Original Article

Prostate Volume and PSA Cutoff Values as Predictive Indices for Success of Doxazocin Treatment in BPH in GHRDS

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is a non malignant enlargement of the prostate. This study was conducted to determine the pattern of presentation of BPH with and without acute urinary retention (AUR) and to determine the risk factors for acute urinary retention, in addition, to assess the results of doxazosin in the treatment of BPH with and without AUR.

Patients and methods: Ninety two patients were enrolled in this study. All patients presented to the emergency department and the referred clinic of the Gezira Hospital for Renal Disease and Surgery (GHRDS) with lower urinary tract symptoms with and without acute urinary retention suggestive of BPH were evaluated according to the European guidelines. All of them underwent trans-rectal ultra sound and measurement for the prostatic volume. Serum PSA level was estimated. Doxazosin was given to all patients and they were followed for twelve weeks. A trial without a catheter at the end of the first week was attempted for patients with acute urinary retention.

Results: The patients' mean age ± SD at baseline was 67.8 ± 7.7 and 69.4 ± 9.9 for Non-AUR/BPH and AUR/BPH respectively. Comparing baseline clinical parameters of patients with and without acute urinary retention revealed that IPSS, prostate volume and PSA level are significantly different between the two groups with P< 0.01, 0.01 and 0.00 respectively. In the TWOC, 65% of patients passed urine spontaneously. By the end of the study, the overall response of patients showed 78.9% successful rate (n=73) and 21.1% failure rate (n=19). Prostatic volume and PSA level were found to affect doxazosin treatment significantly. With cutoff values of 41cc and (3.45) ng/ml, prostatic volume and PSA level influenced doxazosin treatment failure.

Conclusion: Serum PSA and prostate volume are powerful predictors of the risk of AUR. Alpha blockers are efficacious in treating retaining and non-retaining BPH patients. Knowledge of baseline serum PSA and/or prostate volume are useful tools to aid physicians and decision makers in predicting the risk of BPH-related outcomes and choosing dexazosin as therapy for BPH.

Keywords: BPH, AUR, doxazosin, Sudanese

Benign prostatic hyperplasia (BPH) is a common disease that has been reported to occur in 19-30% of men older than 50 years[1.] Long-term consequences of the disease may include acute urinary retention (AUR) and the need for surgery, as well as urinary tract infection, bladder function deterioration, and rarely renal failure due to obstruction[2-4].

In addition to symptom severity, the serum prostate-specific antigen (PSA) level and prostate volume (PV) have been described as significant prognostic factors that predict treatment outcome in patients with lower urinary tract symptoms due to BPH treated with either a 5-alpha-reductase inhibitor or placebo[5–9].

Alpha blockade became established as a therapy for BPH on the basis of its effects on symptoms and flow rates. The benefits of α1-blockade therapy appear shortly after starting therapy due to the alteration in dynamic smooth muscle tension within the prostate and the bladder neck[10]. With regard to BPH progression; a number of studies have examined the effect of the α1-blocker alfuzosin on the risk of AUR. However, none have shown conclusively that there is a risk reduction[11.]

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This study aimed to evaluate the pattern of presentation of BPH in Gezira State, Central Sudan, and to assess the results of the use of doxazosin in both Non-AUR/BPH and AUR/BPH patients, as well as, to identify the factors that might be associated with the clinical progression of the disease on the overall response for α1-blockers in the treatment of BPH.

MATERIAL AND METHODS

This is a prospective observational analytical study conducted in Gezira Hospital for Renal Disease and Surgery (GHRDS) in the period from June 2006 to December 2006. GHRDS provides service for a large number of patients in a wide geographical area. We used IPSS points ranging from (0-35) for the assessment of LUTS. All the study subjects gave informed consent to the study, which was approved by the Institutional Medical Ethics Review Board of the University of Gezira.

Trans-rectal ultra sound was performed to estimate the prostatic volume and exclude any other co-morbidity. Width, height, and depth were measured and the volume calculated using the formula; volume = width× height × depth × 0.5 (all dimensions measured in cm). Physical examinations and routine heamtologic and serum chemistry tests were performed yearly. Patients receiving alpha blocking agents or antiandrogens and patients with prostate cancer, prostatitis, previous prostate surgery/invasive therapy, clinical neurological defect, gross haematuria, bladder stone evidenced by U/S or taking anti-androgen therapy were excluded.

