Original Article

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Sonographic Association and Prediction of Treatment Response to Medical Therapy in Patients with Benign Prostatic Hyperplasia: A Prospective Cohort Study

Surgery Section

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ABSTRACT

Introduction: Benign Prostatic Hyperplasia (BPH) is mainly managed with alpha-blocker and 5 alpha reductase inhibitors. Non responders are offered surgery. To wait for the drug response is sometimes cumbersome for the patients with bothersome symptoms and may also lead to complications. On the other hand, some have minimal symptoms on drugs but silently develop obstructive complications.

Aim: To understand the role of sonographic parameters of prostate and bladder of BPH patients in predicting and assessing response to medical treatment.

Materials and Methods: This prospective cohort study was conducted in the Department of Urology at Army Hospital Research and Referral, New Delhi, India. The duration of the study was 15 months, from October 2017 to January 2019. A total of 100 consecutive patients of BPH with Prostate-specific Antigen (PSA) <4 ng/mL and prostate of >35 cc were given three months of alpha-blocker and dutasteride. Based on there subjective response, they were grouped into Symptomatic Improved (SI) and Not Improved (NI) group. Values of sonographic parameters including Prostate Volume (PV), prostatic capsular artery Resistance Index (RI), Intravesical Protrusion of Prostate (IPP), Detrusor Wall Thickness (DWT) and Post-void Residual volume (PVR), as well as, International Prostate Symptom Score (IPSS) and Uroflowmetry (UFM) at baseline and after three months of treatment were analysed and compared in both the groups. The significance of change in parameters was analysed using paired t-test and two sample Student's t-test.

Results: The mean age of the study participants was 64.8±5.86 years. There was an association between IPSS and flow with initial reading of PV, PVR, DWT, RI and IPP. Post-treatment both, SI (n=74) and NI (n=26) group showed valuable difference in DWT, PV and PVR but it was significantly more in improved group. Significant change in RI was observed only in SI group and IPP did not change in either group. Area Under Curve (AUC) under Receiver Operating Characteristic (ROC) was suggestive of higher sensitivity for IPP in predicting drug outcome.

Conclusion: Combined use of Ultrasonography (USG) and Kidney, Ureter, and Bladder (KUB) parameters as described above like RI, DWT, PV and IPP can be used to predict and assess the objective response to drug in BPH. This helps in determining therapeutic plan and the need for further medical therapy or surgical intervention.

Keywords: Intravesical, Prostate, Resistive index, Ultrasound, Uroflowmetry

INTRODUCTION

The BPH is one of the commonest causes of Lower Urinary Tract Symptoms (LUTS) in old patients. With age the prevalence also rises. Approximately, the worldwide prevalence is 10% in 4th decade and 80% in 8th decade [1-4]. Initial evaluation of BPH includes IPSS, urine analysis, UFM, serum PSA and USG with PVR urine and for follow-up IPSS score, UFM and PVR are required. IPSS is an international scoring of prostate symptoms, developed for the initial evaluation of LUTS. It can classify the symptoms into mild, moderate and severe [3]. Management of mild LUTS due to BPH includes modification in fluid intake and voiding habits. For moderate to severe LUTS medical or surgical treatments are available [5]. Apart from this, there are absolute indications for surgery for BPH e.g., refractory retention, obstructive uropathy etc., [6].

Only the trial of drug can tell its true efficacy for that patient. It is difficult to predict the treatment response to medical therapy, based only on prostate size as atleast 25% to 30% of BPH patients with similar baseline parameters show no response to medical treatment [7]. Some patients continue to have bothersome LUTS on medical management and develop BPH related complications like bladder stones, hydronephrisis and urinary tract infections [8,9]. Some inspite of good subjective response silently develops obstructive complications [10]. So, to predict the drug response, better sonographic parameters are required. Inspite of poor predictor of invasive therapy, PVR is the most common sonographic parameter utilised to monitor treatment response in BPH, as it can be measured easily in office USG using simple bladder scanner [11,12]. Other USG parameters like RI and IPP are not routinely utilised in view of varying results in various studies [12,13]. The present study was done to establish the role of sonographic parameters of prostate and bladder of BPH patients in predicting and assessing response to medical treatment.

