Original Article

Evaluation of ultrasonographic predictors of alpha-blocker mono-therapy failure in symptomatic benign prostatic enlargement

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Abstract

Objectives: Many sonographic parameters for predicting treatment failure for benign prostate enlargement have been described. Patients may take alpha-blockers for a long time at high cost before conversion to surgery.

Purpose: Evaluation of the sonographic parameters that predict alpha 1 adrenoreceptor blocker monotherapy outcomes in symptomatic patients with benign prostate enlargement.

Patients and Methods: Between June 2016 and July 2019, we prospectively enrolled 750 symptomatic patients with benign prostate enlargement. Trans-rectal ultrasonography was performed, and patients were given Tamsulosin (0.4 mg) oral tablets once daily for 6 months. Treatment outcomes were determined using quality of life, the International Prostatic Symptom Score, and maximum urine flow rate measures. The values of the measured baseline sonographic parameters on treatment outcomes were statistically analyzed.

Results: Seven-hundred and fifty patients completed the study, and treatment was ineffective in 225 of them (30%). From the measured prostate and bladder sonographic parameters, intra-vesical prostate growth was only significant. Using a cutoff value of 8.2 mm, the area under the receiver operator characteristic curve for intra-vesical prostatic protrusion was 0.866. Using this cutoff value (with 95% confidence interval), both positive and negative predictive values were 73.3% and 98.18%, respectively.

Conclusion: Based on sonographic parameters, only the intravesical prostate protrusion was valid for predicting alpha-blocker monotherapy failure in symptomatic benign prostate enlargement patients. This information helps determine a medical therapeutic plan and the need for surgical intervention.

Keywords: Bladder outlet obstruction, lower urinary tract symptoms, prostate

INTRODUCTION

Many treatments are available for symptomatic benign prostate enlargement (BPE).[1] Alpha-blockers, which are commonly used in the treatment of symptomatic BPE, have limitations and complications.[2] The predictive value of some sonographic parameters on benign prostatic obstruction (BPO) treatment outcomes has previously been studied.[3,4] These studies assessed only one parameter per the study, and only one study assessed combined sonographic parameters for

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predicting the outcome of alpha blocker-related medical treatment for lower urinary tract symptoms (LUTSs) due to BPO.[5] The aim of this study was to detect the sonographic parameters that significantly affected treatment outcomes of LUTS in BPE patients treated with Tamsulosin 0.4 mg for 6 months. The parameters of interest were bladder wall thickness (BWT), ultrasound (ultrasonography)-estimated bladder weight (USEBW), and intravesical prostate protrusion (IPP). Furthermore, we assessed the predictive value of these parameters for that purpose.

PATIENTS AND METHODS

This prospective study was conducted on 750 symptomatic patients who complained of LUTS/BPE at our department between June 2016 and July 2019. We evaluated patients by taking a complete medical history in addition to the International Prostate Symptoms Score (IPSS), quality of life (QoL) scores, serum creatinine, serum prostatic-specific antigen (PSA), urine analysis, uroflowmetry, and measuring postvoid residual (PVR) urine volume. We conducted trans-abdominal and trans-rectal ultrasonography (TRUS) for all patients.

Age ≥ 50 years old, moderate (8–19), and severe (20–35) LUTS according to IPSS (Q_{max}) <15 ml/s and prostate size ≤ 45 g were the inclusion criteria.

While, history of taking drugs that affect voiding patterns (such as beta-agonists), allergy to Tamsulosin, diabetes mellitus and neurological diseases, urinary tract infection and/or stones, urethral stricture, suspicion of prostate cancer, PVR urine volume >200 ml, and renal insufficiency were the exclusion criteria.

Ethical consideration

The ethical committee approval was taken under the number (30995/06/16), and the study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all participants in this research after full explanation of the risks of the study. There were sufficient provisions to keep the privacy of participants and confidentiality of the data as every patient had a code number; the name and the address were kept in a private file linked to the research; the results of the study were used only for scientific purpose and not for any other purposes.

