Original Research Article

ASSESS THE MEAN CHANGE IN OUTCOMES OF SILDENAFIL IN THE TREATMENT OF LOWER URINARY TRACT SYMPTOMS AND ERECTILE DYSFUNCTION DUE TO BENIGN PROSTATIC HYPERPLASIA

ABSTRACT:

OBJECTIVE: To assess the mean change in outcomes of sildenafil in the treatment of lower urinary tract symptoms and erectile dysfunction due to benign prostatic hyperplasia.

STUDY DESIGN: This is a quasi experimental study.

SETTING: Study carried out at OPD of Department of Urology, Jinnah Postgraduate Medical Centre, Karachi, from January 26, 2018 to July 26, 2018.

MATERIAL & METHOD: 50 patients fulfilling selection criteria were included in the study through OPD of Department of Urology, Jinnah Postgraduate Medical Centre, Karachi Informed consents were obtained. Demographics (name, age and contact) werel also be obtained. All patients were subjected to detailed history and clinical examination for BPH and ED according to the IPSS and IIEF. Mean change in urine flow rate assessed through uroflowmetry and Mean change in post-void residual (PVR) urine was assessed through ultrasound on the same day and on follow-up after 10th weeks in OPD before and after the tablet sildenafil 50 mg OD at night to every patient.

RESULTS: Mean age of patients was 58.42±9.76 (45-80) years. pre and post treatment International prostate symptom score (IPSS) score mean 17.78±2.91 and 12.94±2.79 (p-value=0.0001) respectively, erectile function score (IIEF) score mean 17.64±2.69 and 21.86±4.47 (p-value=0.0001) respectively, Urinary flow rate (UFR) pre and post treatment mean 8.32±1.62 and 12.46±1.83 (p-value=0.0001) respectively, Post-void residual (PVR) urine pre and post treatment mean 62.64±6.29 and 54.72±5.04 (p-value=0.0001) respectively.

CONCLUSION: Improvement of erectile dysfunction and reduction of urinary tract symptoms in men with sildenafil was associated with improved quality of life and satisfaction with treatment. Daily doses of sildenafil can improve lower urinary tract symptoms.

KEY WORDS: Benign Prostatic Hyperplasia, Erectile Dysfunction, Ejaculatory Dysfunction, Lower Urinary Tract Symptoms.

INTRODUCTION:

An aging person faces many health problems. Hypertension, diabetes, androgen deficiency, depression, and cardiovascular disease seriously threaten the longevity of men[1]. Many of these diseases manifest themselves in urinary and sexual functions. The benign prostatic hyperplasia (BPH) was found approximately in 40% upto age of 50 years men, while this problem increased with age and found 80% of men by age 80 years[2].

The prevalence of erectile dysfunction (ED) problems increases with increased of concomitantly with age. By age 40, 40% of men will experience some form of ED.[2] The doubles risk by age of 50 years and five times by age 60 [3]. Some international studies have shown the lower urinary tract symptoms (LUTS) and comorbidity of ED. Study conducted by Lauman and colleagues in the National Health and Social Life Survey show that LUTS is a significant risk factor for ED. Severe LUTS is associated with erectile dysfunction and ejaculatory dysfunction in a Dutch survey of older men. These symptoms are 10 times more common in men in their 70s than men in their 50s[4,5].

Lower urinary tract symptoms (LUTS) in men are due to some diseases associated with prostate and bladder. The international guidelines of National Institute of Health and Clinical Excellence (NICE) reported LUTS comprising Storage symptoms (urgency, increased frequency, urgency incontinence and nocturia), Voiding symptoms (weak or intermittent urinary stream, straining, hesitancy, terminal dribbling and incomplete emptying) and postmicturition symptom is postmicturition dribbling, affecting the lower urinary tract.Although LUTS do not usually cause serious disease, they can significantly reduce men's quality of life and may herald serious disease in the genitourinary system. Storage LUTS are often more prevalent and more bothersome than voiding LUTS[6-10].

The aim of this study was to investigate the effects of sildenafil in treating the symptoms of lower urinary tract symptoms and erectile dysfunction due to benign prostatic hyperplasia.

