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Can We Use the Silodosin as Second Line Treatment of Benign Prostate Hyperplasia?

Benign Prostat Hiperplazisi Tedavisinde Silodosin İkinci Basamak Kullanılabilinir mi?

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Abstract

Objective: We aimed to investigate the efficacy of silodosin in patients with lower urinary tract symptoms (LUTS) caused by benign prostatic hyperplasia (BPH) refractory to previous α-adrenergic receptor (AR) blocker therapy.
Materials and Methods: Patients who did not benefit from alpha-blocker therapy but avoided surgical treatment constitute the population of our study. Seventy-five patients were studied in each group; Group 1 was given 8 mg of silodosin, while Group 2 continued the previous alpha-blocker treatment.
Results: The initial mean international prostate symptom score (IPSS) was calculated as 20.81±0.97 in Group 1, in the third month there was a decrease of 17.12±1.25 ($p<0.05$). No significant change was observed in Group 2. In addition, a significant decrease was observed in IPSS subscores (storage and voiding symptoms) in Group 1 compared to baseline at the third month. There was an improvement in residual urine in the silodosin group and no improvement in the other group.
Conclusion: In patients with BPH who refuse surgical treatment and could not achieve adequate symptom relief with other α-blockers in routine practice, silodosin was found superior in terms of LUTS recovery. Silodosin is also an effective option in patients who cannot undergo surgical treatment due to comorbidities.

Keywords: silodosin, alpha blocker, benign prostate hyperplasia, BPH treatment

Öz

Amaç: Daha önce alfa bloker tedavi ile iyileşme sağlanamayan benign prostat hiperplazisi (BPH) ile ilişkili alt üriner sistem semptomlu (AÜSS) hastalarda silodosin etkinliğinin ortaya konulması amaçlandı.
Gereç ve Yöntemler: Alfa bloker tedavisinden fayda görmeyen ancak cerrahi tedavi istemeyen hastalar bu çalışmaya dahil edildi. Kayıt sırasında, sırasıyla Grup 1 ve Grup 2'ye 75'er hasta kaydedildi. Grup 1 tedavide silodosin 8 mg alan, Grup 2 diğer α blokerleri alan grup olarak belirlendi.
Bulgular: Grup 1'de başlangıçta ortalama IPSS skoru 20,81±0,97 iken üçüncü aylarda anlamlı olarak 17,12±1,25'e düşmesine rağmen, Grup 2'de anlamlı bir değişiklik gözlenmedi. Grup 1'de ise her iki IPSS alt puanı için de düşüş gözlendi, üçüncü ayda başlangıca göre anlamlı olarak azaldı. Üçüncü ayın sonunda silodosine geçildikten sonra bu parametrede ilk değere göre ($p<0,05$) anlamlı bir iyileşme gözlendi. Rezidü idrar ile ilgili olarak silodosin grubunda iyileşme belirgin iken Grup 2'de anlamlı bir iyileşme gözlenmedi.
Sonuç: Bu çalışmada, cerrahi tedavi öncesi rutin klinik uygulamada diğer α-blokerlerle tatmin edici semptom kontrolü sağlanamayan BPH'li hastalarda silodosinin AÜSS iyileşmesi üzerinde etkisi daha fazla bulundu. Silodosin, cerrahi morbiditesi olan BPH'li hastalarda daha etkilidir. Böylece en azından farklı komorbiditeleri olan hastalar cerrahinin morbiditelerinden korunmuş olacaktır.

Anahtar kelimeler: silodsin, alfa bloker, benign prostat hiperplazisi, BPH tedavisi

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Introduction

Benign prostatic hyperplasia (BPH) is a widespread disease among elderly men. It was also known that in men beyond the age of 50 histological BPH will develop [1]. As a result of the proliferation of epithelial and stromal cells, prostate gland growth occurs and it is characterized with an increase in the micturition frequency, difficulties in initiating micturition, nocturia, urgency, a low stream of urine, and a prolonged period of micturition [2]. All these disorders should be called as lower urinary tract symptoms (LUTS). Stimulation of α-adrenergic receptors (ARs), resistance increases in hyperplastic prostate tissue, capsule, prostatic urethra and, bladder outlet. This is an important pathological mechanism in BPH-associated LUTS [3]. α1A-ARs and α1D-ARs mRNA are present in hyperplastic stromal prostate as well as in normal human prostate. Expression of α1A-AR is particularly increased in BPH [4-7]. The stromal α1A-ARs play an important role in the contraction of the prostate and, consequently, in the dynamism of BPH. Their antagonism may explain the relief of micturition difficulty [8]. In the prostatic contraction, the predominance of the α-1ARs subtype may play a primary role, so that this has led to investigation the α-1ARs-selective compounds in the notion of uroselectivity or prostate selectivity [9].