Procedures

All sonographic parameters were measured by one operator. Trans-abdominal ultrasound was completed

with the patient in the supine position with a bladder volume of 100–200 ml. Bladder volume was measured using a 3.5 MHz convex probe (BK medical Flex Focus ultrasound system) and the prolate ellipsoid method in which volume = (length) × (width) × (height) × 0.52. For BWT, we measured the hypoechoic layer (using the 7.5 MHz linear probes) since the bladder wall is formed by detrusor muscle, which is represented by a hypoechoic layer between two hyperechoic layers (serosa and mucosa). UEBW was calculated from the estimated BWT and bladder volume. Trans-rectal ultrasound was then performed during the same session in the left lateral decubitus position using the same ultrasound system. IPP was estimated using a midline sagittal image by drawing a line through the bladder base. Subsequently, IPP was measured as the vertical distance from the tip of the protrusion to the bladder base. Transitional zone volume (TZV) was scanned in the transverse and sagittal planes using the prolate ellipsoid method. Total prostate volume (PV) was measured using the previously mentioned prolate ellipsoid method. Tamsulosin 0.4 mg oral tablets were given once daily to each patient for 6 months. Patients were followed up by measuring the QoL and IPSS scores and Q_{max}.

Treatment outcomes were measured by comparing pre- and 6-month posttreatment follow-up values of IPSS, QoL scores, and Q_{max}. Symptom response (IPSS) to therapy was calculated according to Homma *et al*.[4] and Ahmed.[5]

Posttreatment IPSS/pretreatment IPSS; the value was then categorized:

Excellent response if ≤ 0.25 classified, good response if >0.25–≤ 0.5, fair response if >0.5–≤ 0.75, and poor response if >0.75. The QoL score was obtained as a part from the IPSS score (ranged 0–6).
- The QoL score to therapy was calculated according to Homma *et al*.[4] and Ahmed:[5] Pretreatment QoL score − posttreatment QoL score. The score was then categorized: (1) Excellent response = 4–6, (2) good response = 3, (3) fair response = 1–2, and (4) poor response = 0.

As regard (Q_{max}) to therapy, it was calculated according to Homma *et al*.[4] and Ahmed:[5] Posttreatment Q_{max} − Pretreatment Q_{max}. Scores were categorized: (1) Excellent response >10, (2) good response = 5–10, (3) fair response ≥ 2.5–5, and (4) poor response <2.5. The overall efficacy was calculated as the median grade of the three aspects and was considered effective for excellent and good grades and ineffective for fair and poor grades.[4,5]

Statistical analysis

For data analysis, we used IBM SPSS software package version 21 **(**Armonk, NY, USA: IBM Corp**)**. We used the Kolmogorov–Smirnov test to verify the normality of the data distribution. Quantitative data were described using the median and range. The Mann–Whitney *U* or Chi-square test was used, and logistic regression analysis was performed to determine the independent factors of ineffective treatment. Receiver operating characteristic (ROC) curve analysis was performed for the parameters that have a significant difference to identify the predictive performance of sonographic parameters. *P* < 0.05 was accepted to indicate a significant difference.

RESULTS

Seven-hundred and fifty patients completed the follow-up. The median age of the patients was 57 (50–66) years. The median total PSA was 1.4 (0.5–3.9) ng/ml. Comparison of baseline IPSS and QoL scores and Q_{max} values with scores at the end of the study revealed that Tamsulosin led to a significant improvement in the IPSS, QoL score, and Q_{max} values (*P* < 0.001), as shown in Table 1. The overall treatment efficacy rates were 70% (525 cases) for the effective group and 30% (225 cases) for the ineffective group. Patients in the ineffective treatment group experienced significantly higher IPSS (*P* < 0.001), IPP (*P* < 0.001), and lower Q_{max} (*P* < 0.001), as shown in Table 2. Regarding the sonographic parameters, BWT and UEBW were not significantly related to monotherapy failure. IPP of the three studied parameters was significantly related to treatment failure. Moreover, the total and transitional PVs were of a highly significant [Table 3]. Logistic regression analysis was performed to determine the independent factors of ineffective treatment. The ROC curve was significant for the IPP parameter. The area under the curve was (0.866) using a cutoff value of 8.2 mm. Using this cutoff value (with 95% confidence interval), both positive and negative predictive values were 73.3% and 98.18%, respectively.