MATERIAL & METHOD:

50 patients fulfilling selection criteria were included in the study through OPD of Department of Urology, Jinnah Postgraduate Medical Centre, Karachi. Informed consent were obtained. Demographics (name, age and contact) were also be obtained. All patients were subjected to detailed history and clinical examination for BPH and ED according to the IPSS and IIEF. All male patients age between 45 to 80 years with complaining of of LUTS

caused by BPH (after exclusion of other causes of LUTS like stricture, catheterization on history) for ≥3 months with international prostate symptoms score (IPSS) > 7 were included in this study. Those patients with previous prostatic surgery or other less invasive surgical interventions for BPH as per record of patient, active urinary tract disease that may causes LUTS, like cystitis or bladder stones, as per record of patient, patients with PSA >10 as per record of patient, patient who are not candidates for medical treatment for ED (as patients with cardiac problems which contraindicate the use of PDE 5 inhibitors or patients with previous unresponsiveness to PDE 5 inhibitors) as per record of patient and Patients who don't give consent of participation were excluded from this study.

Mean change in urine flow rate assessed through uroflowmetry and Mean change in post-void residual (PVR) urine was assessed through ultrasound on the same day and on follow-up after 10th weeks in OPD before and after the tablet sildenafil 50 mg OD at night to every patient. (Reminder were given to every patient at 9^{th} week for follow-up on phone call on his personal number by the researcher to minimize the chances of follow-up lost and to reduce bias).

RESULTS:

A total of 50 patients were included in this study, mean age of patients was 58.42±9.76 (45-80) years. Mean BMI of the patients was 27.2±3.05, mean duration of the symptoms in patients was 13.5±5.2, mean duration of marriage was 23.9±5.9 years (Table No.1). In table 1 distribution of qualitative variables were stated, overweighr/obese patients were 33(66%), 27(54%) patient's duration of symptoms was more than 1 years, 22(44%) patients have duration of marriage more than 20 years.20(40%) patients were from lower class, 22(44%) patients were from middle class and only 8(16%) patients were from upper class.27(54%) patients from urban area and 23(46%) patients were from rural area. 29(58%) patients have more than 55 years of age and 21(42%) patients have age <55 years of age.

In table 2 descriptive statistics and comparison of pre and post treatment outcomes were stated, International prostate symptom score (IPSS) score showed significance difference between pre and post treatment finding pre and post treatment mean 17.78±2.91 and 12.94±2.79 (p-value=0.0001) respectively, erectile function score (IIEF) score showed significance difference between pre and post treatment finding pre and post treatment mean 17.64±2.69 and 21.86±4.47 (p-value=0.0001) respectively, Urinary flow rate (UFR) showed

significance difference between pre and post treatment finding pre and post treatment mean 8.32±1.62 and 12.46±1.83 (p-value=0.0001) respectively, Post-void residual (PVR) urine showed significance difference between pre and post treatment finding pre and post treatment mean 62.64±6.29 and 54.72±5.04 (p-value=0.0001) respectively.

In table 3-6 stratification for mean change in IPSS, IIEF, UFR, PVR urine have done with respect to age, BMI, duration of symptoms, duration of marriage to see the effect modifications. Post stratification paired t-test and ANOVA was applied. P-value≤0.05 were considered as significant. Stratification findings showed non-significance results with p value>0.05.

Table: 1

DESCRIPTIVE STATISTICS OF QUANTITATIVE VARIABLES

VARIABLES		**Frequency**	**Percent**
AGE GROUP	• **≤55 year**	21	42.0%
	• **>55 year**	29	58.0%
	Mean 58.42±9.76 (Rang 45 - 80 years)		
BODY MASS INDEX	• **≤25kg/m**	17	34.0%
	• **>25kg/m**	33	66.0%
	Mean 27.2±3.05 (Rang 23.4 - 30.2)		
DURATION OF SYMPTOMS	• **≤1 year**	23	46.0%
	• **>1 year**	27	54.0%
	Mean 13.5±5.2 (Rang 4 - 25 years)		
DURATION OF MARRIAGE	• **≤20 year**	28	56.0%
	• **>20 year**	22	44.0%
	Mean 23.9±5.9 (Rang 14 - 49 years)		
SOCIOECONOMIC STATUS	• **Lower**	20	40.0%
	• **Middle**	22	44.0%
	• **Upper**	8	16.0%
RESIDENTIAL STATUS	• **Rural**	23	46.0%
	• **Urban**	27	54.0%