For the present analysis, all patients were given doxazosin (α1-blocker) starting with small dose of 1-2 mg and increased to a fixed dose of 4 mg to the end of the study. Non AUR/BPH were given the drug for 12 weeks (six weeks intervals), while the AUR/BPH patients were followed for one week without catheter intervention. The drug was administered to non AUR and to AUR patients who successfully passed the urine one week after follow up without catheter intervention. Responsiveness of treatment was indicated by the one level reduction of IPSS and completion of the period without complications or serious side effects.

Blood samples were collected in 5 ml sterile vacutainers containing ethylene diamine tetra acetic acid (EDTA). After blood clotting, the samples were centrifuged within 20 minutes after collection at 500 x g for 10 min, and sera were stored at -20 ºC until assay.

The total prostate-specific antigens were assessed using an immunoradiometric assay (Skybio, London, UK) based on two anti-PSA antibodies: ^{125}I- labeled and other one as solid phase. All tubes were counted for 100 seconds on multi-well gamma counter and data was processed by a computer program.

The mean, STD and minimum and maximum values were calculated and the baseline parameters values in (none-AUR) and (AUR) groups were analysed using student unpaired t-test. Receiver operating characteristic curve (ROC) used to test the impact of the prostate volume and PSA on the response of those patients to doxazosin. Particularly to test their implication on patients who did not respond. All data were analyzed by using the SPSS computer program and the $P<0.05$ was considered to be statistically significant.

RESULTS

In this study, patients came from different nearby and distant states. The majority of patients came from the Gezira and central states. BPH patients comprised almost 40% of all patients presented to the emergency department and referral clinic. 92 Sudanese patients complaining of lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) were included in this study. After reviewing and analyzing the pattern of presentation, we found that 21.7% (n=20) of patients presented with acute urinary retention due to benign prostatic hyperplasia (AUR/BPH) while 78.3% (n=72) of patients presented with symptoms of benign prostatic hyperplasia without acute urinary retention (Non-AUR/BPH).

The patients' mean age ± SD at baseline was 67.8 ± 7.7 and 69.4 ± 9.9 for Non-AUR/BPH

and AUR/BPH respectively, and the follow up was 12 weeks for the doxazosin (α1-blocker). A significant deference (P< 0.01) was reported for the mean of total IPSS points at baseline for AUR/BPH and Non AUR/BPH which were 27.5 ± 7.8 and 21.8 ± 6.1 respectively **(Table 1)**.

Table (1): Illustrating different parameters in Non- AUR /BPH & AUR/BPH patients.

Parameters	Non-AUR n=72 Mean ± SD	AUR n=20 Mean ± SD	Significance
Age	67.8 ± 7.7	69.4 ± 9.9	0.32
Prostate volume	43.4 ± 15.6	55.3 ± 25.1	0.01
PSA	3.4 ± 2.1	5.7 ± 2.7	0.00
IPSS (baseline)	21.8 ± 6.1	27.5 ± 7.8	0.01

Significant p value less than 0.05

Prostate volume was measured by transrectal ultrasound, the frequency of prostate volume measured >40cc comprises 45.8% for patients with Non-AUR/BPH and 75% for patients with AUR/BPH, the frequency of prostate volume and the presentation of IPSS in Non-AUR/BPH were shown in **(Table 2)**.

Table (2): The frequency of different groups of prostate volume in Non-AUR/BPH patients & AUR/BPH patients (n 92)

Prostate volume group	Non-AUR (%)	AUR (%)	Total
Less than 20cc	1.4	0	1.1%
20cc – 40cc	52.8	25.0	46.7%
>40cc	45.8	75	52.2%

P value 0.037

In this study, as shown in **Table 1**, there is a significant difference in the mean of prostate volume and the PSA level (P<0.01 & P< 0.00) between Non-AUR/BPH (43.4 ± 15.6 cc & 3.4 ± 2.1 ng/ml) and AUR/ BPH (55.3 ± 25.1 cc & 5.7 ± 2.7 ng/ml) respectively.
In a trial without a catheter (TWOC) after one week of treatment by doxazosin, 65% (13/20) of the AUR/BPH patients succeeded in passing urine spontaneously and continued to have the drug to the end of the period of the study, while 35% (7/20) of them failed to do that and stopped taking the drug and treated surgically.

A total of 85 BPH patients (72 with Non-AUR/BPH, 13 with AUR/BPH) were followed up for 12 weeks and their response to doxazosin was assessed by the IPSS points **(Figure 1)** and the reduction of the obstructive symptoms **(Figure 2)**.

