three (1.5%) out of 200 patients in the primary group, discontinued the treatment because of intolerance. As adverse effects, dizziness-hypotension (primary group, n=10; 10%, and secondary group, n=2; 2%) (*p*<0.001) was observed. Skin rashes (n=1; 0.5%), constipation (n= 1; 0.5%), and finding of capsules in the stool (n=3; 1.5%) were also noted.

Discussion

Results of our study have demonstrated that in patients refractory to alpha-blockers, doxazosin XL 8 mg therapy can be

Table 1. Comparison of baseline values of both groups

	Primary group	Secondary group	P
Age (year)	62.0±8.5	62.4±7.4	0.709
Total PSA (ng/dL)	2.7±2.3	2.8±2.9	0.520
PV (mL)	52.0±21.2	49.2±21.7	0.277
IPSS	19.4±2.2	19.9±2.2	0.078
QoL	4.8±0.6	4.7±0.6	0.783
Qmax (mL/sec)	11.0±1.7	10.7±1.6	0.456
PMR (mL)	70.7±63.4	60.6±48.6	0.434
Follow-up period (mos)	10.7±6.3	10.7±6.4	0.964
PSA: prostate specific antigen; PV: prostate volume; IPSS: International Prostate Symptom Score; QoL: quality of life scale; Qmax: peak urinary flow rate; PMR: postmicturitional residual urine			

Table 2. Comparison of changes in values in both groups

		Before Doxazosin XL 8 mg (Mean±SD) (N=100)	After Doxazosin XL 8 mg (3. month) (Mean±SD) (N=100)	Change between pre-, and post-treatment values (%)	p
Primary group	PMR	70.7±63.4	50.9±45.1	28.0%	<0.001
	IPSS	19.4±2.2	12.5±3.9	35.6%	<0.001
	QoL	4.8±0.6	2.7±1.2	43.8%	<0.001
	Qmax	11.0±1.7	15.2±2.7	38.2%	<0.001
Secondary group	PMR	60.6±48.6	42.9±31.9	29.2%	<0.001
	IPSS	19.9±2.2	13.0±4.0	34.7%	<0.001
	QoL	4.7±0.6	2.9±1.2	38.8%	<0.001
	Qmax	10.7±1.6	14.8±2.6	38.3%	<0.001

IPSS: International Prostate Symptom Score; QoL: quality of life scale; Qmax: peak urinary flow rate; PMR: postmictional residual urine; SD: standard deviation

an alternative. Any difference between both groups, as for response to the treatment was not found. BPH is one of the most important health problems of elder men, and clinically manifests itself with LUTS.^[7] In 25-50% of the patients with BPH, clinical symptoms as difficulty in urination, inability to empty the bladder completely are found.^[8] LUTS, effects daily life of the individual with a decline in the quality of life of the patient.^[9]

The number of alpha-adrenergic receptors increases in the tissue of benign prostatic hyperplasia. In patients with symptomatic BPH, contractile response of these receptors increases in intensity. Alpha-blockers alleviate increased adrenergic activity, and relax smooth muscles of prostate, and bladder outlet with resultant symptomatic improvement related to dynamic component of BPH.^[10] Its effects start within a few days, and reaches to maximal levels within 1-2 weeks.^[11] Studies performed with alpha-blockers, detected 2-4 point-decreases in IPSS scores, and increments of 2-3 mL/sec in Qmax with onset of its effectiveness within one week which was maintained for nearly 5 years.^[12] In our study, an increase of more than 4 mL/sec in Qmax values was detected, while IPSS values decreased nearly 7 points.

Doxazosin is a long-acting quinazoline derivative with a half-life of nearly 22 hours. Symptomatic improvement is seen approximately within a week. It exerts its effect by decreasing urethral resistance at an early stage. Its gastrointestinal therapeutic system (GITS) formulation reaches peak plasma levels within 14.-16 hours. This form is very different from its non-GITS formulation of doxazosin which reaches to its peak plasma level within 2-3 hours. Steady drug release of its GITS formulation provides a side effect profile similar to that of placebo, and discards the need for titration.^[13] In a multicentered, placebo-controlled study performed with doxazosin, increases

varying between 2.3-3.6 mL/sec were observed, and its efficacy over placebo has been proved. MacDiarmid et al.^[14] conducted a study on efficacy, and tolerability of 4 mg, and 8 mg doxazosin in the treatment of BPH, and 8 mg dosage forms had demonstrated more effective performance with similar side effect profile. As an outcome of our study, both in the primary, and secondary groups, doxazosin XL 8 mg demonstrated its efficacy with tolerable side effects.

The general idea in the literature about whether another alpha adrenergic receptor blocker would provide any benefit is that if adequate response was not gained in the treatment by one type of alpha adrenergic receptor blocker, similar results would be reached with the others. Indeed in a randomized, prospective study on 50 male patients with BPH-related LUTS, Samli et al.^[15] changed the drug which provided less than 20% improvement in IPSS, and peak urinary flow rate. Based on the study outcomes of their study, switching to another drug did not achieve a significant symptomatic improvement. The authors emphasized that in refractory cases, crossing over to another alpha-blocker did not make any sense.^[15] Still, Senkul et al.^[16] performed an investigation on 40 male patients with BPH-related LUTS, and reported that changing therapeutic drug had not achieved an additional symptomatic benefit. However in our study, in patients unresponsive to standard dose alpha-blockers (secondary group) doxazosin XL 8 mg provided adequate effectiveness. Based on this experience of ours, preoperative use of doxazosin XL 8mg in refractory cases is a rational therapeutic approach. We think that this approach will protect some patients from operative morbidity.

Even though minimal differences exist between alpha-blockers, generally they have the same side effect profile, and they can induce orthostatic hypotension, feelings of prostration, headache, asthenia, nasal congestion, and retrograde ejaculation.^[17] The

most frequently seen adverse effect of tamsulosin is retrograde ejaculation which is seen at a rate of 4.5-11% when compared with placebo.^[18] In a study performed by Lepor et al.^[19] 10% of the patients under terazosin therapy discontinued drug use because of headache, asthenia, and stupor. Standard doxazosin has side effects as dizziness, asthenia, edema, shortness of breath, and hypotension which do not increase in severity, and frequency with age.^[2] However in our study where we used controlled-release GITS formulation of doxazosin, only 3 (1.5%) patients withdrew from the treatment because of intolerance to the drug therapy. In 12 (6%) patients (10 patients in the primary group) mild side effects such as dizziness, malaise, and hypotension were seen. We attributed this lower rates of intolerance to the extended-release formulation of the drug we used.

Limitations of our study include its single centered design, and lack of a different alpha-blocker group designated as a placebo group.

Once daily doses of doxazosin XL 8 mg demonstrated similar effectiveness in the treatment of benign prostatic hyperplasia in both primary, and secondary groups. Its clinical effectiveness has been shown using both subjective (IPSS, and QoL), and objective (Qmax, Qave, and PMR) criteria. In our study, once daily doses of doxazosin XL 8 mg was found to be a safe drug with acceptable side effect rates. In the light of our findings, in patients refractory to other alpha-blocker drugs, before surgical treatment alternatives, trial of doxazosin XL 8 mg is a rational approach. By this means, at least a patient group will be protected from morbidities of surgery.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Haydarpaşa Training and Research Hospital.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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