Table: 2. DESCRIPTIVE STATISTICS AND COMPARISON OF PRE AND POST TREATMENT OUTCOMES

Outcome variables	Mean	Std. Deviation	P-value
• PRE/IPSS	17.78	2.909	0.0001
• POST/IPSS	12.94	2.788	
• PRE/IIEF	17.64	2.694	0.0001
• POST/IIEF	21.86	2.466	
• PRE/UFR	8.32	1.622	0.0001
• POST/UFR	12.46	1.832	
• PRE/PVR	62.64	6.288	0.0001
• POST/PVR	54.72	5.043	

(IPSS) International prostate symptom score, (IIEF) International Index of Erectile Function Score, (UFR) Urinary flow rate, (PVR) Post-void residual urine.

Table: 3. DESCRIPTIVE STATISTICS AND COMPARISON OF CHANGE IN OUTCOMES WITH RESPECT TO BMI

BMI		N	MEAN	STD. DEVIATION	P-VALUE
• **CHANGE/IPSS**	**≤25kg/m**	17	4.35	1.998	0.287
	>25kg/m	33	5.09	2.429	
• **CHANGE/IIEF**	**≤25kg/m**	17	-5.06	3.508	0.1
	>25kg/m	33	-3.79	1.867	
• **CHANGE/UFR**	**≤25kg/m**	17	-4.18	1.944	0.925
	>25kg/m	33	-4.12	1.965	
• **CHANGE/PVR**	**≤25kg/m**	17	8.29	5.108	0.46
	>25kg/m	33	7.73	3.502	

(IPSS) International prostate symptom score, (IIEF) International Index of Erectile Function Score, (UFR) Urinary flow rate, (PVR) Post-void residual (PVR) urine.

TABLE:4. DESCRIPTIVE STATISTICS AND COMPARISON OF CHANGE IN OUTCOMES WITH RESPECT TO DURATION OF SYMPTOMS

DURATION OF SYMPTOMS		N	Mean	Std. Deviation	P-value
• **CHANGE/IPSS**	**≤1 year**	23	4.35	2.102	0.164
	>1 year	27	5.26	2.411	
• **CHANGE/IIEF**	**≤1 year**	23	-3.83	1.850	0.324
	>1 year	27	-4.56	3.068	
• **CHANGE/UFR**	**≤1 year**	23	-4.35	1.873	0.49
	>1 year	27	-3.96	2.009	
• **CHANGE/PVR**	**≤1 year**	23	7.61	3.474	0.623
	>1 year	27	8.19	4.574	

(IPSS) International prostate symptom score, (IIEF) International Index of Erectile Function Score, (UFR) Urinary flow rate, (PVR) Post-void residual (PVR) urine

Table: 5. DESCRIPTIVE STATISTICS AND COMPARISON OF CHANGE IN OUTCOMES WITH RESPECT TO DURATION OF MARRIAGE.

DURATION OF MARRIAGE		N	Mean	Std. Deviation	P-value
• **CHANGE/IPSS**	**≤20 year**	28	4.89	2.097	0.85
	>20 year	22	4.77	2.581	
• **CHANGE/IIEF**	**≤20 year**	28	-4.39	3.023	0.59
	>20 year	22	-4.00	1.927	
• **CHANGE/UFR**	**≤20 year**	28	-4.18	2.091	0.87
	>20 year	22	-4.09	1.770	
• **CHANGE/PVR**	**≤20 year**	28	8.79	3.966	0.09
	>20 year	22	6.82	4.031	

(IPSS) International prostate symptom score, (IIEF) International Index of Erectile Function Score, (UFR) Urinary flow rate, (PVR) Post-void residual (PVR) urine

