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EFFICACY OF LOW DAILY DOSE OF TADALAFIL AS MONO-THERAPY FOR DIABETIC PATIENTS WITH LOWER URINARY TRACT SYMPTOMS SUGGESTIVE OF BENIGN ENLARGEMENT OF PROSTATE

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Abstract

Objective: *To assess efficacy of tadalafil or tamsulosin versus placebo for LUTS/BEP.*

Methods: *This was a triple blind randomized control trial (RCT). This study was done on 150 cases of well controlled diabetic patients with LUTS/BEP after screening. The patients were >45 years of age, international prostate symptom score (IPSS) > 13, maximum urine flow rate (Qmax) 10-15 ml/sec. Selected patients were randomized in to 1:1:1 ratio to once-daily tadalafil 5 mg, tamsulosin 0.4 mg, or placebo for 12 weeks. Efficacy measures were assessed by IPSS, Qmax, post-voidal residue (PVR) in ultra-sonogram.*

Results: *IPSS significantly improved versus placebo through 12 wk with tadalafil (-4.81; p<0.001) and tamsulosin (-4.03; p<0.001) and as early as 1 wk (tadalafil -2.04; p=0.001 and tamsulosin -2.14; p < 0.001). The IPSS Quality-of-Life Index improved significantly versus placebo with tadalafil (p<0.001) and with tamsulosin (p<0.001) but outcome was better with tadalafil. Qmax increased significantly versus placebo with both tadalafil (6.52 ml/s; p<0.001) and tamsulosin (6.64 ml/s; p<0.001). Adverse event profiles were consistent with previous reports.*

Conclusion: *Monotherapy with 5 mg daily tadalafil or 0.4 mg daily tamsulosin resulted in significant and similar improvements versus placebo in IPSS+QOL in diabetic patients with LUTS/BEP staring from week one and maintained throughout the week 12. It However, Tadalafil also significantly improve Qmax. The adverse event profile was minimal and consistent with those previously reported with these drugs.*

Key words: Tadalafil, Diabetic, Benign enlargement of prostate

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Introduction

Medical therapy for LUTS/BPH consists of á-blockers, 5á-reductase inhibitors or combination therapy. In spite of having a good efficacy, these therapies have some potential side effects including sexual dysfunction. Tadalafil is a phosphodiesterase type 5 (PDE5) inhibitor (PDE5-I) widely approved for the treatment of ED. Several placebo-controlled studies in men with LUTS/BPH have demonstrated improvements with tadalafil. There is no study of their effects on diabetic patients with LUTS/BPH of Bangladesh. In our set up, we encounter these patients regularly. A study on this patient group to see outcome of different treatment options are imperative. So, in BIRDEM General Hospital it is provoking to design a study with these groups of patients.

Methodology

It was a randomized, double-blind, placebo controlled, parallel-group study in the department of Urology, BIRDEM General Hospital, Dhaka, from July 2014 to July 2016. Study population were diabetic patients presented with LUTS/BPH in Urology Department of BIRDEM General Hospital. Total 150 patients were studied. Patients included had following criteria: age > 45 yr who had LUTS/BPH for >6m at screening, IPSS > 13 and maximum urinary flow rate (Qmax) 10 to 15 ml/

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s prior to the study. Patient excluded were those with PSA > 10.0 ng/ml, PVR > 100 ml at screening, lower urinary tract stones within 6 months, patient with urethral stricture, neurogenic bladder and men who have used finasteride or dutasteride within 3 or 6 months respectively. Patients who were included, were randomized in 1:1:1 ratio to once-daily tadalafil 5 mg, tamsulosin 0.4 mg, or placebo for 12 weeks after taking written informed consent. Drugs of three groups were leveled in container as Drug-A, Drug-B and Drug-C by a non-biased third person who kept the information secret till the end of data collection. Patients were then followed up according to the protocol of visit and all data were documented in the data sheet.