Studies have reported that silodosin has a higher affinity for the α1A-ARs than the α1B-ARs subtype and also higher selectivity for the lower urinary tract. Silodosin has >162-fold greater selectivity for the α1A over the α1B subtype and >50-fold greater selectivity for the α1A over the α1D subtype [10]. Thus, of all commercially available α1-AR blockers, silodosin is the most uro-selective and most potent relaxant in vitro to the prostate mediated by α1-ARs [5,11–14]. Oral silodosin is a highly selective α -1A-ARs antagonist which rapidly improves LUTS caused by BPH and allows the improvements in storage and voiding symptoms [15].

In our study, we evaluated the efficacy of silodosin in patients with LUTS caused by BPH refractory to previous AR blocker therapy.

Matherials and Methods

Prior to this study, approval was obtained from the Derince Training and Research Hospital Ethics Committee (Approval no: 2020/62). In our study, patients who switched to silodosin treatment were retrospectively examined. Patients whose alpha-blocker treatments other than silodosin were ineffective and who did not prefer surgical treatment were included in this study. Other inclusions criteria were as follows: international prostate symptoms score (IPSS) ≥8 points, quality of life (QoL) scale ≥3 points, prostate volume by ultrasonography <40 mL; maximal urinary flow rate (Qmax) <15 mL/s and post-voiding residual (PVR) ≤150 ml; prostate specific antigen (PSA) <4 ng/ml. Exclusion criteria were as follows: patients with a diagnosis of neurogenic bladder, with concomitant prostate or urethral carcinoma, with urinary tract infections, using drugs such as anticholinergic agents, beta-3 adrenoceptor agonists and 5-α reductase inhibitors, and those with a history of prostate surgery.

Study Setting and Design

This was a retrospective, single-center study conducted at urology clinic of Derince Training and Research Hospital.

Study Procedures

The patients were informed that silodosin is a new α-blocker that was recently released that could be more effective for their symptoms and could have a different side effect profile. When the patient agreed to undergo this change, we switched the drug after 2 weeks of washout period. Oral administration of silodosin at a daily dose of 8 mg started.

A total of 150 patients were divided into two equal groups of 75 patients each. Group 1 received silodosin 8 mg and Group 2 received their previous α blocker. The symptom scores and uroflowmetry with PVR evaluation were measured in both groups after 3 months.

Study Endpoints

The primary end-point of evaluation for efficacy was the change in total IPSS from baseline and the quality of life (QoL) scale; secondary end-points were changes in Qmax, residual urinary volume and evaluation of subjective symptoms as IPSS voiding and storage subscores and QoL scale. A 20% decrease in baseline IPSS and a 20% increase in baseline Qmax were considered as improvement [16].

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. 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

Patient Population

There was no difference between the two groups in terms of age, prostate volume, IPSS and Qmax **(Table 1)**. The mean duration of previous drug use was calculated as 22.66±25.84 months. All of the patients in group 1 used silodosin (n=75) and in the Group 2 tamsulosin (n=25), alfuzosin (n=20) and doxazosin (n=30) were used . During the 3-month treatment period, no patients discontinued silodosin due to adverse effects.