Table: 6. DESCRIPTIVE STATISTICS AND COMPARISON OF CHANGE IN OUTCOMES WITH RESPECT TO AGE GROUPS

Age groups		n	Mean	Std. Deviation	Std. Error Mean	P-value
• CHANGE/IPSS	≤55 year	21	4.90	2.322	.507	0.86
	>55 year	29	4.79	2.320	.431	
• CHANGE/IIEF	≤55 year	21	-4.29	2.630	.574	0.88
	>55 year	29	-4.17	2.592	.481	
• CHANGE/UFR	≤55 year	21	-4.00	1.949	.425	0.66
	>55 year	29	-4.24	1.958	.364	
• CHANGE/PVR	≤55 year	21	7.52	3.995	.872	0.56
	>55 year	29	8.21	4.178	.776	

(IPSS) International prostate symptom score, (IIEF) International Index of Erectile Function Score, (UFR) Urinary flow rate, (PVR) Post-void residual (PVR) urine

DISCUSSION

There is evidence of an association between LUTS and ED by various pathogenic systems, and LUTS has been clearly implicated in ED; Moreover, the severity of ED increases with the severity of LUTS, and this can be explained by several theories[10]. High levels of the norepinephrine cause both vascular and cavernous smooth muscle contractions, leading to erectile dysfunction. Alpha-adrenergic blockers block the effect of norepinephrine and can cause erection[11]. Some alpha-blockers used to treat LUTS induced by BPH have positive erectile effects, such as doxazosin and alfuzosin; in addition, PDE-5 inhibitors have positive effects in reducing the severity of LUTS, most Possibly through the NO pathway that mediates smooth muscle relaxation in the bladder and prostate[12].

In the first group of patients, we attempted to show the effect of sildenafil as a single agent on both symptoms after 4 months of follow-up. Study conducted by Ying et al. and reported, 32 patients with ED and BPH received oral sildenafil and were reviewed in questionnaires (IIEF) and (IPSS) before and 6 months after sildenafil use. At 6 months, the IIEF-5 score increased by 42.36%, and the IPSS score decreased by 20.14%, which was statistically significant ($P<0.01$)[13]. In this study, the mean pre-treatment flow rate was 9.82 ml/s, which increased to 10.58 ml/s after 4 months of treatment. CemGüler et al. The report said that Qmax in 38 patients with obstructive LUTS, they were evaluated before and after 3 months of treatment with sildenafil 50 mg. The mean Qmax before and after sildenafil was 11.4 and 12.3 ml/s, respectively[14]. Positive effect on urinary PVR occurred due to prostate smooth muscle relaxing by sildenafil. In our study, the mean urinary PVR was 65.8 ml before treatment, which decreased to 59.6 ml after 4 months of treatment. From these results, we observed that sildenafil alone slightly improved IPSS, further improved IIEF scores.

In second group of patients, our goal was to demonstrate the effect of doxazosin as the single agent on both symptoms after a 4-month follow-up. This is according to Demir et al.[15] the study included 53 LUTS patients (IPSS score >7) with a maximum flow rate (Qmax) <15 ml/s. The efficacy of drug doxazosin on LUTS was assessed by IPSS and by the Erectile Function Assessment (IIEF) efficacy at the six week. The doxazosin significantly improved mean overall IPSS score (4.7) ($P = 0.001$) and mean Qmax (+3.2 ml/s) ($P = 0.002$) from baseline. The mean improvement in IIEF score after the treatment period was (+2.3) ($P = 0.0002$). Average mean pre-treatment flow rate after four months of treatment was 10.02

ml/s, which increased to 12.32 ml/s (***P*** = 0.001). An international study conducted by Demir et al [263] also supports this results. Urine flow rate better improve with the treatment of doxazosin than sildenafil. The average PVR urine before treatment was 66.7 ml and after 4 months of treatment it decreased to 41.2 ml, which is better than the first group. This means that doxazosin has a better effect on lowering PVR than sildenafil. We found that doxazosin alone led to greater improvement in IPSS, flow rate, and PVR urine, and less improvement in IIEF scores.