- **Protocol of visit:**
- **Visit 1: screening:** IPSS+QoL, Uroflowmetry, USG-PVR
- **Visit 2: Randomization** – week 0
- **Visit 3: week 1:** IPSS+QoL
- **Visit 4: week 4:** IPSS+QoL, Uroflowmetry, USG - PVR
- **Visit 5: week 8:** IPSS+QoL
- **Visit 6: week 12** or early if required: IPSS+QoL, Uroflowmetry, USG- PVR

At every visit all patients were asked for any adverse effect he noted, or worsening of LUTS. Every patient also asked, if he wanted to continue to participate in the study till the next visit. Of 150 patients 94% of subjects completed the study. Six patients in placebo group discontinued the treatment at different stages for worsening of symptoms. In tadalafil group one patient discontinued the treatment due to severe headache and in tamsulosin group two patients discontinued the treatment for postural hypotension.

Results

Treatment groups were well balanced concerning clinical characteristics as shown in table 1. These ensured matched patient groups in all three treatment arms.

At fourth week, all patients were assessed with IPSS+QOL, ultrasound measurement of PVR and Qmax. One patient in tadalafil group and one patient in tamsulosin group discontinued the study for severe headache and postural hypotension respectively. Improvement was significant (table-2) against placebo for both tadalafil 5 mg group and tamsulosin group for IPSS voiding and storage subscore, nocturia question; total IPSS, QOL, Qmax and PVR.

Table-I

Baseline characteristics of all randomized subjects (n=150)

Baseline characteristics	Placebo (n=50) Mean±SD	Tadalafil 5mg (n=50) Mean±SD	Tamulosin 0.4 mg (n=50) Mean±SD
IPSS voiding subscore	10.88±2.34	11.14±2.45	11.58±2.40
IPSS storage subscore	8.80±1.40	8.80±1.40	8.66±1.55
IPSS nocturia question	2.32±0.84	2.28±0.90	2.50±0.91
IPSS total	19.68±3.05	19.94±3.20	20.24±3.26
QOL	3.62±0.60	4.08±0.60	4.04±0.67
HbA_1C	7.19±0.70	7.15±0.71	7.10±0.79
Serum creatinine	1.02±0.19	1.03±±0.19	1.03±0.19
Serum PSA	2.38±0.74	2.39±0.73	2.39±0.73
Prostate size	48.64±14.93	50.96±16.14	50.28±15.33
PVR	61.24±14.67	64.64±17.00	65.86±17.53
Q max	13.14±1.53	12.56±1.88	12.28±1.84

Table-II

Change from baseline to after 4 weeks

	Placebo (n=50)	Tadalafil 5mg (n=49)	Tamsulosin 0.4 mg (n=49)
IPSS voiding subscore	n=50	n=49	n=49
Change from baseline mean±SE	-0.20±0.17	-2.96±0.09	-3.55±0.12
Change vs placebo, mean±SE	-	-2.43±0.48	-2.72±0.48
p value	-	<0.001*	<0.001*
IPSS storage subscore	n=50	n=49	n=49
Change from baseline mean±SE	-0.16±0.10	-2.06±0.06	-2.10±0.07
Change vs placebo, mean±SE	-	-1.91±0.29	-2.10±0.29
p value	-	<0.001*	<0.001*
IPSS nocturia subscore	n=50	n=49	n=49
Change from baseline mean±SE	-0.10±0.09	-1.02±0.09	-1.35±0.10
Change vs placebo, mean±SE	-	-0.97±0.17	-1.07±0.17
p value	-	<0.001	<0.001
IPSS Total	n=50	n=49	n=49
Change from baseline mean±SE	-0.36±0.21	-5.02±0.09	-5.65±0.15
Change vs placebo, mean±SE	-	-4.34±0.64	-4.8±0.64
p value	-	<0.001*	<0.001*
QOL	n=50	n=49	n=49
Change from baseline mean±SE	-0.02±0.11	-1.837±0.09	-1.67±0.10
Change vs placebo, mean±SE	-	-1.39±0.14	-1.27±0.14
p value	-	<0.001*	<0.001*
Change from baseline mean±SE			-2.02±0.28
Change vs placebo, mean±SE	-	-2.11±0.28	<0.001*
p value		-	<0.001*
PVR	n=50	n=49	n=49
Change from baseline mean±SE	3.28±2.70	-31.73±2.17	-34.26±2.75
Change vs placebo, mean±SE	-	-31.44±3.45	-32.87±3.45
p value	-	<0.001*	<0.001*
Qmax	(n=50)	n=49	n=49
Change from baseline mean±SE	0.12±0.23	4.35±0.24	4.63±0.32
Change vs placebo, mean±SE	-	3.59±0.48	3.67±0.48
p value	-	<0.001*	<0.001*