MATERIALS AND METHODS

The prospective cohort study was conducted in the Department of Urology at Army Hospital Research and Referral, New Delhi, India. The duration of the study was 15 months, from October 2017 to January 2019. The study protocol was cleared by Institute Ethical Committee (letter no. 72/2017 dated 23 Oct 2017). Informed consent were taken from all patients.

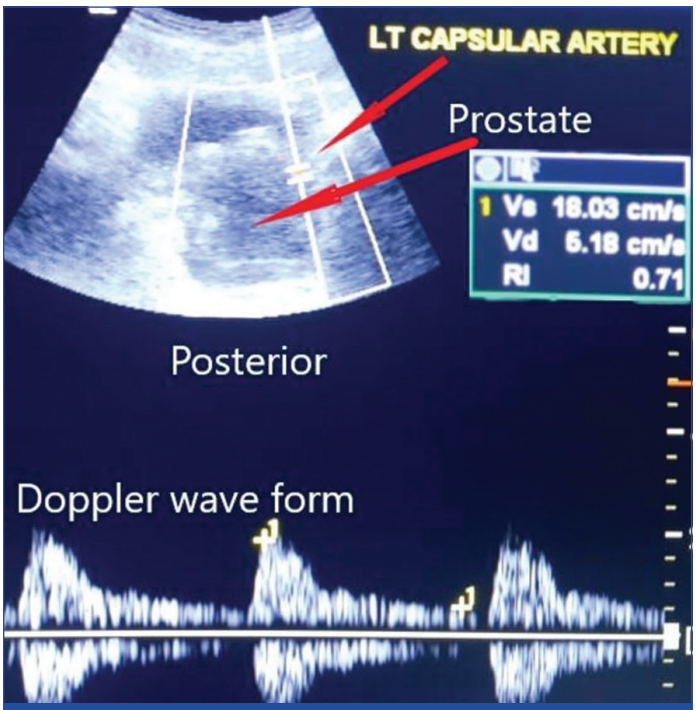
Inclusion criteria: All patients who presented with LUTS with prostate size of 35 cc or more and PSA <4 ng/mL were included in the study.

Exclusion criteria: Patients with the presence of other causes of LUTS like stricture urethra, Urinary Tract Infection (UTI), Carcinoma (Ca) prostate etc., were excluded from the study.

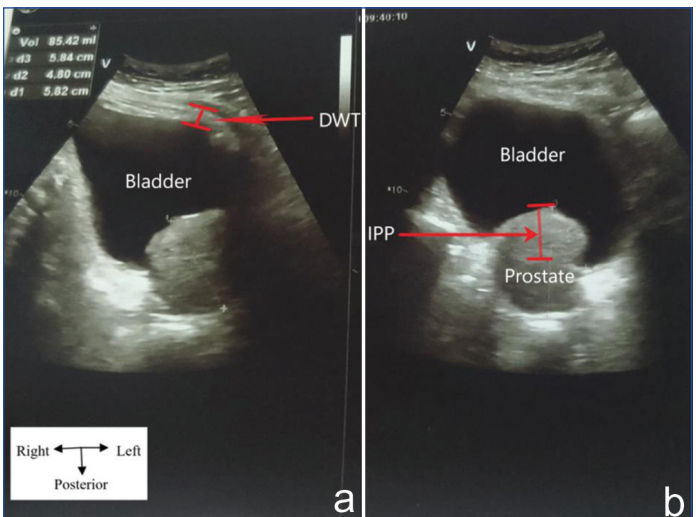
Sample size calculation: With 5% level of significance, 90% power of study, assuming the lost to follow-up up to 20% and by using difference in means in various sonographic parameters in previous studies the sample size calculated was 96 [14,15]. Considering the interruption of study due to various reasons and the availability of patients, 113 were analysed.

