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Research Article

Combination of alfa blocker with low dose tadalafil in benign prostatic hyperplasia with erecticle dysfunction management

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ABSTRACT:

Objective: To study the combination therapy with daily low dose tadalafil (5mg) and alpha blockers for the treatment of BPH-LUTS and Erecticle dysfunction (ED).

Materials and Methods: The medical records of 168 patients who had medical management for symptomatic BPH/LUTS with or without ED from January 2010 to December 2013 were reviewed retrospectively. All patients were divided into 2 groups. Group-1(n: 74) included patients received a single daily dose of tamsulosin 0.4mg or alfuzosin 10mg . Group-2 (n:75) patients with LUTS and BPH who were previously managed with alpha blockers (tamsulosin 0.4mg or alfuzosin 10mg) were included in our study by addition of 5mg phosphodiesterase type 5 inhibitor (tadalafil), which has been reported to be useful in the management of BPH/LUTS and ED. We analysed the International Prostate Symptom Score (IPSS), IIEF Score, BPH Impact Index (BII) and Quality of Life (QoL).

Results: Before the inclusion of tadalafil patients exclusively on alpha blockers had a mean IPSS score of 21.51 ± 2.89). IPSS improved to a mean of 11.34 ± 1.56 ($p<0.001$) after the addition of a single daily dose of 5mg tadalafil. A previous mean BPH Impact Index of 8.52 ± 1.22($p<0.001$) improved to 4.38± 0.89 ($p<0.001$). Quality of Life index was graded with a mean of 3.76 ± 1.10 before addition of tadalafil and improved to a mean of 2.22 ± 0.76 ($p<0.001$). IIEF-5 scores changed from 15.54 ± 3.68 to 7.89 ± 3.84 ($p<0.001$), after 12 weeks of treatment.

Conclusion: We recommend tadalafil 5mg once daily dose for BPH/LUTS patients with higher IPSS score, diabetes, smaller prostate and inoperable patients.

Keywords: Prostate hyperplasia, Phosphodiestrase inhibitors, Erecticle dysfunction.

INTRODUCTION:

The enlarged gland has been proposed to contribute to the overall lower urinary tract symptoms (LUTS) complex via at least two routes: (1) direct bladder outlet obstruction (BOO) from enlarged tissue (static component) and (2) from increased smooth muscle tone and resistance within the enlarged gland (dynamic component). Voiding symptoms have often been attributed to the physical presence of BOO. Detrusor overactivity is thought to be a contributor to the storage symptoms seen in LUTS. The prevalence of Benign Prostatic Hyperplasia (BPH)-lower urinary tract symptoms (LUTS) is currently reported as 10%–25% for the male population and is estimated to rise to 1.1 billion affected males by the year 2018.[1–4] LUTS vary in severity, ranging from mild to severe, affecting patients' quality of life (QoL) accordingly. Prior to the early 1990s, symptomatic BPH was commonly treated with surgery, most notably transurethral prostatectomy. Although LUTS secondary to BPH (LUTS/BPH) is not often a life-threatening condition, the impact of LUTS/BPH on quality of life (QoL) can be significant and should not be underestimated. A variety of pharmacologic classes are employed including alpha-adrenergic antagonists (alpha-blockers), 5-alphareductase inhibitors (5-ARIs), anticholinergics and phytotherapeutics. Choosing the correct medical treatment for BPH is truly complex and ever-changing. In the early 1990s, as a result of medical therapy using non-selective α-blockers, use of transurethral prostatectomy declined significantly. Around this time, 5α-reductase inhibitor therapy with finasteride was introduced, but initially struggled to find its ideal target patient. Combination therapies with α-blockers and 5α-reductase inhibitors have evolved, and have now become a safe and effective treatment for men with larger prostate volumes.[5]

Furthermore, the prevalence of erectile dysfunction (ED) also increases concomitantly with age. By the age of 40 years, 40% of men will experience some form of ED.[6] ED has been observed to coexist with BPH and is more common as men age. [7-11] In a multinational survey of aging males, LUTS were

identified as a risk factor for ED. [10] Phospho Diesterase Enzymes (PDE) are involved in the regulation of the nitric oxide (NO)–cyclic GMP– protein kinase pathway and are effective in reducing smooth muscle tone and are the current first-line treatment option for the majority of men with ED due to their excellent efficacy and safety profile[8]. Early clinical research showed that all PDE5i are also beneficial for the treatment of LUTS. However only tadalafil 5 mg once daily has been approved for the treatment of BPH associated LUTS in men with or without ED [12].

