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TO DETERMINE THE EFFECTIVENESS OF TAMSULOSIN ON DECREASING BLADDER OUTLET OBSTRUCTION BY EVALUATING ITS INDIRECT EFFECT ON BLADDER WEIGHT

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Abstract:

Introduction: *Urinary Bladder wall thickness and weight tend to be more in patients with urinary outlet obstruction caused by BPE (Benign Prostate Enlargement) in compensated early phase of the disease.*

Aim: *The purpose of the study was to determine the effectiveness of Tamsulosin on decreasing bladder outlet obstruction by evaluating its indirect effect on bladder weight.*

Materials and Methods: *The material in this study was composed of 63 patients, aged more then 45, with the present lower urinary tract symptoms (LUTS) caused by benign prostatic enlargement, who had not been treated for the previous 3 months. The inclusion criteria were also the value of (IPSS) IS ≥ 8 points, PMRV (post-void residual urine volume) <100ml, (PSA) <4nanogram/ml. The enrolled patients took Cap Tamsulosin 0.4 mg once daily and the evaluation parameters during the research were measured at time intervals of 4, 12 and 24 week. The parameters for evaluations was primary and secondary. Primary parameter was the (UEWB) ultrasonic estimated bladder weight, and the secondary were assessments of IPSS score, the quality-of-life determination (IPSS -QoL), and the amount of post-voided residual volume (PMRV), as well along with the determination of the number and strength of adverse reactions.*

Results: *At the time of the enrollment of the patients in the study, the arithmetic means of UEWB was 55g, PMRV was 43 ml, and IPSS of 20.97, and IPSS-QoL 5 points. After 24 weeks of management, the values were the following: the arithmetic mean of UEWB 30g, PMRV 6ml, IPSS 7 Point and the IPSS-Quality of life 2 point. The obtained outcomes of this study were processed by descriptive statistics (standard deviation and arithmetic mean) and analytical statistics by using Student's t-test for dependent (paired) sample. The drug side effects (Dizziness 3%and ejaculation problems3% and headache 6%) were well tolerated and acceptable and did not lead to the discontinuation of the treatment.*

Conclusion: *We conclude that UEBW is a reliable, objective test for diagnosing BOO due to BPE. Moreover, it can also be used to monitor the effect of medical therapy for BPE via its indirect effect on detrusor hypertrophy.*

Key words: *Benign Prostatic Enlargement, Tamsulosin, Ultrasound Bladder Wall Thickness, Ultrasound Estimated Bladder Weight.*

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INTRODUCTION:

Bladder outlet obstruction (BOO) in men due to enlarged prostate has presented clinical problem and health burden throughout medical history. Prostatic enlargement affects approximately 50 % of men sixty years old and some estimate the prevalence to be approximately 80% by age 80 years 1. Benign prostate enlargement/Hypertrophy (BPE/BPH) is characterized by increase in size of prostate, lower urinary tract symptoms (LUTS) and Bladder outlet obstruction (BOO). Lower urinary tract symptoms can be caused by problems other than BPH (e.g. urethral stricture, bladder neck stenosis etc.). Men without LUTS can still have BOO(silent obstruction),which may alter bladder or kidney function and may lead to renal failure .

BOO leads to a variety of structural and functional changes in the bladder wall muscle, as a positive compensatory response in order to overcome the resistance to bladder emptying.

Currently, there are many treatment options available for management of BOO due to prostatic enlargement including pharmacologic therapy, which include alpha blockers and 5-α reductase inhibitors, minimal invasive procedures such as laser prostatectomies, transurethral hyperthermia, ultrasonic radiofrequency ablation and surgical intervention. Highly selective Alpha -adrenergic receptor antagonists are considered to be the first line drugs when pharmacologic therapy is indicated 2. They act by decreasing smooth muscle tone in bladder neck and the prostate, leading to decrease in tension on the bladder wall, consequently decreasing the detrusor muscle hypertrophy and bladder weight.