DISCUSSION

Troublesome symptoms included urinary frequency, urgency, urinary incontinence, and nocturia. Those patients with LUTS were frequently bothered by voiding and bladder outlet obstruction (BOO) symptoms as decreased urinary flow and incomplete bladder emptying.[6] The response to alpha-blockers is variable, and the identification of baseline parameters that can predict the treatment outcomes is mandatory.[7] Noninvasive methods to diagnose BPO included several parameters:

(1) symptom evaluation (IPSS); (2) PSA measurement; (3) ultrasonography (US)-derived parameters, such as PV and BWT; and (4) IPP.[3,4] Most urologists use the US estimation of the prostate size and PVR with uroflowmetry to determine the presence of BPO. At the same time, the use of IPSS has its limitations regarding its specificity.[8] At the same time, prostate size and PVR measurements are not crucial for an obstruction diagnosis. Studies have shown that the urinary flow rate is the best predictor of BPO. Moreover, ultrasound estimated prostate weight and the TZV could predict obstruction.[9,10] Compensatory changes cause an increase in BWT and BW following BOO[11] and can be measured by US.[12] Many studies have concluded that BWT may be correlated with the grade of obstruction.[13,14] These discrepancies may originate from the use of different sonographic measurement techniques. Oelke *et al*.[15] concluded that BWT decreased rapidly throughout the initial bladder filling and then reached a plateau phase after the first 250 ml. There is disagreement on the best cutoff value of BWT that can be used to diagnose BPO. For the diagnosis of BPO, Manieri *et al*.[16] used 5 mm as a cutoff point for BWT, while, Kessler *et al*.[17] stated that BWT 2.9 mm is the best cutoff point for the diagnosis of BPO. Park *et al*.[18] investigated the relationship between BWT and responses of LUTS to Tamsulosin therapy in patients with BPE and found a negative correlation between the response of the IPSS score and BWT. Moreover, Salah Azab and Elsheikh[19] found that alfuzosin was less effective after 8 weeks of treatment in patients with BWT >5 mm, which confirms the negative correlation between posttreatment BWT and IPSS score improvements and PVR and Q_{max}. According to our results, patients who had ineffective treatment outcomes did not experience significantly higher BWT than patients with effective treatment outcomes at the same bladder volume. This finding may be because the early response of the BWT to BPE is variable across patients. Furthermore, the patient cohorts consisted of only 74 in Park *et al*.[18] and 125 in the Salah Azab and Elsheikh[19] study, which may reflect Type II statistical errors. Measuring UEBW reflects bladder hypertrophy grade and allows patients with LUTS to be evaluated according to bladder hypertrophy.[20] Kojima *et al*.[21] reported that by using a cutoff value of 35.0 g, UEBW predicted the infra-vesical obstruction in 86% of patients. Furthermore, Ochiai and Kojima[22] reported that UEBW was higher in BPE patients (range 15.3–129.5 g) than in those with a normal prostate (range 11.1–58.1 g) and that there was a significant correlation between UEBW and the IPSS symptom scores, PVR, and PV. According to our results, UEBW ranged from 22.9 to 43.7 g, with a median of 32.4 g in the studied patients. Although it was

Table 1: Effect of tamsulosin therapy on the International Prostate Symptoms score, quality of life score and Qmax values