Tadalafil was approved for daily use in the treatment of BPH in October 2011 and represents a novel mechanism of action for treatment of the signs and symptoms of BPH [13]. As a natural progression, tadalafil has been used in combination with α-blockers and 5α-reductase inhibitors. This article reviews recent clinical data and makes recommendations as to ideal patients for therapy.

MATERIALS AND METHODS:

The medical records of 168 patients who had medical management for symptomatic Benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) men with or without ED from January 2010 to December 2013 were reviewed retrospectively. Our study was approved by our institutional ethics committee. Written informed consent was taken from all patients for photographing, recording and also its use for scientific and medical education purposes. Patients presented to the outpatient clinic with clinical features suggestive of BPH/LUTS and with or without ED. The patients were subjected to a complete work up as per protocol i.e. history taking and general physical examination to identify any anatomical disorders or congenital anomalies. Complete blood count, urine analysis, urine for culture and sensitivity, coagulation profiles, electrolyte tests, renal function tests, uroflometry, serum PSA were conducted along with an ultrasonography. Inclusion criteria were 1) Patients from the age of 40 to 70 years, who presented with clinical features of BPH/ LUTS with or without ED. 2) had an IIEF-5 score of 18 on screening, and 3) were willing and able to participate in this clinical study. The following individuals were excluded from the study: those who 1) had shown hypersensitivity reactions to PDE5i, 2) were being treated with drugs that are known to affect erectile function (eg, antiandrogens and 5a-reductase inhibitors), 3) had undergone surgery for ED, 4) had taken a PDE5i for a month before our study, and 5) were being treated with nitrate preparations and nitric oxide providers. Exclusion criteria were also in patients with acute retention of urine, stricture urethra, neurogenic bladder, patients with large prostates (>60ml), carcinoma prostate, PSA >10.0 ng/mL (or PSA $\geq$ 4.0 to $\leq$10.0 ng/mL if malignancy had not been excluded). Patients underwent ultrasonography and uroflometry and their IPSS score, BPH Impact Index (BII) and Quality of Life (QoL), International Index of Erectile Function (IIEF), reflecting male sexual function; were assessed. All patients were divided into 2 groups. Group-1(n=82) included patients BPH/ LUTS without ED received a single daily dose of tamsulosin 0.4mg or alfuzosin 10mg. Group-2 (n=86) patients with LUTS and BPH with ED who were previously managed with alpha blockers (tamsulosin 0.4mg or alfuzosin 10mg) included in our study by addition of 5mg phosphodiesterase type 5 inhibitor (tadalafil), which has been reported by various well designed studies to be useful in the management of erectile dysfunction (ED), BPH and LUTS.

The patients were told that they should take tadalafil at least 6 hours after taking the alpha blockers (AB). Efficacy was analysed by mean change in the IPSS, a scoring system to analyse the baseline characteristics in patients medically managed by alpha adrenergic blocker, before inclusion of PDE5 inhibitor. Patients were also analysed by secondary measures using BPH Impact Index [BII], International Index of Erectile Function (IIEF), reflecting male sexual function; and IPSS Quality of Life [IPSS-QoL] adapted from American Urological Association Education and Research, Inc. [12] The efficacy and safety of this regimen were assessed at 4 weeks and 12 weeks after starting tadalafil administration and followed upto 26 weeks.

Statistical analysis:

The data values have been entered into MS-Excel and statistical analysis has been done by using IBM SPSS Version 20.0. For continuous variables, the data values are represented as mean and standard deviation. To test the mean difference between two groups, student's t-test (Independent sample t-test) was used. All the p values are having less than 0.05 are considered as statistical significant.

