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Comparative Study of Tadalafil And Tamsulosin in Benign Hyperplasia of Prostate For Lower Urinary Tract Symptoms (LUTS)

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Abstract:
Objectives*: Tadalafil has been approved by the U.S. Food and Drug Administration in 2011 to treat the signs and symptoms of Lower Urinary Tract symptoms (LUTS) due to benign hyperplasia of prostate(BHP). Tamsulosin is being used to treat LUTS due to BHP. Tadalafilacts by inhibiting phosphodiesterase-5 (PDE5) thereby improving the erectile function by increasing the amount of cyclic guanosine monophosphate in the smooth muscle of the corpus cavernosa. This study aims for the comparison of tadalfil with other established drug tamsulosin in Indian population*
Methods*: A total of 100 patient presenting with lower urinary tract symptoms(LUTS) due to BPH were selected and randomized with card method to receive either 5mg tadalafil daily or 0.4 mg tamsulosin daily. The parameters recorded includes Q max, PVR(post void residual urine), IPSS(International prostate symptom score), IIEF(International index of erectile function-erectile function) at the start of study and at end of 12 weeks. Data was analysed using Student T Test.*
Results*: The groups were identical for statistical analysis. LUTS was improved by both tamsulosin and tadalafil. But tamsulosin is slightly more effective than tadalafil but notstatistically significant (p > 0.05) in relieving LUTS. Only tadalafil significantly improved erectile dysfunction (p<0.05).*
Conclusion*: Tadalafil is effective in treating the both LUTS and erectile dysfunction.*

I. Introduction

BHP – non malignant cause for LUTS in the men above 50 years of age[1]. BHP causes bladder outlet obstruction by either static or dynamic mechanism. Static mechanism is by the enlarged gland which can cured by surgery. The second mechanism is dynamic which responds to pharmacological management especially with alpha antagonists.[2,3]The phosphodiesterase inhibitor Tadalafil has been recently approved for the management of BHP, however the precise mechanism of action by which LUTS is reduced has not been determined. The PDE 5 inhibition by tadalafil increases the cyclic guanosine monophosphate in cavernosal smooth muscle thereby increasing the blood flow , resulting penile erection during sexual stimulation. The same mechanism also improves the blood supply in bladder neck and prostate.[4]In male erectile dysfunction old age is an important risk factor.This was shown by Kinsey et al,- the prevalence of ED increased with age from 0.1% at 20 years to 75% at 80 years of age[5]. The MMAS (12) showed that the prevalence of ED increased from 39% in men in their 40s to 67% for men in their 70s. Thus erectile dysfunction and BHP are both the disease of old age and they seem to co-exist simultaneously. Our study is mainly aimed to study about the effect of Tadalafil – PDE5 inhibitor in alleviating the LUTS in BHP patient.

II. Methods

The randamozied controlled single blind study conducted in the Department of Urology, Government Stanley Medical College, Chennai. The study period was for one year 2015-2016. The patients were randomised into two groups by card method - Tamsulosin group (group T)- 0.4 mg of tamsulosin hydrochloride once daily in the evening, and Tadalafil group (group D) - 5 mg of tadalafil in the evening.a totalof 100 male patients who visited the out patient department of Department of Urology satisfying the inclusion criteria were included in the study. Inclusion criteria were Men age more than 50 years, history of storage symptoms (increased day time frequency, urgency and nocturia and or voiding symptoms (hesitancy, incomplete voiding, impaired stream or interruption of stream), nocturia>2, IPSS >13 points, international prostatic symptom bother score >3 points, maximum flow rate <15 ml/sec with a voided volume of at least 150 ml, postvoid residual urine less than 100 ml by transabdominal ultrasound. Patients who had previous prostate surgery, severe visceral disease, postural hypotension, neurogenic bladder dysfunction, suspected prostate cancer (elevated PSA), urethral stricture

disease, bladder neck disease, acute bacterial prostatitis, acute urinary tract infection, urolithiasis, active hematuria, renal insufficiency (serum creatinine >2.0mg/dl), concomitant medication that may alter the voiding pattern before inclusion, patients on antipsychotic medications, insulin dependant diabetes mellitus, history of severe heart disease were excluded. Evaluation included clinical determination of IPPS, QoL, IIEF, uroflowmetry parameters (maximum flow rate (ml/s), time to maximum flow, average flow rate) postvoid residual urine volume and prostate size by ultrasonographically were recorded inclusion, 1 month and 3 month respectively. Data obtained were analysed using Student T Test.

III. Results

The patients included in the study was 100(n). The parameters analysed included age, prostate size, postvoid residual urine, uroflow parameters, IPSS and IIEF score.Mean age of patients was comparable 65.3+/-11.3 for tamsulosin group and 64.2+/-10.8 in tadalafil group. Mean prostate size was 54gms and 50gms respectively. Datas for Prostate size, postvoid residue uroflow parameters and IPSS scores are shown in Tables 1,2,3 and 4. The drugs did not decrease the size of the glands however post void residual urine was reduced by tamsulosin and not by tadalafil.The effect on LUTS and uroflow parameters was shown by both the drugs. However the erectile function was improved only by tadalafil as shown by IIEF questionnaire. 68 patients out of 100 were sexually active of which32 were in tamsulosin group and 35 were in tadalafil group. Patients tolerated both the drugs with no severe reaction wanting the patient to stop the drug. 2 patient on tamsulosin group reported weakness and one had mild headache. While in tadalafil group 2 patients had head ache and 2 had nasal congestion.

