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RESEARCH ARTICLE

INTRAVESICULAR PROSTATIC PROTRUSION AS A PREDICTOR OF SILODOSIN RESPONSE: RESULTS FROM AN OBSERVATIONAL STUDY

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ABSTRACT

Background: Ultrasound measurement of the IPP has been previously described as an effective instrument for the evaluation of benign prostatic obstruction (BPO) and could help in clarifying the role of silodosin in patients with (BPE).Aim of our study was to investigate the efficacy of silodosin in patients with lower urinary tract symptoms (LUTS) and benign prostatic enlargement (BPE) with intravesical prostatic protrusion (IPP). **Methods:** In this observational study Patients with BPE and LUTS were enrolled. Intravesical prostatic protrusion was graded as grade 1 (< 5 mm), 2 (5 < IPP < 10 mm) and 3 (> 10 mm). Patients were treated with silodosin for twelve weeks. International Prostate Symptom Score (IPSS) and uroflowmetry was performed before and at the end of treatment. Patients were considered responders if a reduction of IPSS > 3 points was noted. **Results:** Of the sixty eight patients enrolled, two patients were excluded because of incomplete data. 26 patients showed an IPP grade 1 (group A), 27 a grade 2 (group B) and 13 grade 3 (group C). Treatment success was obtained in 80 %, 44 % and 7.5% of patients respectively; these differences (group A vs B-C and group B vs C) were highly significant. The odd ratio to obtain a treatment success was of 52 and 10 in group A and group B respectively, in comparison to group C. After a multivariate regression, the relationship between IPP grade and treatment success remained significant. Improvement of uroflowmetry parameters has been reported in all the groups especially in patients with a low grade IPP .Prostate volume seems not to influence this relationship. **Conclusion:** Intravesical prostatic protrusion has found to be significantly and inversely correlated with treatment success in patients with LUTS and BPE under silodosin therapy. silodosin odd ratio of success is 52 times higher in patients with a low grade IPP in comparison to patients with a high grade.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a progressive disease that has been on the rise in men over 50.Benign prostatic hyperplasia – also called as prostate gland enlargement is the most frequent cause of bladder outlet ob-struction (BOO) in males over the age of 50 who present with LUTS (Martin *et al*., 2011). In BPH patients, medical management is commonly used (Gravas *et al*., 2016). And provides relief in symptoms and improvement in disease progression (Mc Connell *et al*., 2003). But, not all patients get benefit from medical management. Therefore, it would be beneficial to identify patients that will not respond to medical treatment. The American Urological Association (AUA) guidelines for treatment of BPH recommend that initial evaluation of patients includes a history and focused physical, including digital rectal examination, urinalysis, prostate-specific antigen in selected patients, and an AUA/international prostate symptom score (IPSS). Optional diagnostic testing includes uroflow and postvoid residual urine (PVR). There are several non invasive measures to know the severity of BPH. Some of them are non-invasive pressure-flow testing (Pel *et al*., 2002), detrusor wall thickness (Oelke *et al*., 2007; Blatt *et al*., 2008), bladder weight by US(7), and US measurement of the intravesical prostatic protrusion (IPP) (Pel *et al*., 2002; Chia *et al*., 2003; Kessler *et al*., 2006). US measurement of IPP was first described in 2003 by Chia *et al*. to correlate well with BPO on urodynamic testing, with a PPV of 94% and a NPV of 79% (Chia *et al*., 2003). The principle behind the clinical significance of IPP is that protrusion of the median lobe of the prostate into the bladder can cause a "ball valve" type of benign prostatic obstruction with incomplete opening and disruption of the funneling effect of the bladder neck (Chia *et al*., 2003; Zheng *et al*., 2015). Chia *et al*. showed that an IPP of more than 10 mm was associated with a higher BOO index than an IPP of 10 mm or less in patients with BOO confirmed by pressure-flow study. Moreover, IPP also seems to predict successfully the outcome of a trial void after episode of acute urinary retention (Mariappan *et al*., 2007) and also predict the success rate of TURP (Lee *et al*., 2012). Studies investigating the relationship be-tween IPP and alpha-blockers therapy outcomes (Park *et al*., 2012; Cumpanas *et al*., 2013).

have shown that it may be correlated to reduced efficacy of silodosin in patients with IPP and mild/moderate (< 40 ml) prostate volume . However, to our knowledge, no data are available on patients with PV ≥ 40 ml. Aim of this study was to investigate the efficacy of an alpha-blocker (Silodosin) in patients with lower urinary tract symptoms (LUTS) and BPE with or without IPP.