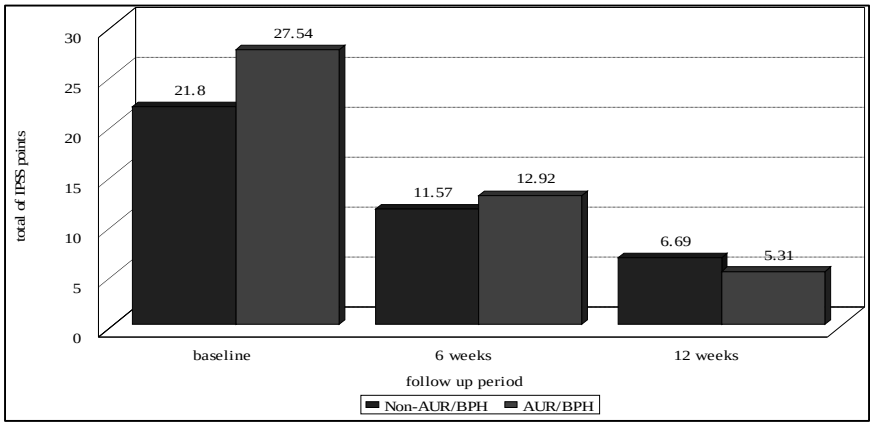

Figure (1): Response of total IPSS in Non-AUR/BPH & AUR/BPH patients (n=85)

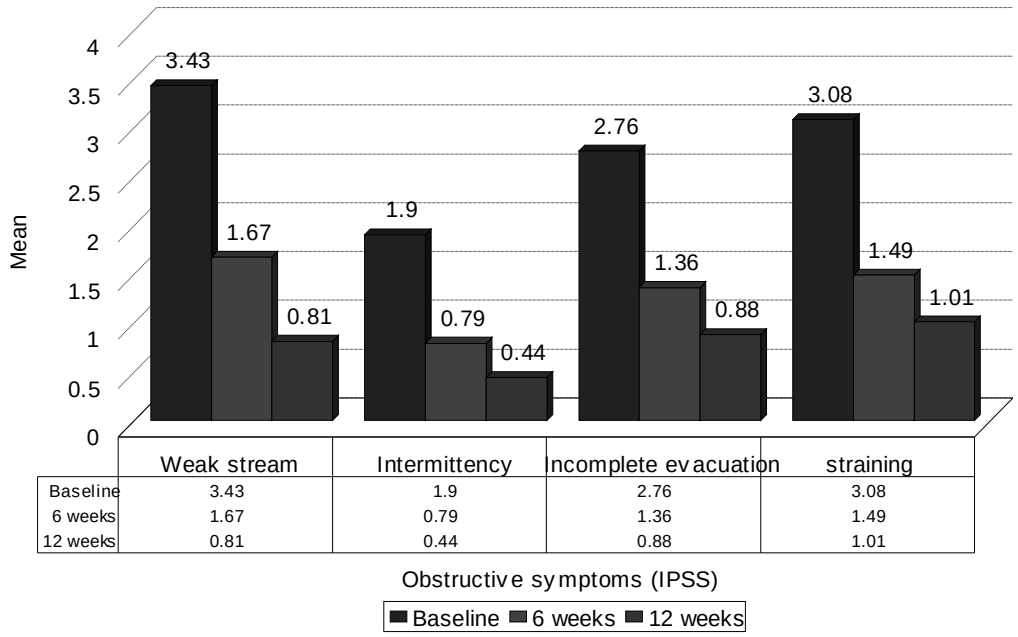

Figure (2): Response of different obstructive symptoms (IPSS) in Non-AUR/BPH patients (n=72)

Prostatic volume and PSA levels were tested to identify their impact and magnitude on determining the state of non-response which showed by those 16% (10/72) of patients with Non-AUR/BPH and 10% (2/13). There is a significant difference (P<0.01) in the mean of PSA between responded (3.2 ± 1.8 ng/ml) and non responded (5.1 ± 2.1 ng/ml) Non-AUR/BPH patients. While the prostate volume reported significant difference (P<0.05) between AUR/BPH patients responded or not responded to TWOC (Table 3).

Table (3): Means of the PSA level and prostate volume in AUR and Non-AUR/BPH patients who responded and did not respond to doxazosin.