	Total (*n*=750), *n* (%)	Effective (*n*=525), *n* (%)	Ineffective (*n*=225), *n* (%)	Test of significant	*P*
Symptoms (posttreatment I-PSS/pretreatment I-PSS)					
Excellent (≤0.25)	218 (29.1)	218 (41.5)	0	χ^2=750.0*	<0.001*
Good (>0.25-≤0.5)	307 (40.9)	307 (58.5)	0		
Fair (>0.5-≤0.75)	225 (30.0)	0	225 (100)		
Poor (>0.75)	0	0	0		
Minimum-maximum	0.16-0.75	0.16-0.50	0.54-0.75	U=0.0*	<0.001*
Median (IQR)	0.41 (0.23-0.58)	0.31 (0.21-0.42)	0.63 (0.60-0.68)		
QoL (pretreatment QoL score minus posttreatment QoL score)					
Excellent (4-6)	61 (8.1)	61 (11.6)	0	χ^2=463.820*	<0.001*
Good (3)	382 (50.9)	382 (72.8)	0		
Fair (1-2)	307 (40.9)	82 (15.6)	225 (100)		
Poor (0)	0	0	0		
Minimum-maximum	1.0-4.0	1.0-4.0	1.0-2.0	U=9315.0*	<0.001*
Median (IQR)	3.0 (2.0-3.0)	3.0 (3.0-3.0)	1.0 (1.0-2.0)		
Posttreatment Qmax minus pretreatment Qmax					
Excellent	0	0	0	χ^2=680.556*	<0.001*
Good (5-10)	540 (72)	525 (100)	15 (6.7)		
Fair (≥2.5-5)	105 (14)	0	105 (46.7)		
Poor (<2.5)	105 (14)	0	105 (46.7)		
Minimum-maximum	2.10-10.0	5.0-10.0	2.10-5.0	U=217.50*	<0.001*
Median (IQR)	5.80 (4.0-7.0)	6.20 (5.60-7.20)	2.90 (2.30-4.0)		

χ^2, *P*: χ^2 and *P* values for Chi-square test for comparing between the two groups, *U*, *P*: *U* and *P* values for Mann-Whitney test for comparing between the two groups. *Statistically significant at *P*≤0.05. I-PSS: International prostate symptom score, QOL: Quality of life

Table 2: Comparison between the effective and ineffective groups according to Q max, quality of life

	Total (*n*=750)	Effective (*n*=525)	Ineffective (*n*=225)	*U*	*P*
Qmax (ml/s)					
Pre					
Minimum-maximum	7.0-13.0	8.50-13.0	7.0-9.0	2557.50*	<0.001*
Median (IQR)	9.20 (8.50-10.40)	10.0 (9.0-11.0)	8.0 (7.0-8.50)		
Post					
Minimum-maximum	9.10-19.0	14.0-19.0	9.10-13.0	0.0*	<0.001*
Median (IQR)	16.0 (12.20-17.40)	16.50 (15.80-17.5)	10.90 (9.70-12.0)		
P_1	<0.001*	<0.001*	<0.001*		
Qol score					
Pre					
Minimum-maximum	3.0-6.0	3.0-6.0	4.0-4.0	48375.0*	<0.001*
Median (IQR)	4.0 (4.0-4.0)	4.0 (3.0-4.0)	4.0		
Post					
Minimum-maximum	0.0-3.0	0.0-3.0	2.0-3.0	9315.0*	<0.001*
Median (IQR)	1.0 (0.0-2.0)	1.0 (0.0-1.0)	3.0 (2.0-3.0)		
P_1	<0.001*	<0.001*	<0.001*		
IPSS					
Pre					
Minimum-maximum	17.0-26.0	17.0-24.0	19.0-26.0	18105.0*	<0.001*
Median (IQR)	19.0 (18.0-21.0)	19.0 (17.0-20.0)	21.0 (20.0-24.0)		
Post					
Minimum-maximum	3.0-18.0	3.0-9.0	12.0-18.0	0.0*	<0.001*
Median (IQR)	8.0 (4.0-12.0)	6.0 (4.0-8.0)	14.0 (13.0-15.0)		
P_1	<0.001*	<0.001*	<0.001*		

U, *P*: *U* and *P* values for Mann-Whitney test for comparing between the two groups. P_1: *P* value for Wilcoxon signed-ranks test for comparing between pre- and post-in each group. *Statistically significant at *P*≤0.05. IQR: Interquartile range, QOL: Quality of life, I-PSS: International prostate symptom score

higher, UEBW was not significantly higher in the ineffective treatment group compared to the effective treatment group. This finding could be ascribed to the fact that there was a Type II statistical error in the previous studies due to an insufficient number of patients. The intravesical prostatic protrusion (IPP) can be measured by the TRUS.[23] Seo and Kim[3] concluded that in the presence of IPP, alfuzosin was less effective in improving PVR, IPSS, and Q_{max}. Moreover, Park *et al*.[2] showed that Tamsulosin was less effective in facilitating improvement in clinical symptoms in patients with moderate or severe IPP than in those with mild IPP. Our results confirm a negative correlation between Q_{max} and IPP. In addition, IP*P* values (*P* < 0.05) were found to be significantly correlated with pretreatment IPSS values