RESULTS:

We reviewed 168 patients with BPH and LUTS, with or without ED. Age of inclusion was 40 to 70 years. The mean age was 55.52. Of these, 8 men (9.75%) in Group-1 and 11 men (12.79%) in Group-2 respectively had dropped out of the study. Consequently, 149 men had completed the study. In Group-1(n=74) included patients with BPH/ LUTS and without ED exclusively on alpha blockers had a mean IPSS score of 23.84 ± 1.72 which improved to 11.34 ± 1.56 with 4 weeks of treatment. Group-2 (n=75) patients with LUTS and BPH with ED patients who were previously managed with alpha blockers (tamsulosin 0.4mg or alfuzosin 10mg) were included in our study by addition of 5mg phosphodiesterase type 5 inhibitor (tadalafil), which has been reported to be useful in the management of erectile dysfunction (ED), BPH and LUTS. Before the inclusion of tadalafil in patients, patients exclusively on alpha blockers had a mean IPSS score of 23.84 ± 1.72. After the inclusion of tadalafil to the treatment regime, improvement of IPSS scores were noted in all patients. Incomplete emptying improved from a previous mean of 4.39 ± 0.64 to 2.42 ± 0.72 ($p<0.001$). Frequency improved from a mean of 4.17 ± 0.815 to 2.07 ± 0.51 ($p<0.001$). Intermittency improved from a previous mean of 3.43 ± 0.671 to 1.64 ± 0.52 ($p<0.001$). Urgency improved

from a previous mean of 4.12 ± 0.71 to 1.56 ± 0.48 (p<0.001). Weak stream improved from a previous mean of 3.28 ± 0.68 to 1.68 ± 0.73 (p<0.001). Straining improved from a previous mean of 2.89 ± 0.82 to 1.72 ± 0.76 (p<0.001). 58 patients suffered from nocturia, and after the addition of tadalafil, 34 patients did not experience nocturia. Thus, IPSS improved to a mean of 11.34 ± 1.56 (p<0.001) after the addition of a single daily dose of 5mg tadalafil. The main outcomes of these trials have included the effect of therapy on the International Prostate Symptom Score (IPSS) and BPH Impact Index, used to track BPH symptomatology; International Index of Erectile Function (IIEF), reflecting male sexual function; and maximum urinary flow rate (Qmax). Treatment with PDE5-Is resulted in significantly improved IPSS and IIEF-5 scores compared to patients exclusively on alpha blockers. Moreover, IIEF-5 scores improved the most in those on combination therapy compared to those in the other group. IIEF-5 scores changed from 15.54 ± 3.68 to 7.89 ± 3.84 (p<0.001), after 12 weeks of tadalafil treatment. BPH Impact Index was also analysed and revealed the following. A previous mean of 8.52 ± 1.22 improved to 4.38 ± 0.89 (p<0.0001). Physical discomfort to patients reduced from a previous mean of 2.83 ± 0.94 to 1.37 ± 0.57 (p<0.0001), patients were more comfortable and less worried about their health (p<0.0001); bothersome urination reduced from a previous mean of 2.51 ± 0.37 to 1.61 ± 0.46 (p<0.0001), patients were comfortable to do their daily work (p<0.0001).Quality of Life index was graded with a mean of 3.76 ± 1.10 and improved to 2.22 ± 0.76 (p< 0.0001) after addition of tadalafil.

On uroflometry analysis, patients presented with a mean Q max of 8.96mL/sec; and a mean post void residual volume on ultrasonography of 110ml. Additional therapy showed positive change with good improvement in Q max (13.6mL/sec) and a mean residual volume of 40 ml. Our findings suggest that combination therapy resulted in significant improvement in the total IPSS. Mean change from 23.84 ± 1.72 to 11.34 ± 1.56 and the difference –17.44 ± 1.95. We identified good outcomes in IPSS voiding and storage scores. Patients with small prostate volumes on Tamsulosin / Alfuzosin had yielded better results. Significant change on uroflometry results were also noted, along with reduced post void residual volumes on ultrasonography in the follow-up period. The complications noted were headaches in 16 patients; dyspepsia in 8 and nasopharyngitis in 6 patients. Most patients were accommodating to the additional therapy.

The only limitation of our study is that we concentrated on patients with a high IPSS score. Since all the patients were already on alpha adrenergic blocker therapy, we added tadalafil to the on-going treatment regime and did not consider a washout period of 4 weeks.