Results are expressed as Mean±SD.Unpaired Student's t-test was performed to compare between groups. The test of significance was calculated and p values < 0.05 was accepted as level of significance. n= number of patients, *= significant

On eight week, patients were assessed with IPSS+QOL. Six patient of placebo group left the study for worsening of LUTS. Another patient of tamsulosin group discontinued for postural hypotension. At this point, tendency of improvement was like previous weeks (table-III).

Table-III
Change from baseline to after 8 week

	Placebo (n=44)	Tadalafil 5mg (n=49)	Tamsulosin 0.4 mg (n=48)
IPSS voiding subscore	n=44	n=49	n=48
Change from baseline mean±SE	-0.477-0.119	-3.55±0.13	-3.56±0.12
Change vs placebo, mean±SE	-	-2.32±0.42	-1.93±0.42
p value	-	<0.001*	<0.001*
IPSS storage subscore	n=44	n=49	n=48
Change from baseline mean±SE	-0.23-0.09	-2.38±0.10	-2.10±.068
Change vs placebo, mean±SE			
p value			
IPSS nocturia subscore	n=44	n=49	n=48
Change from baseline mean±SE	-0.18-0.09	-1.16±0.11	-1.35±0.10
Change vs placebo, mean±SE	-	-0.96±0.16	-0.96±0.16
p value	-	<0.001*	<0.001*
IPSS Total	n=44	n=49	n=48
Change from baseline mean±SE	-0.70-0.09	-5.94±0.17	-5.67±0.15
Change vs placebo, mean±SE	-	-4.44±0.55	-3.96±0.55<0.001*
p value	-	<0.001*	
QOL n=44	n=49	n=48	
Change from baseline mean±SE	-0.16-0.09	-2.12±0.13	-1.75±0.11
Change vs placebo, mean±SE	-	-1.38±0.12	-1.03±0.12
p value	-	<0.001*	<0.001*

Results are expressed as Mean±SD.Unpaired Student's t-test was performed to compare between groups. The test of significance was calculated and p values < 0.05 was accepted as level of significance

Lastly, on twelve week, patients were assessed with IPSS+QOL, PVR and Qmax. Here it was evident that there was significant improvement against placebo (table 4) for both tadalafil 5 mg group and tamsulosin group for IPSS voiding subscore (p <0.001, <0.001), storage subscore (p <0.001, <0.001), nocturia question (p <0.001, <0.001), total IPSS (p <0.001, <0.001), and QOL (p <0.001, <0.001). PVR (p <0.001, <0.001) and Qmax (p <0.001, <0.001) were also significantly improved.