Study Procedure

During initial evaluation IPSS scoring was done. IPSS includes symptoms of incomplete voiding, urgency, frequency, nocturia, decreased urine flow, straining and intermittency. Each is given score from 0 to 5. Maximum IPSS symptom score is 35 and minimum is 0. Severity of symptoms were classified into mild (0-7), moderate (8-19), and severe (20-35) [16]. UFM (normal Q max is less than 15 mL/second) [17] and sonographic parameters of, prostatic capsular artery RI (normal RI is <0.70) [18] [Table/Fig-1], RI (normal IPP is <5 mm) [19] [Table/Fig-2a,b], DWT (normal DWT is 1.2 to 1.4 mm) [20], PV (normal PV is <25 cc) [21] and PVR Volume (normal PVR is 50 to 100 mL) were recorded [13].



[Table/Fig-1]: Resistive Index (RI) of left capsular prostatic artery calculated by using colour doppler ultrasound of prostate. Vs: Velocity systolic; Vd: Velocity diastolic.



[Table/Fig-2]: Abdominal ultrasound showing a) Detrusor Wall Thickness (DWT); b) Intravesical Protrusion of Prostate (IPP).

Patients were given alpha-blocker (tamsulosin 0.4 mg or alfuzosin 10 mg or silodosin 8 mg) with dutasteride 0.5 mg once a day for three months [9]. After three months, patients were asked about the improvement in symptoms and the response was recorded in 5-point Likert scale from 5-marked improvement, 4-moderate, 3-slight, 2-no improvement to 1-worsening of symptoms. Based on this, patients were divided into SI (Likert scale 4 and 5) and symptomatically NI group (Likert scale below 4) [22]. The baseline value of sonographic parameters and their change with treatment were analysed separately in both the groups.

STATISTICAL ANALYSIS

The changes in above parameters were tested in both the groups for significance using paired t-test. For comparison of change in parameters between, two sample Student's t-test was used. The p-value <0.05 was considered statistically significant. All statistical analysis was done using Statistical Package for Social Sciences (SPSS) software version 24.0.

RESULTS

In the present study, out of 113 treatment naïve patients of BPH, who were enrolled, 13 patients were excluded as three developed acute urinary retention, five were lost to follow-up, one patient developed postural hypotension, due to alpha-blocker, two patient opted for surgery and two developed UTI before completion of study. Finally, 100 patients were evaluated. Their mean age was 64.8±5.86 (48-76) years. At the time of presentation 99 patients had weak stream, 98 patients had incomplete bladder emptying, 96 showed intermittency and straining. A total of 60 patients had moderate and 40 had severe IPSS symptom score. After three months of medical management, patients were categorised as SI (n=74) and NI (n=26). [Table/Fig-3] shows normal, baseline and post-treatment values of various parameters. At baseline, the mean uroflow was 9.09±1.93 mL/s. All the patients showed statistically significant increase in the uroflow (Q max) values, but the SI group showed 96% increase in the uroflow values as compared to a 20% increase in the NI group. Normal values, baseline values and change in parameters.