BPH at presentation		Responded to treatment		Did not responded to treatment at 12 weeks	
		No (%)	Mean ± SD	No (%)	Mean ± SD
Non-AUR/BPH (n=72)	PSA level	62 (86)	3.2 ± 1.8	10 (14)	5.1 ± 2.8*
	Prostate Vol.		43.2 ± 16.0		44.8 ± 13.3
AUR/BPH (n=20)	PSA level	11 (55)		9 (45)	
	TWOC	13 (65)		7 (35)	

We used the ROC curve also to test the sensitivity of measuring the prostatic volume and the baseline PSA level in determining the state of no response to treatment with doxazosin. As shown in (Figure 3), the two lines representing the two tests appear to the left of the reference diagonal line and close to the Y axis (sensitivity), which confirms their sensitivity in determining doxazosin treatment failure. Area under the curve for the prostatic volume measurement is 0.663 and the cutoff value selected is ≥ 41cc, above which the probability of doxazosin treatment failure increases dramatically.

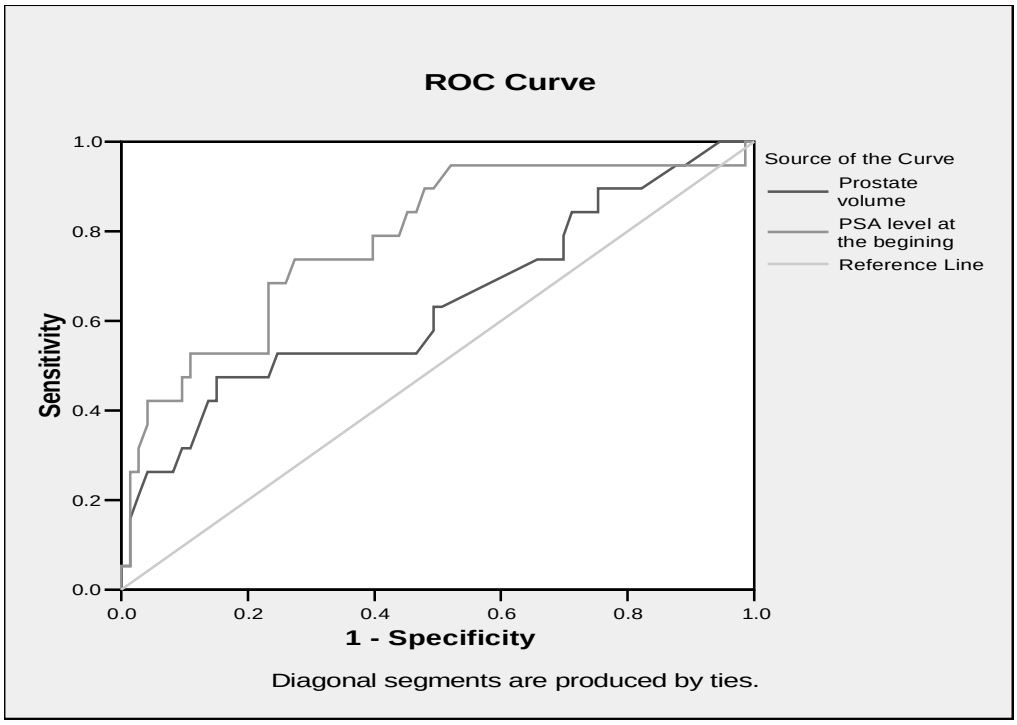

Figure (3): ROC curve illustrating sensitivity of the PSA level and the prostatic volume in determining the state of non response to doxazosin

The estimated area under the curve for PSA level is 0.783 and the cutoff value selected is ≥ 3.45ng/ml. The probability for doxazosin treatment failure increases in levels more than that.

Discussion:

Serum PSA is currently the most widely used marker for prostate cancer detection, and a yearly measurement is recommended in men older than 50 years to aid in the early detection of prostate cancer. The observation that there is a strong loglinear relationship between serum PSA and prostate volume in men with BPH[12] has led us to consider that PSA may also predict those men at increased risk of developing AUR or needing BPH related surgery.

BPH presentation with severe symptoms and complication can only be explained by the lack of knowledge about the disease among patients and junior doctors. The small size of the sample might give an explanation but still there is a high rate of late presentation. The observed high level of IPSS severity associated with patients with AUR/BPH is comparable to results considered severe IPSS as one of the strong predictors for BPH progression[13, 14].