Table-IV

Change from baseline to after 12 weeks

		Placebo (n=44)	Tadalafil 5mg (n=49)	Tamsulosin 0.4 mg (n=48)
IPSS voiding subscore		n=44	n=49	n=48
	Change from baseline mean±SE	0.48±0.12	-3.77±0.11	-3.56±0.12
	Change vs placebo, mean±SE	-	-2.55±0.42	-1.94±0.43
	p value		- <0.001*	<0.001*
IPSS storage subscore		n=44	n=49	n=48
	Change from baseline mean±SE	-0.16±0.11	-2.46±0.09	-2.10±0.07
	Change vs placebo, mean±SE	-	-2.26±0.28	-2.09±0.28
	p value		- <0.001*	<0.001*
IPSS nocturia subscore		n=44	n=49	n=48
	Change from baseline mean±SE	-0.14±0.09	-1.16±0.11	-1.35±0.10
	Change vs placebo, mean±SE	-	-1.01±0.16	-1.01±0.17
	p value		- <0.001*	<0.001*
IPSS Total		n=44	n=49	n=48
	Change from baseline mean±SE	-0.64±.098	-6.24±0.16	-5.67±0.15
	Change vs placebo, mean±SE	-	-4.81±0.56	-4.03±0.57
	p value		- <0.001*	<0.001*
QOL		n=44	n=49	n=48
	Change from baseline mean±SE	-0.07±0.10	-2.14±0.14	-1.77±0.11
	Change vs placebo, mean±SE	-	-1.49±0.14	-1.14±0.14
	p value		- <0.001*	<0.001*
PVR		n=44	n=49	n=48
	Change from baseline, mean±SE	-2.09±1.37	-45.33±2.45	-46.42±2.77
	Change vs placebo, mean±SE	-	-39.16±2.38	-39.55±2.39
	p value		- <0.001*	<0.001
Qmax	Change from baseline mean±SE	n=4	n=4	n=4
		40.36±1.31	97.53±0.36	87.89±0.45
	Change vs placebo, mean±SE	-	6.52±0.59	6.64±0.59
	p value		- <0.001*	<0.001*

Results are expressed as Mean±SD.Unpaired Student's t-test was performed to compare between groups. The test of significance was calculated and p values < 0.05 was accepted as level of significance. n= number of patients, *= significant

Table-V
Adverse events

	Placebo (n=50) No. (%)	Tadalafil (n=50) No. (%)	Tamsulosin (n=50) No. (%)
Subjects with one or more TEAE	3(6.0%)	7(14.0%)	6(12.0%)
Headache	1(2.0%)	3(6.0%)	1(2.0%)
Postural hypotension	0	02(4.0%)	
Stuffy nose	2(4.0%)	2(4.0%)	0
Dizziness	0	1(2.0%)	1(2.0%)
Dyspepsia	0	1(2.0%)	1(2.0%)
Ejaculatory dysfunction	0	01(2.0%)	
Subject discontinuing because of TEAE	0	1(2.0%)	2(4.0%)

There were no severe adverse events in any of the active treatment groups and placebo (table 5). The most common TEAEs with tadalafil were headache (n=3) followed by stuffy nose (n=2), dizziness (n=1), and dyspepsia (n=1), while with tamsulosin the most common events were headache (n=6) followed by postural hypotension (n=2), dyspepsia (n=1) and dizziness (n = 1). One subject in the tamsulosin group reported ejaculatory dysfunction (retrograde ejaculation and semen volume decreased). There were no clinically significant changes in laboratory measurements or vital signs. One patient in tadalafil group discontinued the study for severe headache and two patient of tamsulosin group discontinued treatment for postural hypotension.