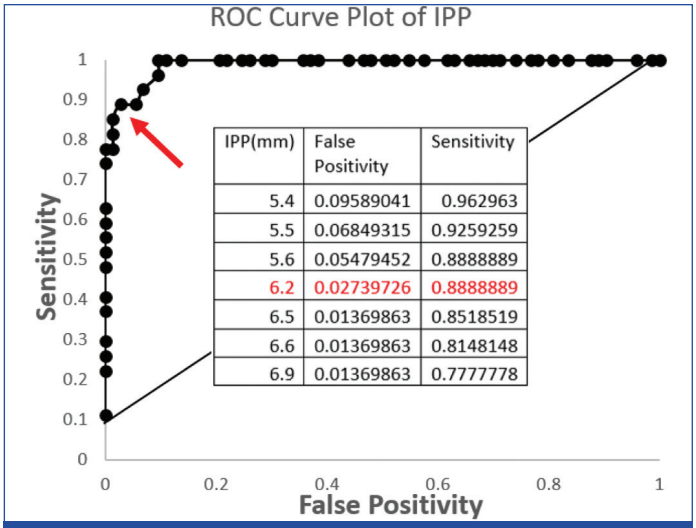
There was no significant difference in baseline RI between the groups (SI=0.76±0.06, NI=0.67±0.09). But the mean RI value was significantly decreased in the SI group (difference 0.15±0.06, p <0.0001*). It did not show significant decrease in NI group (difference 0.04±0.08, p=0.021) [Table/Fig-3]. The study population exhibited only a slight change in IPP value after three months of treatment in both the groups. However, the NI group patients had higher pretreatment mean IPP value (8.26±1.32 mm) as compared to the SI patients (3.40±1.41 mm). Mean value of DWT after treatment was significantly reduced in both the groups, it was 27% in SI group and 4% in NI group. Similarly, the mean values of prostatic weight and PVR of the patients, who showed symptomatic improvement were significantly decreased after three months of treatment in comparison to before treatment (p<0.0001). It was observed that, there was no significant difference in pre and post-treatment IPP in both the groups however, the mean baseline IPP was higher in NI group. The difference of pre and post-treatment values of DWT, PV and PVR showed significant difference in both the groups, but it was more in SI group. A 26% of patients in NI group had higher mean prostatic volume (44.3±7.04 cc), at the time of presentation as compared to SI group (38.91±4.86). Negative correlation was found between post-treatment difference in RI and Q max (r=-0.42) [Table/Fig-4] and unlike other parameters, which showed significant change with treatment in both the groups, RI showed significant post-treatment difference only in SI group. Strong correlation was found between post-treatment difference in prostate volume and Q max (r=-0.48; p<0.001), DWT and PVR (r=0.31; p<0.001) and DWT and Q max (r=-0.68). There was 27% decrease in value of DWT after treatment with decrease in PVR (95.46±29.68 vs 63.66±22.02, p<0.0001).

Parameters for BPH evaluation	Symptomatic response to three months treatment {SI (n=74), NI (n=26)}	Before treatment (mL/s) (Mean±SD)	After three months of treatment (mL/s) (Mean±SD)	Paired differences			t-value	p-value
				Δ (Mean±SD)	95% CI of the difference			
					Lower	Upper		
IPSS	Improved	17.07±3.47	8.86±2.35	8.2±3.65	7.36	9.05	19.34	<0.0001*
	Not improved	23.27±2.69	20.31±2.62	2.96±1.99	2.16	3.77	7.59	<0.0001*
	Overall	18.68±4.27	11.84±5.59	6.84±4.02	6.04	7.64	17.02	<0.0001*
UFM/Q max	Improved	8.52±1.65	16.7±1.45	-8.17±2.03	-8.64	-7.70	-34.57	<0.0001*
	Not improved	10.72±1.75	12.94±1.82	-2.22±2.49	-3.23	-1.22	-4.56	<0.0001*
	Overall	9.09±1.93	15.72±2.26	-6.63±3.39	-7.30	-5.95	-19.55	<0.0001*
RI	Improved	0.76±0.06	0.61±0.04	0.15±0.06	0.13	0.16	20.92	<0.0001*
	Not improved	0.67±0.09	0.63±0.09	0.04±0.08	0.01	0.07	2.46	0.021
	Overall	0.74±0.08	0.62±0.06	0.12±0.08	0.10	0.14	14.60	<0.0001*
IPP	Improved	3.40±1.41	3.22±1.26	0.18±2.04	-0.29	0.65	0.76	0.449
	Not improved	8.26±1.32	8.16±1.45	0.1±1.9	-0.67	0.86	0.26	0.798
	Overall	4.53±2.56	4.64±2.53	-0.11±2	-0.50	0.29	-0.54	0.588
DWT	Improved	5.63±0.92	4.11±1.12	1.51±0.43	1.41	1.61	30.47	<0.0001*
	Not improved	4.52±0.82	4.34±0.84	0.18±0.14	0.12	0.23	6.61	<0.0001*
	Overall	5.34±1.02	4.17±1.05	1.16±0.7	1.03	1.30	16.72	<0.0001*
PV	Improved	38.91±4.86	34.41±5.42	4.5±1.35	4.17	4.80	28.42	<0.0001*
	Not improved	44.3±7.04	40.56±6.54	3.74±2.78	2.57	5.11	6.7	<0.0001*
	Overall	40.31±5.9	36.03±6.3	4.29±1.8	3.91	4.64	23.09	<0.0001*
PVR	Improved	95.46±29.6	63.66±22	31.8±8.31	29.88	33.73	32.92	<0.0001*
	Not improved	99.48±17.5	81.18±22	18.30±9.2	14.56	22.03	10.090	<0.0001*
	Overall	96.50±27.0	68.21±23	28.29±10	26.23	30.35	27.228	<0.0001*