BOO can be assessed and diagnosed by many methods. Clinically, patient symptoms can be assessed by questionnaire method. Several questionnaires have been developed to assist in the identification of patients with symptoms of sub-vesical obstruction. The two commonly used ones are the International Prostate Symptom Score and the AUA Symptom Score [3]. Uroflowmetry is carried out to determine how fast urine flows out of the urinary bladder. Ultrasound is used in addition to determine bladder emptying through measuring post-void residual urine and may give additional information about associated causes for obstruction such as vesical stones etc. All these methods are indirect evidence of BOO and not specific to benign prostatic enlargement. Urodynamic study (pressure/flow) is the gold standard method for diagnosing bladder outlet obstructions. However, this method is invasive, costly and hence not commonly available. Moreover, it has certain morbidity such as urinary tract infection, urinary retention, gross hematuria and fever. Therefore, efforts have been made to find a less invasive alternative method to diagnose BOO.

A promising new technique to diagnose BOO objectively is ultrasound estimated bladder weight (UEBW) [4]. This technique is simple, require only an ultrasound machine [5]. It measures bladder wall thickness /volume, thus calculating bladder muscle weight. Bladder muscle weight reflects the amount of detrusor muscle, which in turn depends upon the amount of work detrusor muscle has to do. Consequently, if alpha blockers are effective in reducing BOO, it leads to less work by detrusor muscle, resulting in decreased muscle mass, and thus it can be measured objectively by this technique.

Many studies have been done that prove the efficacy of Tamsulosin in the management of sub-vesical obstruction caused by BPH [6]. The parameters used to assess the efficacy were mostly subjective in nature (questionnaire)or nonspecific (Uroflowmetry). Snjezana Milicevic published a study describing marked reduction in ultrasound estimated bladder weight in response to Tamsulosin therapy in a small number of patients [7]. However, there are no other studies reported so far on this subject.
This study aims to determine the efficacy of highly selective α-blocker, Tamsulosin, in reducing

subvesical obstruction by ultrasonic measurement of change in bladder weight in a larger number of patients to further validate the findings of a single published study prior to recommending it as an assessment method for routine use in clinical practice.

2. MATERIALS AND METHODS:

2.1 Study Design

Quasi experimental study (before and after study). Based on the hypothesis that there is significant decrease in bladder weight after starting oral treatment with highly selective alpha1-a blockers Tamsulosin.

2.2 Study place

Outpatient department of Mayo hospital, Urology unit I & II. MHL is a teaching tertiary care institute attached with King Edward Medical University, Lahore.

2.3 Durations of the study

The study period was 6 months

Sample size

Sample size was 63.

Sample size was calculated using the formula: n $=z^2pq/d^2$, where, n =total sample size z=1.28(for 8o% confidence level).

p= 57.7 % (percentage of change in bladder weight pre-and post-medication) (7) q=100-p=43% d=8(precision and permissible errors)

n= (1.28) $^2\times57x43$

$(8)^2$

N=63.

Sample Technique

Non-probability consecutive sampling

Selection criteria

Inclusion criteria

- Males above 45 years of age presenting with LUTS.
- Patients who haven't been treated for LUTS within the last 3 months as determined by patients" symptoms history.
- IPSS (International Prostate Symptom Score) ≥8, calculated by using the IPSS scoring system.
- Post-void residual urine volume (PVR) ≤100 on ultrasound assessment. • PSA ≤4 Nano gram/ml.

Exclusion criteria

i. Patients who are already on Tamsulosin therapy on history or has been on Tamsulosin therapy for in the last 3 months.

ii. Patients who have undergone any prostate surgery before presentation.

iii. Patients who have a history of bladder outlet obstruction due to other causes (bladder stones, Tumors, stricture urethra).

iv. Patients having neurogenic bladder dysfunction on history and physical examination.

v. Patients presenting with LUTS caused by biopsy proven prostatic cancer.

Data Collection Procedure

- Patients of BPH presented to Urology outpatient department of unit I&II fulfilled inclusions criteria were enrolled in this study. • At presentation patients' history and physical examination findings including DRE as well as PSA were entered into a case report form.
- Patients were given capsule Tamsulosin 0.4mg orally once daily at bedtime.
- Patient's data were recorded at baseline, at 4^{th}, 12^{th} and 24^{th} weeks.
- At each visit, UEBW, IPSS, PVR, QOL score were recorded.
- Ultrasound estimated bladder Wight was measured by employing the formula

:

$$UEBW = \frac{4\pi}{3}\left(\left(\sqrt[3]{\frac{3V}{4\pi}}\right)+D\right)^3 - V$$

Where UEBW= Ultrasound Estimated Bladder Weight, V= mean bladder volume, D= mean value of detrusor muscle thickness. π= **3.14 (7)**

Detrusor thickness: was measured by a single operator with 6-10 MHz linear multifrequency probe in all the patients in the supine position, on the anterior side in medial line, with at least three measurements done at the distance of 1 cm each between them, whereby the mean value will be taken as detrusor thickness(D).