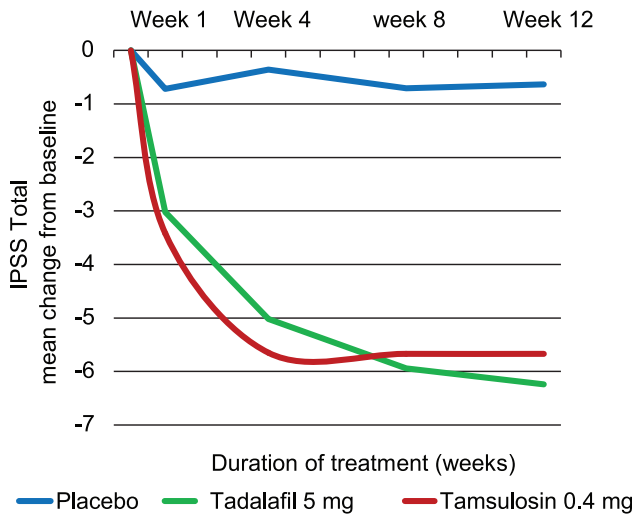

Fig.- 1: *Changes in total IPSS from baseline*

Change from baseline up to 12 weeks for total IPSS showed significant and similar impreovement for both tadalafil 5 mg group (p=<0.001) and tamsulosin 0.4 mg group (p=<0.001) in this graph. The change is significant even at week one for both tadalafil and tamsulosin.

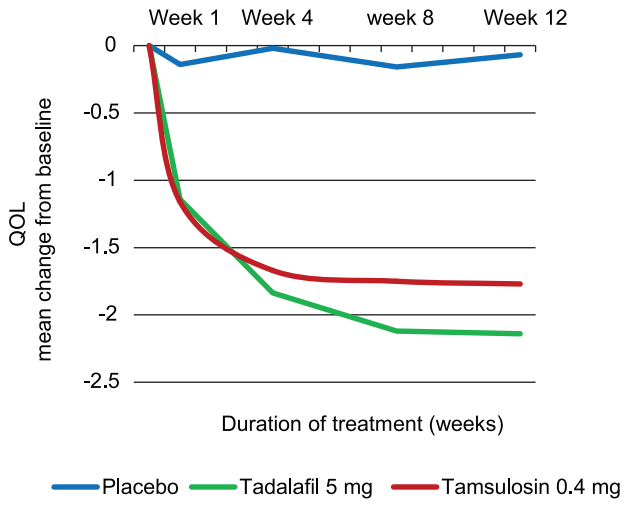

Fig.-2: *Changes in QOL from baseline*

Above graph shows significant improvement in QOL form baseline to week 12 for both tadalafil 5 mg group (p=<0.001) and tamsulosin 0.4 mg group (p=<0.001). Here, tadalafil (mean change + SD = -2.14 ±. 014) shows better outcome than tamsulosin (mean change + SD = -1.77 ± 0.11).

Discussion

In this, triple blind randomized controlled trial, evaluating tadalafil or tamsulosin (as an active control) for LUTS/

BEP, tadalafil 5 mg once daily for 12 weeks resulted in significant and clinically meaningful improvements in LUTS/BEP similar to tamsulosin 0.4 mg once daily.

In our study, mean age of the patients was 63.6 years. Mean + SD of age for placebo was 64.7 + 9.5, for tadalafil 64.7 + 9.2 and for tamsulosin 61.6 + 5.9. So age distribution was balanced in all three groups. In study by Oelke et al. [1], mean age was 64 yr, in Broderick et al. [2], 62.6 yr and in Porst et al. [3], 65 yr. Thus the age distribution was matched most of the international study.

Mean + SD baseline total IPSS was 19.68 + 3.05 in my study. It was 17.4 + 6.0 in Oelke et al. [1], 18.5 + 5.6 in McVary et al [4], 17.77 + 5.60 in Roehrborn et al. [5], 18.5 + 5.8 in study of Egerdie et al. [7]. Baseline QOL (mean + SD) in my study was 3.62 + 0.60 and was 3.8 + 1.4 in McVary et al [4], 3.6 + 1.2 in Broderick et al [2].

Baseline Qmax (mean + SD) in this study was 12.28 + 1.84. It was 10.5 + 4.1 in Oelke et al [1], 11.8 + 1.8 in McVary et al [6], 11.7 + 4.4 in Porst et al. [3]. 78.6% of subjects had ED at baseline in my study. It was 69% in Oelkey et al [1], 84% in McVary et al [4], 64% in Roehrborn et al. [5] and 68% in Porst et al. [3].

From above discussion it can be concluded that baseline parameter of my study was nearly similar to most of the similar international study. However, contrast to the other study all my patients were diabetic, which made this study a unique one.