MATERIALS AND METHODS

This is an observational prospective study performed from march 2018 to December 2018 in the Department of Urology, Stanley medical college hospital. Chennai, we enrolled male patients between fifty and sixty years of age, affected by BPH defined as transrectal ultrasound (TRUS) estimated PV ≥ 40 ml, in whom silodosin had been prescribed for LUTS.

Exclusion criteria were

Prior urologic surgery; Previous history of bladder tumor, vesical calculus or any neurological abnormality; Prior treatment with alpha blockers and 5alpha reductase inhibitors; Absence of intravescical prostatic protusion. All patients underwent a basic evaluation by history, administration of the International Prostate Symptom Score, transrectal ultrasound of the prostate and uroflowmetry. All TRUS were performed by the same physician and at the standard bladder filling of 150 ml. IPP was measured by the vertical distance from the tip of the protruding prostate to the base of the urinary bladder in the sagittal plane of transrectal ultrasonography in millimetres.

IPP estimated by TRUS was then graded as Grade 1 (<5 mm), Grade 2 (5 - 10 mm) and Grade 3 (> 10 mm). PV measurement was obtained during TRUS. All patients enrolled were then treated with silodosin (8 mg/day) for 12 weeks and reevaluated after treatment by means of IPSS Score and uroflowmetry.

Patients were considered responders (Treatment success) if showing a reduction of IPSS > 3 points.

Statistical analysis

All data were classified in an Excel Database. All analyses were performed by means of the STATA 13.0. Univariate logistic regression was used to evaluate relationships between each parameter (IPP grade, PV, IPSS, Qmax, PSA) and treatment success. One way anova was used for comparison between the three groups. Odd Ratio (OR) and relative 95% confidence Interval (CI 95%) were reported. A stepwise logistic regression was applied considering as independent factor IPP grade, age PSA, PV and baseline value of Qmax IPSS. A p value < 0.05 was considered statistically significant.

RESULTS

68 patients were enrolled. 2 patients were excluded because of incomplete data. Of the remaining 66 patients, 26 (38.5%) showed an IPP grade 1 (group A), 27 (40%) an IPP grade 2 (group B) and 13 (21.5%) an IPP grade 3 (group C). Baseline features of patients are showed in Table 1. Treatment success, defined as post-treatment IPSS score reduction > 3 points, was obtained in 82%, 38.5% and 7.1% of patients respectively. The odd ratio to obtain a treatment success was of 52 (CI 95% 11.8–296) and 10 (CI95% 1.7–38) in group A and group B respectively, in comparison to group C (Table 2). Moreover, there is a positive improvement of uroflow parameters in each group (with a better improvement after treatment with patients with a low grade IPP with respect to patients with a higher grade IPP. After multivariate regression, the relationship between IPP grade and treatment success remained significant. Interestingly the multivariate regression shows that Prostate Volume seems not to influence this relationship and is not included in the final model.

DISCUSSION

IPP refers to a morphological change in which the prostate protrudes into the bladder during the process of prostatic enlargement (Kojima *et al*., 1996).

Table 1. Baseline Features of the Patients

	Age,		Prostate volume,		Estimated IPP,		Pre-treatment Qmax,		Pre-treatment IPSS,		Pre-treatment PSA,	
	mean (DS)		mean (DS)		mean (DS)		mean (DS)		mean (DS)		mean (DS)	
Group A	62	8.9	45.5	16.9	2.7	0.8	10.5	2.9	17.7	3.9	3.5	2.5
Group B	64	9	53.2	21.2	6.5	1.3	9.3	1.5	18	4.1	2	1.4
Group C	66	8.6	54.6	13.1	11.4	1.1	8.8	2.3	22.2	5.1	3.1	1.7

Table 2. Relationship between IPP graded and treatment success

	Responders	Not responders	OR	CI 95%	P
Group A	21	5	52	10.8–224	< 0.001
Group B	12 (31.7%)	15 (47.8%)	10	1.6–34	0.008
Group C	1 (3.2%)	12 (38.8%)	1		

Table 3. Pre post-treatment Qmax differences

	Pre-treatment Qmax,		Post-treatment Qmax,		Pre post-treatment Qmax differences		p Value
	Mean	SD	Mean	SD	Mean	(SD)	
Group A	10.9	2.9	14.1	3.2	3.6	1.4	P<0.001
Group B	9.3	1.5	11.7	2.7	2.4	2.7	P<0.001
Group C	8.8	2.3	10.8	2.7	2.0	2.2	P<0.001