In our third group of patients, we followed 4 months of follow-up for the effect of combine therapy doxazosone and sildenafil on both symptoms.While compared with pilot study conducted by Steven A. Kaplan [16] , found good efficacy of combination of durgs on LUTS symptoms. This showed a significant improvement in IPSS over 3 months of treatment but the highest combination (24.1%) compared with doxazosin (15.6%) and sildenafil (16.9%) alone ($P < 0.03$). In our observation that a combine (sildenafil and doxazosin) treatment has good improvement in all of the comparative parameters. Some international studies reported in urology clinics men presented with LUTS, out of this 46% were impotence according to NIH criteria, erectile dysfunction observed in 56%. While no association between total IPSS and sexual function inventory scores. The satisfaction scores of various aspects of sexual function were depends upon the BPH effect index [17,18,19]. These authors concluded that sexual activity may be more closely linked to the effect that urinary symptoms have on the quality of life rather than the urinary symptoms. While in our study almost same finding and there was no association of IPSS or QoL score and IIEF variables. Overall treatment response was positive and improve sexual function. The observed changes in quality of life may be due to a positive response to ED treated with sildenafil. Changes in IPSS and QoL components were strongly correlated with changes in IIEF after treatment of 3 months, suggesting that this was due to sildenafil-induced sexual changes leading to improvement in urinary symptoms. This is important because if there is a relationship, then it could mean an improvement in erection and a life-changing outcome that could lead to an improved urine score.

In the current study, patients who complained of intermittent LUTS had better erections after treatment with sildenafil, as did those who did not have such complaints. Also, there has been a distinct relationship between early IPSS and treated sexual function scores. A lower IPSS at baseline appeared to predict higher (i.e. better) IIEF scores after treatment

with sildenafil. These findings suggest that the presence of concomitant LUTS does not alter the ED response to sildenafil, although the response rate may be higher in men with lower IPSS. Sildenafil was only taken 'on demand' before each sexual intercourse and thus it may be difficult to explain its effects under urine, which appear long after sildenafil is completely metabolized[19].

Therefore, we recommend that in men coming with ED, improvement in LUTS after treatment with sildenafil results in muscle relaxation of NO / sildenafil in the lower urinary tract. These findings reinforce further research, evaluating urodynamics and comparing sildenafil with other agents used to treat ED[20]. We acknowledge that this study is not designed to address all of the issues raised by dramatic results, but we hope that the development of future studies examining the relationship between ED and LUTS can identify these deficiencies and resolve them adequately. We recommend treating patients who come with ED and LUTS-related Sildenafil, provided there are no contraindications for its use.

A study of sexual dysfunction in 1,274 European men with LUTS showed that ED was very close to age, LUTS, indicator of weight gain, high blood pressure, and similar anti-calcium channel treatment, while decreased ejaculation was significantly related and age, LUTS and BPH in the past[21]. Men with LUTS were twice as likely to have ED and had lower ejaculation compared with men without, and both ED and ejaculatory dysfunction were worse. An international Cologne Male Survey conducted on 4489 men, which reported that 72% men has Cologne Male Survey and ED while 38% men with normal erectile function[22]. Finally, Hansen found that LUTS is an independent risk factor for sexual dysfunction 7,741 men and women between the ages of 40 and 65 years.

The amount of PDE5 in the prostate may be sufficient to respond for the demanded Viagra use, as was carried out in this study, and have a beneficial effect on LUTS. Sildenafil is used on average twice a week and if a person admits to having a 4-hour erectogenic action period, this indicates that chronic PDE5 inhibition may not be necessary to make changes to LUTS.

CONCLUSION:

Erectile dysfunction and lower urinary tract symptoms were improved with the treatment of sildenafil in men, while quality of life improving and patients satisfaction of

treatment. There are many treatments and surgeries available to treat BPH. Many of these drugs have side effects that can affect a patient's health and sexual side effects. It is important for health professionals to look at these sexual side effects and discuss them with their patients before starting treatment.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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