Table 3: Sonographic parameters in relation to treatment failure

	Total (*n*=750)	Effective (*n*=525)	Ineffective (*n*=225)	*U*	*P*
TPV (cm³)					
Minimum-maximum	31.0-44.80	31.0-44.80	37.80-44.40	11302.50*	<0.001*
Median (IQR)	37.60 (34.0-40.70)	35.20 (33.6-38.0)	41.60 (39.8-42.8)		
TZV (cm³)					
Minimum-maximum	18.50-27.50	18.50-27.20	21.50-27.50	21487.50*	<0.001*
Median (IQR)	22.40 (20.40-25.0)	20.70 (19.70-23.5)	25.0 (19.70-23.5)		
TZI TZV/TPV					
Minimum-maximum	0.48-0.73	0.48-0.73	0.52-0.65	57682.50	0.611
Median (IQR)	0.60 (0.55-0.63)	0.60 (0.55-0.65)	0.61 (0.56-0.63)		
BWT (mm)					
Minimum-maximum	3.70-10.90	3.80-10.20	3.70-10.90	55995.0	0.259
Median (IQR)	7.20 (6.20-9.10)	7.30 (6.20-9.20)	7.60 (6.30-9.10)		
UEBW (g)					
Minimum-maximum	22.90-43.70	22.90-40.70	24.70-43.70	57849.0	0.655
Median (IQR)	32.40 (27.10-35.0)	30.60 (27.15-35.0)	32.70 (27.1-34.8)		
IPP (mm)					
Minimum-maximum	0.0-12.40	0.0-12.30	8.80-12.40	15862.50*	<0.001*
Median (IQR)	7.0 (2.50-10.20)	4.0 (1.8-7.1)	10.20 (9.0-11.6)		

U, *P*: U and *P* values for Mann-Whitney test for comparing between the two groups. *Statistically significant at *P*≤0.05. BWT: Bladder wall thickness, TPV: Total prostate volume, TZV: Transitional zone volume, TZI: Transitional zone index, IPP: Intra vesical prostate protrusion, UEBW: Ultrasound-estimated bladder weight, IQR: Inter quartile range

and posttreatment IPSS changes. Keqin *et al*.[24] and Reis *et al*.[25] reported that the ROC curves of IPP yielded an area under the curve of 0.858 and 0.758, respectively. Moreover, Keqin *et al*.[24] reported that the best cutoff value for IPP to predict medical treatment failure was 7.5 mm, while our cutoff value was 8.2 mm. Our results indicate that patients in the ineffective group had higher levels of IPP, which significantly correlated with Q_{max} and symptom severity. This observation can be used for the identification of inappropriate candidates for alpha1-adrenergic receptor (AR) antagonist monotherapy. For patients with LUTS/BPE and a baseline IPP >8.2 mm, alpha-AR antagonist monotherapy appeared to be ineffective for improving symptoms. In our previous study using 45 patients with BPE,[26] we concluded that sonographic parameters (BWT, UEBW, and IPP) can be used to predict alpha-blocker monotherapy failure in BPO patients, and we found that these three parameters significantly correlated with monotherapy failure. These findings were found to have a statistical error type II after completing our results with 750 patients. In this study, the BWT and UEBW increased with monotherapy failure, but they were not significant. This finding may be explained by the individual response to the intravesical obstruction. At the same time, the IPP was only found to be significantly associated with monotherapy failure, which may be related to an anatomical obstruction that would not have changed with medical treatment.

Limitations of this study

A 6-month follow-up may not be sufficient to determine whether to continue or discontinue medical treatment. This study lacked a control arm.

CONCLUSION

The combined use of sonographic parameters, BW, bladder thickness, and USEBW did not increase the predictive ability of alpha-blocker monotherapy failure in benign prostate obstruction patients. Only intravesical prostatic protrusion correlated with treatment failure at a baseline of >8.2 mm.

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Conflicts of interest
There are no conflicts of interest.

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