[Table/Fig-3]: Comparison of mean value of various parameters in Symptomatic Improved (SI) and Not Improved (NI) groups.
Δ=(Before treatment-After three months of treatment); *comparison done using Student's t-test and paired t-test with p-value <0.05 considered statistically significant. UFM: Uroflowmetry; IPSS: International Prostate Symptom Score; RI: Resistive index of prostatic capsular artery; IPP: Intravesicle prostatic protrusion; DWT: Detrusor wall thickness; PV: Prostate volume; PVR: Post-void residue

Post-treatment change in parameters	Δ PV	Δ RI	Δ IPP	Δ DWT
Δ Q max	-0.48 (p<0.001)	-0.42 (p<0.001)	-0.18 (p=0.036)	-0.68 (p<0.001)
Δ PVR	-0.16 (p=0.055)	-0.13 (p=0.098)	-0.1 (p=0.16)	0.31 (p<0.001)
Δ IPSS	0.28 (p=0.002)	0.25 (p=0.006)	0.01 (p=0.46)	0.44 (p<0.001)

[Table/Fig-4]: Correlation coefficient (r) with p-value between change in parameters.
Δ=Difference between pre and post-treatment readings ; UFM: Uroflowmetry; IPSS: International Prostate Symptom Score; RI: Resistive index of prostatic capsular artery; IPP: Intravesicle prostatic protrusion; DWT: Detrusor wall thickness; PV: Prostate volume; PVR: Post-void residue



[Table/Fig-5]: ROC plot of IPP values showing higher sensitivity and lower false positivity at cut-off of 6.2 mm for predicting failure of medical management.

Positive correlation was established between change in IPSS and PV, RI and DWT [Table/Fig-4]. There was no significant correlation found in post-treatment change of IPP with changes in Q max, PVR and IPSS scoring however, negative correlation was found between baseline IPP and post-treatment Q max (r=-0.66, p<0.001). The data supports that, higher IPP at baseline correlates with no improvement of symptoms (r=0.84, p<0.001) in patients with BPH. The ROC plot for pretreatment IPP [Table/Fig-5] showed AUC of > 0.8 with the cut-off value of 6.2 mm. The ROC curve of other parameters had an insignificant AUC (<0.5).

DISCUSSION

The BPH is one of the most common presentation in the OPD of Urology, causing LUTS [1]. For mild LUTS, modification in drinking and voiding habits is sufficient whereas, for moderate to severe LUTS either medical or surgical treatment is done [5]. In the absence of absolute indications for surgery, medical treatment in the form of alpha-blocker is given and 5 alpha reductase inhibitors (5-ARI) is, added for larger prostate [8,9]. Since, 5-ARI takes some time to reduce prostate size and for optimal drug response [14,23], patients either continue to remain symptomatic during this period in anticipation for the symptoms to improve or have risk of developing complications like acute urinary retention, obstructive uropathy or UTI, which is not the desirable situation. Patients are followed-up using subjective, as well as, objective parameters like uroflow and ultrasound, as some patients may silently develop obstructive uropathy even with improved symptoms [10,24]. Although, PVR has been the most common parameter for follow-up, studies have shown no significant correlation between symptomatic improvement with changes in PVR, therefore, there is need to include other USG parameters with better clinical correlation and to predict patients, who may not respond to medical treatment so that, they can be offered an early surgery. Sonography parameters of bladder and prostate have been studied in the past, but only few studies have compared the change in these parameters with the drug therapy but because of inconsistent results these parameters have not been included in the treatment guidelines [Table/Fig 6] [15,25-31].