Symptom score assessments, in conjunction with medical history and physical examination, are the primary tool for LUTS diagnosis and progression, as recommended by the American Urological Association [6]. Total IPSS improvement with tadalafil and tamsulosin was clinically meaningful (improvement of three or more points from baseline) [3,6] and continued throughout the 12 weeks.

In our study, total IPSS reduction was apparent even at one week and was statistically significant with both tadalafil and tamsulosin. It was in contrast with the findings of Oelke et al [1] where though improvement in total IPSS was apparent from week one but it was statistically significant from week four. Changes in total IPSS was significant for tadalafil 5 mg once daily from second week in study of Egerdie et al [7].

Patients of both tadalafil 5 mg and tamsulosin 0.4 mg groups showed significant improvement for IPSS voiding and storage subscores and nocturia question starting from week one and maintained up to week 12. However, for nocturia question patients of tamsulosin group had better outcome than tadalafil group. This findings are consistent with those from a tadalafil dose finding study in >1000 men with BEP/LUTS [8].

Patients of both tadalafil 5 mg daily and tamsulosin 0.4 mg daily showed significant improvement in measures of LUTS/BEP QOL at end point; but patient in tadalafil group do better. This finding also matched with other studies [1]

The magnitude of improvement in total IPSS at end point with tadalafil 5 mg in this study was consistent with several previous reports [3,7], and the improvement was also comparable to that seen in previous studies with alpha blockers like tamsulosin 0.4 mg [1,6]. Gacci et al. [4] reported that the degree of improvement in IPSS after PDE5-I treatment depended on the baseline characteristics of the patients, such as age and the baseline IPSS, indicating that young men with severe urinary symptoms (as measured by IPSS) are the best candidates for PDE5-I therapy.

Both tadalafil 5 mg daily and tamsulosin 0.4 mg daily were significantly superior to placebo on improving Qmax. This result is consistent with findings of Oelke et al [1] and Yang et al [8]. In most of the previous study improvement in Qmax was small for tadalafil and was not significant [2-5].

Theoretically, the relaxation of the prostate and bladder neck after PDE5-I treatment could increase urinary flow; however, the concomitant relaxation of the detrusor muscle counteracts this effect, thereby preventing the observation of a final improvement in Q max that is found in these study. However, the baseline urinary flow rate appears to determine the final result, and a lower baseline could allow more room for improvement, thereby increasing the probability of observing an improvement in Q max [8].

TEAEs were reported more with tadalafil and tamsulosin patients than placebo patients. Headache was most common TEAE for both tadalafil and tamsulosin. There were no novel safety findings in this study, and the most common TEAEs were consistent with the known side-effect profiles of these agents [1,3]. Discontinuation of treatment because of an adverse event was minimal (2%) in this study. Treatment discontinuation was 11.4% in study of Oelke et al [1], 7.7% in Porst et al [3], 10.7% in McVary et al [8].

This study was focused on the short-term impact of tadalafil 5 mg once daily. However, results of an open-

label extension study enrolling 427 men with LUTS/BEP showed that efficacy improvements with tadalafil were maintained for an additional one year of treatment, with a safety profile consistent with that previously reported for long term studies of tadalafil once daily in men with ED [9].

Conclusions and recommendations

Tadalafil 5 mg or tamsulosin 0.4 mg once daily resulted in significant and similar improvements versus placebo in IPSS + QOL in diabetic patients with LUTS/BEP symptoms as early as one week and throughout the 12 weeks treatment period. In addition, tadalafil and tamsulosin similarly improved Qmax through 12 wk. Treatment satisfaction was more with tadalafil than tamsulosin. Monotherapy with low daily dose tadalafil is efficacious and equivalent to tamsulosin in LUTS/BEP. From the result of this study and review of literature, it can be recommended that, tadalafil 5 mg daily can be used safely in patients with LUTS/BEP.

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