Prostate volume was found to be different in patients with BPH with and without AUR. Larger volumes are more frequent among patients with AUR. This difference is statistically highly significant. In addition, we observed statistically significant correlation between prostate volume and PSA level (p value 0.00). Larger prostate volume was also found to be more in AUR/BPH patients who did not respond to doxazosin ($p < 0.05$). Therefore, we can consider prostate volume as a predictor for BPH disease progression and a factor that influence response to doxazosin treatment. In our study, we found strong correlation between PSA and the prostate volume estimated by TRUS. In this study, PSA level of 4-10 ng/ml was considered highly suggestive for BPH. When we subjected PSA level in patients with BPH (with or without AUR) we observed higher

levels of PSA in the group with Non-AUR/BPH and it was highly statistically significant ($p< 0.01$). In the AUR/BPH patients we observed failure of trial without a catheter (TWOC) in 35% of patients who received doxazosin 4 mg orally. Another 10% of them showed no response and needed re-catheterization at the end of the study. In the literature, α-blockers like; phenoxybenzamine, Terazosin, tamsulozin, doxazosin and alfuzosin were tried to manage AUR. Nowadays, TWOC recommended as the first line of treatment for AUR/BPH in all patients. Our study gives estimation to the initial response of those patients to doxazosin and carried a short period of follow up to determine the maintenance of treatment without the need for re-catheterization. We think it needs longer period of follow up to determine the long-term effect of doxazosin in the treatment of patients with AUR/BPH. In this group of patients prostate volume estimated by trans-rectal ultrasound are significantly influencing the early failure of TWOC and we observed larger prostate volumes in AUR/BPH patients who failed to pass urine spontaneously after one week of treatment. In addition, PSA was found to be significantly high in patients who did not respond to doxazosin in the first week in comparison to those who responded. Age and IPSS were not statistically significant like prostate volume and PSA. Therefore, we considered PSA and prostate volume as strong predictors to TWOC (with doxazosin) failure in patients with AUR/BPH. In our study, the results of TWOC are more or less comparable to the results reached by many researchers[15-17].

In the Non-AUR/BPH patients, at the end of the study (12 weeks), 86.1% of patients responded well to treatment by doxazosin and showed marked and statistically significant reduction in IPSS points. However, doxazosin treatment maintained without serious side effects and complications. In the literature, a multi centre controlled trial conducted in Egypt to evaluate response to doxazosin; they reported improvement of the IPSS points from 19.55 (SD 5.27) to 9.25 (SD 3.77)[18].

In our study improvement in the IPSS points is from 21.8 (SD 6.09) to 6.7 (SD 7.2) at the end of the period. We observed side effects in 15% of patients. Despite the difference between our study which is an observational one, and that study which is an interventional one, results look comparable. The observed high rate of side effects in our study is probably due to the nature of the study, in which the criteria are more flexible accepting any complaint without critical measurement. While in the controlled trials more rigid criteria were implemented and more critical measurements were applied. When testing prostate volume and PSA level, we found patients with higher PSA levels didn't respond to doxazosin treatment with significant statistical difference between the two groups ($p<0.01$). Regarding the prostate volume we found it insignificant.

Previous studies have made a conclusion that serum PSA and prostate volume are powerful predictors of AUR and the need for BPH-related surgery[5, 19]. More over, Kurita confirmed that prostate volume and PSA predict treatment failure by tamsulozin[20].

In our study, we used the ROC curve, which confirmed the sensitivity of prostate volume and PSA in determining the probabilities of doxazosin treatment failure. A cutoff value of prostate volume of 41cc was proposed, above which we expect high probability of doxazosin treatment failure. On the other hand, 3.45ng/ml was proposed as a cutoff value for PSA. PSA level > 3.45 ng/ml carries high probability of doxazosin treatment failure. There is no agreement about the cutoff values above which we shift from doxazosin to other drug therapy or to surgery. According to the general consensus, 40cc volume considered as a cutoff value above which anti-androgen therapy is recommended. In one meeting, pioneers of urology who investigated this issue presented their experiences[12]. Roehrborn considered PSA >3.2 ng/ml and prostate volume >50cc as an indication for anti-androgen therapy. Lowe proposed prostate volume of >70cc and Lepor proposed >50cc as cutoff value. More

controlled studies are needed to evaluate these cutoff values.

Conclusion Prostatic volume and PSA level were found to be powerful predictors of the success of doxasocin treatment for BPH. A prostate volume of 41cc or less and a PSA level of (3.45) ng/ml constitute the cutoff values for the best response for doxasocin.

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