DISCUSSION:

Globally, both erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) secondary to benign prostatic hyperplasia (BPH) are highly prevalent in men, and both conditions increase in prevalence with age [14–18]. Results from population–based surveys indicate that LUTS occur “at least sometimes” in up to 72% of middle–aged men [14-16]; while ED prevalence ranges from 2% in men younger than 40 years to 86% in men 80 years and older.[16-18] Strong epidemiological evidence supports a correlation between LUTS and ED [19,20]. LUTS was an independent risk factor for ED [21]. Several mechanisms have been proposed to explain the relationship between LUTS and ED, including pelvic reduction in nitric oxide synthase (NOS)/nitric oxide (NO) [22,23] and autonomic nervous system over activity [22-26]. Abnormal up regulation of the Rho A/Rho kinase (ROCK) pathway, which mediates smooth muscle contraction, might also contribute to the lack of smooth muscle relaxation in the prostate, urethra, bladder neck, and penis [23–25]. Upregulation of the ROCK pathway has been associated with pelvic ischemia and/ or atherosclerosis of blood vessels supplying pelvic organs [19], which is associated with ED and is a pathophysiologic risk factor for LUTS [22-25]. Altered androgen environment and inflammation represent additional pathophysiologic risk factors for LUTS and ED [22, 25].

Because PDE5 is widely expressed in the bladder, prostate, and urethra, the smooth muscle and vasculature within these structures, it represents potential targets for PDE5 inhibitors [22]. PDE5 inhibitors have been shown to relax human smooth muscle samples from the prostate, bladder, and urethra by upregulating NO/cGMP activity [28, 29]. In addition, blocking PDE5 down regulates ROCK activity and has an antiproliferative effect in cultured human bladder cells [30]. Animal models have shown reduced afferent nerve activity in the bladder following PDE5 inhibition [31,32], and a specific action of tadalafil on chronic inflammation in the prostate was recently reported [33]. Thus, the mechanisms by which PDE5 inhibitors improve LUTS/BPH are likely multifactorial: cGMP–mediated vascular relaxation, smooth muscle relaxation of the prostate and bladder, and decreased afferent nerve activity, which may complement vascular effects.

In a randomized double-blind crossover pilot study, Bechara et al [34] assessed the efficacy and safety of tamsulosin versus tamsulosin and tadalafil in patients with LUTS. Thirty men with BPH/LUTS were randomized to receive tamsulosin 0.4 mg/d versus tamsulosin 0.4 mg/d and tadalafil 20 mg/d for 45 days, and then they switched to the other treatment mode for 45 days. Improvements in IPSS and IPSS-QoL was significant with both treatments but greater with the drug combination. Both regimens similarly improved Qmax and decreased the PVR volume from baseline with no significant differences between tamsulosin alone versus tamsulosin and tadalafil. The IIEF domain score improved with tamsulosin and tadalafil but not with tamsulosin alone. Both treatments were well tolerated. This pilot study showed that tamsulosin with tadalafil was more effective than tamsulosin alone for both LUTS and ED [35].

In another study, 60 men with BPH-related LUTS were

randomized to receive sildenafil (25mg) monotherapy (n = 20), tamsulosin (0.4mg once daily) monotherapy (n = 20), or the combination of both (n = 20) for 8 wk [36]. IPSS, Qmax, PVR volume, Sexual Health Inventory for Male (SHIM) scores, and questions number 3 and 4 of the IIEF significantly improved in each group. Improvement in the symptom score was more evident in both the combination (40.1%) and the tamsulosin-only (36.2%) groups as compared with the sildenafil-only group (28.2%) (p<0.0001). Improvement of Qmax and PVR volume were greater in both the tamsulosin-only and in the combination group as compared with the sildenafil-only group. SHIM scores had a significantly greater improvement in both the sildenafil-only (65%) and in the combination (67.4%) group than in patients who received tamsulosin only (12.4%; p < 0.0001), and increases in the IIEF scores were greater in the sildenafil-only and combination group than tamsulosin only. This study showed that treatment with the combination of tamsulosin and sildenafil was not superior to monotherapy with tamsulosin to decrease voiding symptoms.

The efficacy of tadalafil to relieve LUTS secondary to BPH has been reported in a number of clinical trials (Table 3).