Table 1. Comparison of baseline values of both groups (Mann-Whitney U test were used)

	Group 1 (mean±SD)	Group 2 (mean±SD)	P-value
Numbers	75	75	
Age (year)	67,1±2,06	64±2,11	0,989
PV (mL)	38,81±1,94	38,45±1,94	0,491
IPSS (total score)	20,81±0,97	20,77±0,78	0,871
IPSS – storage symptoms	11,09±1,18	11,21±1,19	0,818
IPSS – voiding symptoms	8,55±0,60	10,88±0,73	0,000
Qmax (mL/sec)	8,56±1,58	8,56±1,58	1,000
PVR (mL)	53,67±5,41	53,60±5,30	0,961
QoL	5,19±0,59	5,19±0,59	1,000

PV: prostate volume; IPSS: international prostate symptom score; Qmax: maximum urine flow rate; PVR: post-void residue; QoL: quality of life

Table 2. Comparison of changes in values in both groups (Wilcoxon Signed Rank test were used)

		Pretreatment (mean±SD)	Posttreatment (mean±SD)	Change between pre and posttreatment values (%)	P-value
Group 1	IPSS-total	20,81±0,97	17,12±1,25	17,6	0,000
	IPSS – storage symptoms	11,09±1,18	8,56±0,64	22,3	0,000
	IPSS – voiding symptoms	8,55±0,60	6,99±0,34	18	0,000
	Qmax (mL/sec)	8,56±1,58	11,69±1,20	39,9	0,000
	PVR (mL)	53,67±5,41	35,87±4,96	32,5	0,000
	QoL	5,19±0,59	3,09±0,47	40,2	0,000
Group 2	IPSS-total	20,77±0,78	20,96±0,48	1,0	0,070
	Qmax (mL/sec)	8,56±1,58	8,48±0,67	2,8	0,602
	PVR (mL)	53,60±5,30	57,41±3,65	7,7	0,000
	QoL	5,19±0,59	5,27±0,62	2,0 (%)	0,221

IPSS: international prostate symptom score; Qmax: maximum urine flow rate; PVR: post-void residue; QoL: quality of life

International Prostate Symptom Score (IPSS)

While the initial mean IPSS score was calculated as 20.81±0.97 in Group 1, this value decreased to 17.12±1.25 in the third month with a significant difference ($p<0.05$). No significant change was observed in Group 2. In addition, a significant decrease was observed in IPSS subscores (storage and voiding symptoms) in Group 1 compared to baseline at the third month. Data on IPSS scores are shown in **Table 2**.

Quality of Life Scale (QOLS)

At the end of the third month, a significant improvement in QoL scale was monitored after changing to silodosin, as compared with the first value ($p<0,05$).

Post-void Residue (PVR)

When PVR was compared compared, significant improvement was observed in Group 1 but none in Group 2. After 3 months evaluation , surgical intervention for BPH were applied in 10 (13,3%) patients of the Group 2. The flow chart of study is schematically illustrated in **Figure 1**.

Discussion

To the best of our knowledge, there is many studies for the treatment modalities of BPH with alfa blockers. The guidelines issued by the European Association of Urology (EAU) and American Urological Association (AUA) both states that alpha-blockers should be considered as the first-line medical therapy for men with bothersome, moderate to severe LUTS, and their clinical efficacy are similar in recommended therapeutic dose but for some of these drugs, studies reported that side effect profiles are more favorable [17,18]. Efficacy of all α-AR blockers in appropriate doses seems to be similar in clinical practice treatment efficacy but differs among individuals. Therefore, frequently applied application in clinical practice is switching intra-class α-AR blocker to another [19–21]. One of the surgical indication of BPH is a negative response to conservative pharmacological treatment [22].