	Baseline	**1 month**	**3 month**	**p value**
Group1:Tamsulosin	55.00 ±6.29	54.00 ± 6.47	54.00 ± 7.16	0.15
Group 2: Tadalafil	50.00±7.18	50.00±7.01	50.00±7.17	0.17

Table 1: Prostate Size

	Baseline	**1 month**	**3 month**	**p value**
Group1:Tamsulosin	95.00 ±10.34	35.00 ±9.07	12.00 ±5.78	≤0.001
Group 2: Tadalafil	88.0±9.18	69.00±8.04	57±5.43	0.065

Table 2: Post Void Residual Volume

	Tamsulosin				Tadalafil			
	Inclusion	**Month 1**	**Month 3**	**p value**	**Inclusion**	**Month 1**	**Month 3**	**p value**
Maximum flow rate (ml/s)	9.6 ±0.72	12.45 ± 1.29	12.76 ± 1.32	≤0.001	9.4 ± 0.98	11.5 ± 1.98	11.67± 1.89	0.09
Average flow rate (ml/s)	5.9 ± 0.68	7.2 ± 0.57	7.3 ± 0.76	≤0.001	5.1 ± 0.84	6.4 ± 0.72	7.1 ± 0.84	0.05
Time to Maximum flow	40.0 ± 5.23	36.3 ± 4.67	31.5 ± 3.68	≤0.001	42.4 ± 5.77	37.1 ±2.37	32.60 ± 2.79	0.052

Table 3: Uroflow Parameters

	Tamsulosin				**Tadalafil**			
Scores	**Inclusion**	**Month 1**	**Month 3**	**P Value**	**Inclusion**	**Month 1**	**Month 3**	**P Value**
IPSS	21 ± 3.0	13.0 ± 2.25	11.5 ± 1.85	≤0.001	19.0 ± 2.5	12.5 ± 1.8	10.5± 1.0	≤0.001
IIEF-5	12.4 ± 0.54	12.0 ± 0.46	11.8 ± 0.48	0.525	12.6 ± 0.56	15.5 ± 0.62	17.9± 0.53	≤0.001

Table 4: IPSS and IIEF scores of both the group

IV. Discussion

BHP and ED are both occurring in the old aged men with incidence increasing as age further. The major pharmacological agent used in the management of BHP (alpha blockers) has negative impact on sexual wellbeing adding further to the erectile dysfunction[7,8]. In case of LUTS due to BHP, the selective alpha -1 blocker is the first line pharmacological agent widely used apart from finasteride / dutasteride[16]. The contractile tissue present in the bladder neck, prostate capsule, and stroma are abundant in α_1-adrenergic receptors[17,18] However studies have shown that the incidence of abnormal ejaculation was 30% and erectile dysfunction was 6% in those patients treated with tamsulosin [19].

The prevalence and existence of LUTS and Male sexual dysfunction in old age was studied in The Multinational Survey of the Ageing Male (MSAM7).The prevalence rate of both Erectile Dysfunction (ED – 49%) and Ejaculatory Dysfunction (EjD – 47%) was predominantly age dependent and correlated highly with the severity of LUTS[9]. Erectile dysfunction is primarily managed with PDE 5 inhibitors. Tadalafil (5mg) is

approved by FDA in the treatment of LUTS due to BHP. This is mainly to treat both LUTS and ED simultaneously without worsening either of the disease[10-12].

The mechanism of action of PDE5 inhibitors is upregulation of the NO/cGMP activity. Preclinical studies reported partial reversal of nor-epinephrine- and endothelin-1-reduced prostatic tissue contraction [13]and an anti-proliferative effect on cultured prostate and bladder smooth muscle cells[14]. As a result there is decrease in smooth muscle tension in the prostatic stroma and capsule and also attenuate cellular proliferation associated with prostate/bladder neck hypertrophy respectively. Tadalafil had shown improved blood flow to prostate on color doppler ultrasound[15].

McVary and Roehrborn study showed no change in PVR(post voidal residual volume) in the tadalafil group[20-21]. There was no change in PVR even at end of 3 months in the tadalafil group.The changes in IPSS, peak urinary flow (Qmax) and PVR were small and not clinically meaningful as published by Prost and colleagues[22]. According to Brock and colleagues the changes in IPSS, peak urinary flow (Qmax) and PVR after 12 weeks of treatment with placebo or various doses of once-daily tadalafil were similar in men with or without comorbid ED. Even after 12 weeks, changes in IPSS in men with ED and without ED were not significantly different (subgroup/interaction p values: 0.352/0.644)[23]. The action of tadalafil to reduce LUTS was independent of its action on ED. Similar findings were observed in our study.The safety of tadalafil has also been proved by these studies. As in the classic ED trials, the most common side effects were headache, dyspepsia, nasal congestion, flushing and back pain[24].

Recent literature shows data on combining finasteride with tadalafil and IPSS improved in the combination group[24]. At present of all PDE5 inhibitors tadalafil is the only drug approved for treating both symptoms. The main concern is whether to treat the sexual dysfunction which is subclinical elicited only by questionnaire. However tadalafil can used safely and efficiently in young patients who are sexually active with symptoms of LUTS.

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