Daily tadalafil for BPH-related LUTS (IPSS ≥13), regardless of ED, was studied in a prospective double-blind, placebo-controlled, multicenter parallel-arm trial [36]. Patients were randomized to receive either tadalafil 5 mg (n = 138) or placebo (n = 143) daily; patients were stratified by IPSS (<20 or ≥20), prior a-blocker therapy, and geographic distribution. Patients were evaluated after 6 wk of treatment, and the tadalafil dose was increased to 20 mg daily. IPSS was <20 in 64% of patients. The IPSS change at 6 wk was significantly greater in the tadalafil 5 mg group than in the group receiving placebo (2.8 ± 0.5 vs 1.2 ± 0.5; p = 0.003).

The results from this study demonstrate that addition of tadalafil to existing alpha blocker significantly improved LUTS and QoL in men with BPH/LUTS. The total IPSS score and obstructive and irritative IPSS sub scores were significantly improved after tadalafil therapy in combination with alpha blocker compared with alpha blocker alone. The combination therapy with daily tadalafil and finasteride is ideally suited for men with moderate to severe BPH-LUTS and a prostate volume >30 g. In addition, men with coexisting erectile dysfunction will benefit from PDE5 inhibition. In this group of men, finasteride results in a reduced prostate volume, while tadalafil mediates lower urinary tract smooth muscle relaxation via PDE5 inhibition. This dual mechanism of action results in additive clinical improvements when compared with finasteride alone. The safety profile is consistent with that seen with daily tadalafil therapy.

CONCLUSION:

In conclusion, daily combination therapy with tadalafil 5 mg and alpha blockers (AB) in patients with LUTS/BPH and ED resulted in significant improvements in both LUTS and ED. Moreover, this combination therapy was not associated with any hypotensive interactions. Other adverse side effects were also minimal and self-limiting.

Conflict of Interest: None declared.

Table 1: Change in IPSS Score - Before and after administration of PDE5 inhibitor: Tadalafil Dose 5mg once daily

Variables	Mean ± SD			p value
	Alpha Blocker *(Group-1) [n=74]*	**Alpha Blocker + PDE5 Inhibitor** *(Group-2) [n=75]*	**Total** [n=149]	
Incomplete Emptying	4.39 ± 0.64	2.42 ± 0.72	3.38 ± 1.25	< 0.0001
Frequency	4.17 ± 0.815	2.07 ± 0.51	3.09 ± 1.32	< 0.0001
Intermittency	3.43 ± 0.671	1.64 ± 0.52	2.51 ± 0.68	< 0.0001
Urgency	4.12 ± 0.71	1.56 ± 0.48	2.81 ± 1.16	< 0.0001
Weak Stream	3.28 ± 0.68	1.68 ± 0.73	2.46 ± 0.68	< 0.0001
Staining	2.89 ± 0.82	1.72 ± 0.76	2.29 ± 0.64	< 0.0001
Total-IPPS Score	**23.84 ± 1.72**	**11.34 ± 1.56**	**17.44 ± 1.95**	**< 0.0001**

IIEF-5 scores changed from 15.54 ± 3.68 to 7.89 ± 3.84 (p<0.001),

Table 2: Change in BPH Impact Index and Quality of Life (QoL)

Variables	Mean ± SD			p value
	Alpha Blocker *(Group-1) [n=74]*	**Alpha Blocker + PDE5 Inhibitor** *(Group-2) [n=75]*	**Total** [n=149]	
Physical Discomfort due to urinary problems	2.83 ± 0.94	1.37 ± 0.57	2.08 ± 0.67	< 0.0001
How worried about health	1.74 ± 0.65	0.67 ± 0.52	1.19 ± 0.81	< 0.0001
How bothersome overall	2.51 ± 0.37	1.61 ± 0.46	2.05 ± 0.71	< 0.0001
Have the Symptoms kept from doing work	2.23 ± 0.42	1.22 ± 0.47	1.71 ± 0.68	< 0.0001
BPH Impact Index	**8.52 ± 1.22**	**4.38 ± 0.89**	**6.14 ± 1.39**	**< 0.0001**
Quality of Life (QoL)	**3.76 ± 1.10**	**2.22 ± 0.76**	**2.97 ± 1.48**	**< 0.0001**