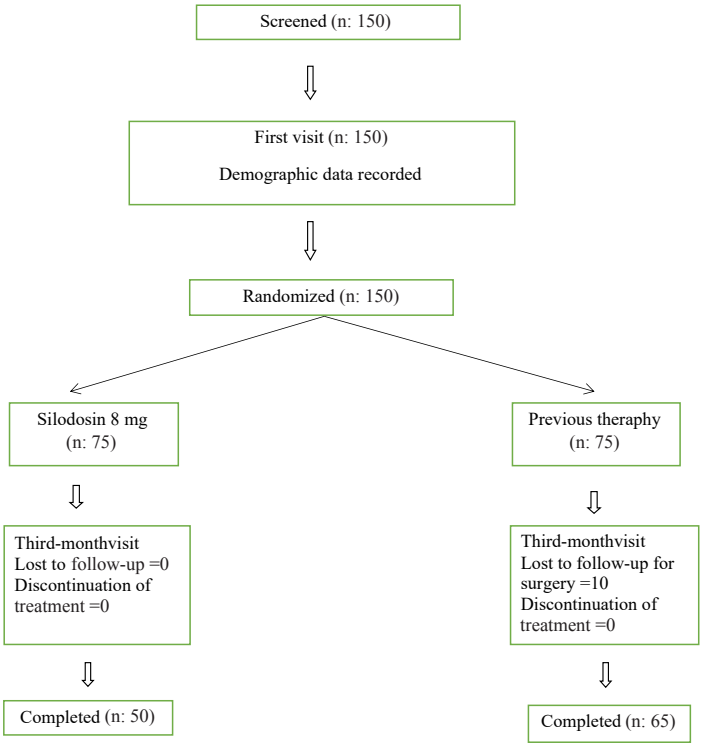

Figure 1. Flow of study participants through the study

In this retrospective study we evaluated the clinical outcomes associated with switching to silodosin in patients who did not respond to other α-AR blockers therapy. According to our study it has demonstrated that in patients refractory to α-AR blockers, silodosin 8 mg therapy can be an alternative for proceeding medical therapy. In LUTS/BPH patients with a poor response to at least 4 weeks of their own α-blocker, switching to silodosin 8 mg improves LUTS/BPH and related QoL.

There are different studies in the literature about switching α-AR blockers to another. Masciovecchio et al. assessed the clinical outcomes associated with switching to silodosin in patients who did not respond to tamsulosin therapy and after a 8-week treatment they found a significant improvement in IPSS total score, and QoL scale [21]. They also analyzed the specific subscores of the IPSS questionnaire and reported that a significant improvement was observed in storage symptoms, but not in voiding symptoms. On the other hand Tanaka et al. reported that switching to silodosin besides improving the other parameters exhibited a more strong effect on voiding symptoms than on storage symptoms, but they have found no significant improvement in the post-micturition symptoms [23]. Recently, a new study was published by Yoshida et al [24] whom declared silodosin as an effective first-line α AR blocker monotherapy, even in those who still have moderate lower urinary tract symptoms in their study. Silodosin, a highly selective α-ARs blocker, is the most recently approved of the commercially available α-blockers [10].

Overall, switching to a 3-months silodosin treatment determined a significant improvement in IPSS total score, and QoL scale was observed. All patients had been previously treated with a recommended treatment associated with LUTS, without showing response; therefore, an improvement in IPSS after switching to silodosin appears clinically relevant.

Noteworthy studies have shown that silodosin also improves the urodynamic parameters [25–27]. In this way silodosin improves voiding, and storage symptoms and Qmax in men with LUTS associated with BPH [15]. In our study, silodosin exhibited a strong effect on both voiding symptoms and on storage symptoms.

This present study has some limitations due to the number of patients which each study arm was relatively small, the short duration of observation, and the lack of a control.

Conclusion

In patients with BPH who did refuse surgical treatment and could not achieve adequate symptom relief with other α-blockers in routine practice, silodosin was found superior in terms of LUTS recovery. Decrease in IPSS, PVR and increase in Qmax and QoL scale were higher in the group receiving silodosin treatment compared to the group using other alpha blockers. Silodosin is also an effective option in patients who cannot undergo surgical treatment due to comorbidities.

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences, Derince Training and Research Hospital, Kocaeli, Turkey (Approval date, and registration number: 11.06.2020/62).
Informed Consent: An informed consent was obtained from all the patients.
Publication: The results of the study were not published in full or in part in form of abstracts.
Peer-review: Externally peer-reviewed.
Authorship Contributions: Any contribution was not made by any individual not listed as an author. Concept – B.V., O.M.; Design – B.V., M.U., O.M.; Supervision – B.V., M.U., L.O.; Resources – O.K., M.U., L.O.; Materials – O.K., O.M., L.O.; Data Collection and/or Processing –O.K., M.U., L.O.; Analysis and/or Interpretation – B.V., O.M., O.K; Literature Search – O.K., M.U., L.O.; Writing– B.V., O.M.; Critical Review – B.V., M.U., L.O.
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