Bladder volume: Bladder volume was measured using ultrasound with 3-5 MHz probe by single operator and calculated with the following formula: Bladder height × Bladder width ×Bladder depth ×0.6.

2.8 Data analysis procedure

- Data were entered and analyzed in SPSS version 20.
- Quantitative variable like age were presented as mean ± SD. Qualitative variable like genders were presented as frequency and percentages.
- Effectiveness of Tamsulosin was assessed by paired T test, comparing premedication bladder weight and bladder weight at final follow up after

treatment. Tests were two tailed and level of significance was at <0.05.

Study Variables

- Bladder weight
- Ipss score
- Age
- IPSS Quality of life
- PMRV

RESULTS AND OBSERVATIONS:

Table-1: Descriptive statistics of age (years)

MEAN	**63.79**
S.D	9.870
RANGE	39
MINIMUM	46
MAXIMUM	85

The mean age of patients was 63.79±9.87 years with minimum and maximum age of 46 and 85 years.

Table-2: Comparison of bladder weight (g) at different visits

		Mean	S.D	Range	Minimum	Maximum	p-value
Bladder Weight (g)	***Baseline***	55.13	9.50	37	38	75	<0.001**
	4th week	43.37	8.20	34	28	62	
	12th week	34.44	6.72	25	26	51	
	24th week	30.00	4.38	25	25	50	

The mean bladder weight at baseline was 55.13 ± 9.50 g that was reduced to 30±4.38 g at 24th week after treatment. The mean reduction from baseline to 24th week was significant, p-value < 0.001**.

Table-4: Comparison of IPSS score at different visits

		MEAN	S.D	RANGE	MINIMUM	MAXIMUM	P-VALUE
IPSS SCORES	***Baseline***	20.96	3.85	17.0	13.0	30.0	<0.001**
	4th week	13.35	4.07	16	5	21	
	12th week	8.16	4.29	18	0	18	
	24th week	6.17	3.89	15	0	15	

The IPSS at baseline was 20.97 ± 3.85 and at 24th week was 6.17±3.8, the change in IPSS score from baseline to 24th week was significant, p-value < 0.001**

Table-5: Comparison of post-void residual urine at different visits

		MEAN	S.D	RANGE	MINIMUM	MAXIMUM	P-VALUE
POST-VOID RESIDUAL URINE	***Baseline***	43.62	32.34	100	0	100	<0.001**
	4th week	20.44	23.67	85	0	85	
	12th week	9.84	16.87	60	0	60	
	24th week	6.59	12.89	50	0	50	

Post void residual urine average at baseline and 2th week was 43.62±32.34 and 6.59±12.89 (S.D is greater than mean due to large variation in data). The mean post residual urine was also significantly reduced from baseline to 24th week p-value < 0.0001

Table-6: Comparison of Quality of life at different visits

		MEAN	S.D	RANGE	MINIMUM	MAXIMUM	P-VALUE
QUALITY OF LIFE SCORE	***Baseline***	5.35	0.48	1	5	6	<0.001**
	4th week	3.33	0.95	2	2	4	
	12th week	2.29	1.25	3	1	4	
	24th week	1.62	1.61	4	0	4	

Quality of life score at baseline was 5.35 ± 0.48 and at 24th week was 1.62±1.61 with significant change at last follow up, p-value < 0.001.

Table-7: Comparison of side effects at different visits

	VISITS	FREQUENCY	PERCENTAGE	P-VALUE
POSTURAL HYPOTENSION	4th week	1	1.58	--
	12th week	0	0	
	24th week	0	0	
HEADACHE	4th week	8	12.69	0.236
	12th week	7	11.11	
	24th week	4	6.34	
DIZZINESS	4th week	2	3.17	0.368
	12th week	1	1.58	
	24th week	1	1.58	
NAUSEA/VOMITING	4th week	3	4.76	0.097
	12th week	1	1.58	
	24th week	0	0	
RETROGRADE EJACULATION	4th week	2	3.17	0.368
	12th week	1	1.58	
	24th week	1	1.58	