A median lobe of prostate tissue can increase bladder outlet resistance by causing a 'valve ball' type of BOO with incomplete opening of the bladder neck and disruption of its funneling effect. IPP is a promising parameter, first described by Chia in 200, 313, that has shown a good correlation with the presence and severity of BPO on urodynamic testing. Further studies have found a strong correlation between IPP and DO, bladder compliance, detrusor pressure at maximum urinary

flow, terminal dribbling, BOO index and PVR while a negative correlation was found between IPP and Qmax and/or alpha-blockers efficacy (Keqin *et al*., 2007; Park *et al*., 2012; Cumpanas *et al*., 2013; Kim *et al*., 2015). Moreover a well-designed study from Luo GC *et al*. has shown that the presence of middle lobe is more obstructive than those of lateral lobes and could better correlate with BOO grade (Luo *et al*., 2013). Data coming from our study suggest that IPP is significantly and inversely correlated with treatment success in patients affected by BPE and with LUTS under silodosin therapy. Alpha-blockers odd ratio of success is 52 times higher in patients with a low grade IPP in comparison to patients with a high grade IPP and 10 times higher with respect to patients with a moderate grade IPP. It is important to underline that the definition of success used in this study (a reduction of IPSS score > 3 points) is in line with previous and contemporary studies, considering this IPSS variation as clinically significant (Barry *et al*., 1995).

Interestingly even after multivariate regression with stepwise logistic regression IPP remains as independent predictive factors for silodosin treatment success. Our data are similar to those in literature; Cumpanas *et al*. analyzed 183 patients with BPH (PV < 40 mL) treated with tamsulosin and found that approximately 40% of the patients in the high IPP group were treatment nonresponders and had significantly worse out-comes than patients in the low IPP group at 3 months (Cumpanas *et al*., 2013); even in a more recent paper Kalkanli *et al*. (2016) showed that an increase in IPP was associated with a lower response level to medical treatment and indicated a significant negative correlation between IPP-Qmax and IPP-post treatmens IPSS. Similar data were also pub-lished by Hirayama *et al*. (2015) in Patients treated with Dutasteride 0.5 mg daily in which IPP was seen to be the strongest predictive factor for failure of medical therapy and conversion to surgical intervention with the optimal cutoff value of IPP of 8 mm. This value yielded a sensitivity of 91% and a specificity of 72%. Interestingly our data show that PV seems not to influence the relationship between IPP and alpha-blockers success rate. This is, to our knowledge, one of the very first papers to investigate this relationship in Patients with PV higher than 40 ml and our results are similar to those already published by Wang *et al*. in 2015 who showed a strong correlation between IPP and BPO and stated that IPP is superior to PV in predicting BPO in patients who present with LUTS.

It is interesting to observe that also Qmax showed a larger improvement in low or moderate IPP grade patients in comparison to severe IPP grade patients (p value = 0.01 Group A-B vs Group C). Further-more, patients with a higher IPP grade showed lower pre-treatment Qmax, in comparison with patients with 1–2 IPP grade (p value = 0.02 Group A-B vs Group C). This finding seems to suggest that the degree of IPP could correlate with the degree of BPO, but the lack of an invasive urodynamic evaluation (pressure/flow study) do not allow us to draw conclusions on that point. The study has several limitations; no RCT, no sample size calculation; non-invasive UD data. Besides we are conscious that EAU Guidelines on "Non neurogenic male LUTS" (Gravas *et al*., 2016) suggest a combination therapy for patients with PV > 40 ml and therefore that the vast majority of patients in our study did not receive a Guideline conform therapy but the aim of this study was not to evaluate the efficay of silodosin monotherapy in PV > 40 ml but to assess the efficacy of silodosin in relationship to the IPP grade. Thus the results of this paper could reinforce the indication of a combination therapy in this patients' population. This study provides further more the information that IPP seems to be a negative prognostic factor for success of silodosin, independently by the prostate volume. The strengths of the study are a proper statistical methodology and the use of a clinically meaningful primary outcome measure as modifications in IPSS score.

Conclusion

IPP seems significantly and inversely correlated with treatment success in patients with LUTS and BPE under silodosin and may be considered a useful tool to discriminate patients in whom medical treatment has higher (low grade IPP) or lower (high grade IPP) probability of success.

Abbrevations

BOO: Bladder outlet obstruction; BPE: Benign prostatic enlargement; BPH: Benign prostatic hyperplasia; BPO: Benign Prostatic Obstruction.

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