Q max of 8.96mL/sec- good improvement in Q max (13.6mL/sec)

Table 3: Score differences and adverse effect profiles reported in meta-analyses comparing PDE5-Is to placebo and tadalafil to placebo

	Gacci et al [33]				**Dong et al [37]**			
	PDE5-Is		**Placebo**		**Tadalafil**		**Placebo**	
Number of patients	1,879		870		1,871		1,042	
Mean score difference	**Score (P-value)**				**Score (P-value)**			
IPSS	***−2.85 (<0.0001)***				***−2.19 (<000001)***			
IIEF	***5.49 (<0.0001)***				***4.66 (<0.0001)***			
Qmax	−0.01				0.34 (0.07)			
IPSS-QoL					***−0.35 (<0.0001)***			
BII					***−0.49 (<0.0001)***			
Adverse effect profile	%		OR	P value	%		RR	P value
Headache	4.6	2.1	**1.88**	0.008	3.6	2.6	**1.14**	0.04
Dyspepsia	3.1	0.8	**1.85**	0.029	3.3	0	**11.38**	<0.00001
Back pain	2.5	1.5	1.18	0.503	2.9	1.3	**2.95**	<0.0001
GERD	1	0.2	2.21	0.063	1.7	0	**7.4**	0.003
Flushing	1.2	0.2	**4.89**	0.007				
Overall	16	6			12.6	4.8		

Note: Bold and italic fonts highlight statistically significant results reported in papers mentioned in the table.
Abbreviations: BII, Benign Prostatic Hyperplasia Impact Index; GERD, gastroesophageal reflux disease; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; IPSS-QoL, IPSS quality of life index; OR, odds ratio; PDE5-Is, phosphodiesterase-5 inhibitors; Qmax, maximum urinary flow rate; RR, relative risk.

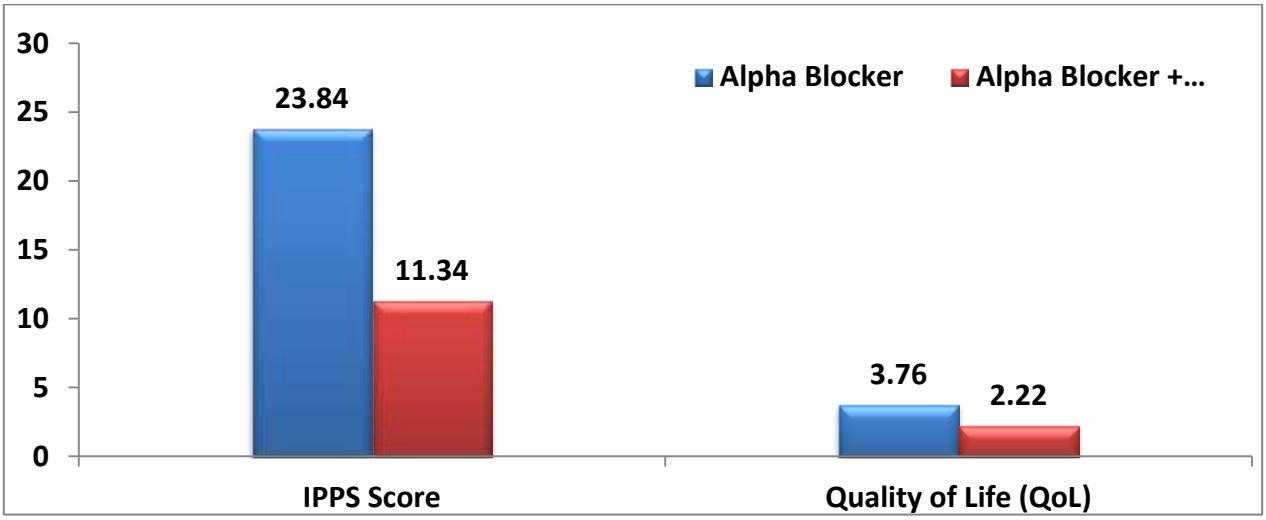

Figure-1: Comparison of mean values of IPSS Score, Quality of Life (QoL) in two groups

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