Postural hypotension was seen in 1(1.58%) case at 4th week, headache was reported by 8(12.69%) cases at 4th week, 7(11.11%) cases at 12th and 4(6.34%) cases at 12th week with no significant difference of headache from baseline to last follow up, p-value >0.05. At 4th week 2(3.17%) cases had dizziness, 1 (1.58%) case had dizziness at 12th and 24th week. There were 3(4.76%) and 1(1.58%) case told that they had Nausea / vomiting at 4th and 12th week respectively. Retrograde ejaculation was also occurred to 2(3.17%) at 4th week and 1(1.58%) patient at 12th and 24th week. There was no significant difference in complications at different visits, p-value > 0.05.

DISCUSSION:

Clinical benign prostatic enlargement BPE is characterized by lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO). The prostate volume is approximately 20 ml after puberty and remains stable until after 5th decade (). Even though prostatic volume continues to increase in most men afterward, no clear co-relation exists between prostate size and BOO, as revealed by multiple studies. Quantifying prostatic enlargement by digital rectal examination or ultrasound is quick and simple as is LUTS (history, IPSS). However, measuring BOO is relatively difficult, currently only pressure- flow analysis by urodynamic is gold standard for measuring BOO. ([8,9])

In routine clinical practice uroflowmetry, prostate size and postvoid residual urine are used to detect Boo. Multiple studies have shown that these tests are poor predictor of obstruction ([10]). Urodynamic study is time

consuming, expensive and invasive .Efforts are undergoing to find an alternative screening test to diagnose BOO.

Ultrasound estimated bladder weight (UEBW) or bladder wall thickness (BWT) has been proposed as a non-invasive and cheap test to determine BOO. There is lot of controversy which parameter is better at defining BOO and matter is not resolved.

Rationality of using UEBW is that as prostatic enlargement causes intravesical obstruction, detrusor muscle has to work extra in order to overcome that obstruction. This overwork causes detrusor hypertrophy resulting in increased mass and hence weight up to a certain stage (compensatory phase). Beyond that stage if obstruction continues, detrusor may fail and mass regresses (decompensated phase).

Kojma et al were the first researchers to report that bladder weight increases upto four-fold in men with bladder outlet obstruction (BOO) as compared to non-obstructed men. They gave a cut off value Of 35 gram for calculating bladder weight. UEBW greater than 35 grams means obstructed bladder. ([11, 12, 13])

Subsequently, researchers have tried to determine the effect of medical therapy on BOO objectively as manifested by decreased UEBW. Rationality is that if medical therapy (α blockers) effectively decreases outflow resistance, detrusor overwork should decrease, resulting in regression of detrusor hypertrophy and hence UEBW.

Melicevic (2012) reported results of a small study of 20 patients having BOO due to BPE. They had mean UEBW of 65gram at baseline, mean postvoid residual volume (PVRV) was 45 ml. Mean IPSS at base line was 15.6. Mean

IPSS-Quality of life (QoL) score at base line was 3.6 after 24 weeks of Tamsolusin therapy mean bladder weight decreased to 28 gm. At 24th week PVR was 21 ml. Mean IPSS after 24 weeks of alpha blockers therapy was 5.0. Mean IPSS-QoL improved to 1.0 after 24 weeks. ([7])

In our study of 63 patients, mean UEBW was approximately 55 gm at baseline and it decreased to 30 gm after 24 weeks of Tamsolusin therapy. The decrease was statically significant ($p<0.05$). Mean PVRV in our study decreased from approximately 44 ml to 7ml (statically significant at $p<0.05$).

The mean IPSS score was 20 at base line and it improved to 7 after 24 weeks of Tamsolusin therapy (statically significant at $p<0.05$). The mean IPSS-QoL was 5 at base line and it improved to 2 after 24 weeks of Tamsulosin therapy (statically significant at $p<0.001$).

Our study, with a much larger sample corroborates the finding of Mlicivic study ([7]). Its objectively shows that α-blockers, by decreasing BOO, cause decreased work load on detrusor muscle resulting in decreased detrusor mass and hence bladder weight over a period of time.

CONCLUSION:

We conclude that UEBW is a reliable, objective test for diagnosing BOO due to BPE. Moreover, it can also be used to monitor the effect of medical therapy for BPE via its indirect effect on detrusor hypertrophy.

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