Studies	Year of study	Sample size	Results	Remarks and drawbacks
Ahmad AF et al., [15]	2015	166	The combined use of sonographic parameters BWT, UEBW and IPP may aid in identifying proper candidates for Alpha1-AR antagonist monotherapy and determining patients at high risk of treatment failure.	a. TRUS was used for initial evaluation instead of abdominal sonography which is more commonly used and is better tolerated. b. Patients with prostate size of less than 45 g were chosen, where medical therapy is usually successful. c. Change in sonographic parameters were not analysed in follow-up.
Kojima M et al., [25]	2000	140	The RI is promising as a new parameter to estimate the intraprostatic pressure to investigate BPH.	a. TRUS was used for initial evaluation instead of abdominal sonography, which is more commonly used and is better tolerated. b. Predictability of drug response was not checked. c. Other parameters were not considered. d. Change in RI was not analysed with treatment.
Ho C C et al., [26]	2014	62	UEBW was the strongest predictor of AUR.	a. Sample size was small. b. Drug response was not-tested.
Matsukawa Y et al., [27]	2017	103	Intravesical prostatic protrusion can be considered a useful predictor of therapeutic response to silodosin.	a. Study was an open label instead of placebo controlled. b. For larger prostate 5-ARI was not added. c. Other parameters were not analysed.
Radwan M et al., [28]	2021	750	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.	a. TRUS was used for IPP measurement instead of commonly used abdominal USG. b. 5-ARI was not used for larger prostate. c. RI was not analysed. d. Post-treatment changes in sonography parameters were not analysed.
Mazaheri M et al., [29]	2021	100	Bladder wall thickness and bladder weight were important to determine response to treatment and severity of disease.	Parameters like PV, PVR, RI were not assessed.
Gabr AH et al., [30]	2019-21	169	TZV/TPV ratio and VUA significantly correlate with the degree of BOO and seem to accurately predict the occurrence of AUR.	a. Only patients with AUR were analysed. b. Response to drugs were not evaluated. c. Other USG parameters were not analysed.
Salah AN et al., [31]	2016-17	45	Combined use of sonographic parameters BWT, UEBW and IPP can predict alpha 1 adreno receptor antagonist mono therapy outcome in BPH patients and aid in identifying proper candidates for therapy and determining patients at high risk of treatment failure.	a. Small sample size. b. For large prostate only tamsulosin was used instead of combination therapy. c. Transrectal USG was used instead of more common transabdominal USG.
Present study	2017-19	100	Sonographic parameters of prostate and bladder of BPH patients were evaluated in predicting and assessing response to medical treatment.	a. Adequate sample size. b. Combination treatment was given. c. Abdominal USG was used. d. Patients with low PV, IPP and DWT improved with medical treatment with IPP being the most sensitive marker of treatment outcome. In follow-up except IPP all the parameters showed reduction with treatment but reduction in RI was more specific for the group which improved with the treatment.

[Table/Fig-6]: Comparison of various studies done on the sonographic parameters in BPH patients [15,25-31].
UEBW: Ultrasound-estimated bladder weight; AR: Adrenergic receptors; AUR: Acute urinary retention; TZV: Transition zone volume; TPV: Total prostate volume; VUA: Vesico-urethral angle; BOO: Bladder outlet obstruction; TRUS: Transrectal ultrasound; PV: Prostate volume

In BPH, prostatic artery RI is elevated due to obstructive blood flow because of the increased intraprostatic pressure due to enlarging gland surrounded by an unyielding capsule. The present study established that, the reduction in RI with treatment significantly correlates with decrease in IPSS and increase in Q max. Various studies have demonstrated that, higher RI is a risk factor for acute urinary retention [18]. Kojima M et al., in an observational study in 140 participants in the year 2000, showed significantly higher RI in patients of BPH (0.72+/-0.06, p<0.0001) compared to the patients with a normal prostate (0.6+/- 0.04) [25]. Puthenveetil RT et al., in a study on 100 patients of BPH, showed a decrease in 25% in RI with the medical management [32]. In the present study, there was no significant difference in baseline RI between the groups. However, there was significant change (p<0.001) of RI after treatment only in SI group. The mean reduction in the RI values was 20% with simultaneous reduction in IPSS score and improved uroflow readings. This decrease in RI can be explained by a decrease in intraprostatic pressure.

In BPH, there is detrusor muscle hypertrophy to overcome distal obstruction. Muscle is hypoechoic, while serosa and mucosa are hyperechoic in sonography. The thickness of this hypoechoic layer is DWT [33]. Basri C et al., in 2010 retrospectively analysed 152 patients results and found that DWT and PVR as predictors for grading the LUTS severity [34]. In the present study, both the groups have showed significant decrease in DWT. They demonstrated strong correlation between prostate volume and Q max (p<0.001), as well as, between DWT and PVR (p<0.001). The present study showed the patients, who improved symptomatically after three months of therapy showed increase in uroflow value and decrease in DWT (27% decrease in mean value) as compared to baseline. The reason for decrease in DWT was reduced outflow obstruction in treated patients. At baseline, there was no statistically significant difference in DWT between the groups. The reduction in DWT in SI group was significant (p<0.0001). Further, the findings were corroborated by decrease in PVR. Patients with no symptomatic releif, also demonstrated higher pretreatment DWT (p<0.0001). Only few studies have analysed change in bladder wall thickness with medical treatment [35].

IPP reduces urine flow by causing ball valve effect at the bladder neck [36]. Aganovic D et al., in 2010, analysed 111 patients of BPH and found that, higher values of IPP were indicative of severe LUTS and predictive of bladder outlet obstruction [36]. They concluded that, the IPP not only correlated well with BOO (positive predictive value 74%, specificity 81.4%) but also correlated well with the severity of obstruction as defined by the higher BOO index (p<0.001). In present study, the NI group had higher pretreatment IPP values as compared to the patients in SI group (p<0.001). ROC plot for pretreatment IPP showed AUC of >0.8 with the cut-off value of 6.2 mm. Above this value one can predict treatment failure with 88% sensitivity. This was not seen with other parameters

(AUC <0.50), which makes IPP as most sensitive predictor of treatment response.

Both SI and NI group showed insignificant change in IPP values after medical management (p value >0.001) therefore, the change in IPP values after treatment did not correlate with change in uroflow, PVR and IPSS. On the other hand, higher baseline value of IPP correlated well with decrease in uroflow (Qmax). This shows that, IPP does not reduce with medical management in comparison to TPV, which reduces by approximately 30% which makes baseline value of IPP more important in predicting treatment outcome and has less role in follow-up. The reason could be that, grade 3 IPP has low proportion of stromal component [37]. The present study is unique in comparing the change in IPP with treatment in SI and NI group.

Prostatic volume and PVR of the 74% patients in SI group were significantly different after three months of treatment in comparison with before treatment. The prostatic volume decreased after treatment (p<0.0001) and the PVR was also reduced after treatment (p<0.0001). This was consistent with improved IPSS score and better uroflow values. Also, the 26% patients of NI group were the ones, who had high mean prostatic volume at the time of presentation as compared to SI group (p<0.0001). This indicates that, symptomatic progression is more in patients with higher prostatic volume.

Limitation(s)

The present study was an open-label study, not a placebo-controlled study. Therefore, placebo effects cannot be excluded in terms of changes in subjective symptoms. Also, a longer follow-up was required to know whether the drug response was temporary or consistent.

CONCLUSION(S)

Successful outcome of medical therapy can be predicted in patients with low PV, PVR and IPP in baseline sonography. Of all these, IPP is the most sensitive parameter to predict the successful outcome. The present study showed that, change in PV, PVR, DWT and RI correlates with the treatment response and can be used for objective assessment of treatment response. More importantly, change in RI was specifically seen in symptomatic improved group. However, the result originated from the current study, needs to be proved by conducting a prospective follow-up of symptomatically non improved groups for longer duration with a larger sample size.

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