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Evaluation of Tadalafil effect on lower urinary tract symptoms of benign prostatic hyperplasia in patients treated with standard medication

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ABSTRACT

Objectives: To evaluate safety and efficacy of tadalafil on lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) in patients treated with standard medication.

Materials and Methods: In this case-controlled randomized clinical trial, from November 2008 to August 2009, 132 patients with obstructive and irritative urinary tract symptoms due to BPH, IPSS ≥ 8, no indication for surgical intervention and that reached plateau levels of response to treatment were selected. These patients were randomly allocated in two groups (each containing 66 patients). The treatment group received standard treatment of BPH and tadalafil (10 mg nightly); the placebo group received only standard treatment of BPH. IPSS, maximum urinary flow rate (Q_{max}) and quality of life were assessed before and after a 3-month period of study.

Results: Before treatment, mean IPSS, Q_{max} and quality of life values in the treatment and placebo groups were 13.06 ± 4.37 and 13.66 ± 4.25, 8.92 ± 2.96 mL/s and 9.09 ± 2.91 mL/s, 2.93 ± 0.86 and 2.66 ± 0.78, respectively. After treatment, mean IPSS, Q_{max}, and quality of life values in treatment group were 7.66 ± 3.99, 9.99 ± 4.76 mL/s and 1.80 ± 0.98, respectively. These findings were compared to corresponding values of the placebo group (11.37 ± 3.64, 8.73 ± 2.22 mL/s and 2.19 ± 0.53, respectively): IPSS and quality of life were significantly different but Q_{max} didn't show a significant change.

Conclusions: Tadalafil improves quality of life and urinary symptoms in patients with LUTS suggestive of BPH, but doesn't have any significant effect on Qmax. Therefore, this drug may be effectively used in combination with standard medical therapies for BPH.

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INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a pathological process responsible for the majority of lower urinary tract symptoms (LUTS) in elderly men (1). In addition, erectile dysfunction (ED), which has negative effect on quality of life (QoL), is another major problem of this age group (2).

The incidence of BPH increases with age. It is observed in about 50% of men over 50 year with prevalence increasing up to 90% in those older than 80 year. Moreover, 25% to 50% of men with histological confirmed BPH have LUTS (3).

The α-blockers and/or 5-α reductase inhibitors are used for the treatment of BPH frequently. The phosphodiesterase inhibitors are

used in the treatment of ED (4,5) and there are increasing data of effects of these drugs on bladder and urethral relaxation as well as of prostatic smooth muscles that may relief the symptoms of BPH (6,7). Preliminary data have suggested that treatment with PDE-5 inhibitors such as sildenafil improves LUTS in men with ED possibly as the result of smooth muscle relaxation of the lower urinary tract (8).

This study was conducted to evaluate the role of Tadalafil (a PDE-5 inhibitor) in combination with standard therapy for the treatment of BPH.

MATERIALS AND METHODS

This study was a randomized double-blind placebo controlled clinical trial which has been approved by the ethical review board of Guilan Medical University. All patients signed an informed consent to participate.

In the beginning of the study, 132 patients with definitive diagnosis of BPH whose response to medical therapy with standard medication had reached plateau levels (the symptoms of patients didn't change in the last three months) were selected. In the placebo group, 23 patients received an α-blocker and 43 patients received an α-blocker plus Finasteride, as well as placebo. In the treatment group, besides Tadalafil, 16 patients received an α-blocker and 50 patients received an α-blocker plus Finasteride.

Inclusion criteria were a total IPSS ≥ 8, Q_{max} from 5 mL/s to 15 mL/s and the plateau response to the routine medical treatment of BPH.

Exclusion criteria included patients with history of refractory urinary retention, persistent gross hematuria, recurrent urinary tract infection (UTI), renal insufficiency, bilateral hydronephrosis and bladder stones all secondary to BPH, spinal cord injury, prostatitis, bladder or prostate malignancy, bladder neck or urethral stricture, post voided residual urine volume greater than 120 CC, pelvic trauma or surgery, recent cardiac infarction (within the last 6 months), unstable angina, concomitant use of nitrates or NO donors, and androgens or anti-androgens, anticoagulants, cytochrome p-450 3A4 inhibitors. Also, if any complication occurred during the study period that needed surgical intervention, the patient was excluded from the study.

Complete history and physical examination, urine analysis, serum creatinine measurement, as well as ultrasonography of kidney, bladder and prostate with post voided residual urine volume measurement; uroflowmetry with measurement of the maximum flow rate (Q_{max}) and the assessment of quality of life (QoL) (Table-1) were performed. Then, the selected patients were randomized in two groups (66 patients in each group) by using random block method generated by Excell program. One group received placebo once nightly and another group received Tadalafil 10 mg nightly, in combination with previous treatment of BPH for 3 months. After 3 months, IPSS, Q_{max}, post voided residual urine volume and quality of life score were determined again.

Furthermore, during the study period, the adverse effects including orthostatic hypotension, headache, flushing, lumbar pain and gastrointestinal complaints were recorded. All patients were evaluated 6 weeks after the beginning of the study and the side effects were assessed as well.

Statistical analysis was performed using SPSS version16 with paired T-Test, independent

Table 1 - Assessment of quality of life in order to quantify urinary problems.

Quality of life due to urinary problems						
Delighted	Pleased	Mostly satisfied	Mixed-about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
0	1	2	3	4	5	6

T-Test, Wilcoxon signed ranks test, and Mann-Whitney test. $P < 0.05$ was considered significant.

This study was approved by the ethical review committee of Guilan University of Medical Science and the trial registered at IRCT.IR (IRCT201008094541N1).

RESULTS

Based on inclusion and exclusion criteria, 132 patients were selected randomly in two groups (66 patients in each group). Mean ages of patients were 64.4 ± 10.33 years in the treatment group and 64.87 ± 9.20 years in the placebo group. Mean prostate volume was 40.29 CC ± 11.18 CC in the treatment group and 42.22 CC ± 12.38 CC in the placebo group. There was no significant difference in the IPSS, post voided residual urine volume, Q_{max} and quality of life score (baseline characteristics) before treatment between the two groups.

After treatment, in relation to the beginning of the study, the placebo group showed reduction of mean IPSS statistically significant. The mean post voided residual urine volume increased but was not statistically significant. The mean QoL score decreased and was statistically significant. The mean Q_{max} decreased but it was not statistically significant (Table-2).

Table 2 - Mean values of variables before and after treatment of the placebo group.

	Before	After	P-value
IPSS	13.66 ± 4.25	11.37 ± 3.64	0.001
Residual Urine volume	26.87 ± 23.85	26.91 ± 23.17	0.86
Quality of life	2.66 ± 0.78	2.19 ± 0.53	* 0.001
Q_{max}	9.09 ± 2.91	8.73 ± 2.22	0.308

*Wilcoxon Signed Ranks Test

After treatment, in relation to the beginning of the study, in the treatment group the mean IPSS and QoL score decreased, a difference that was statistically significant. The mean Q_{max} increased but it was not statistically significant. The mean post voided residual urine volume decreased and the difference was statistically significant (Table-3).

At the end of study, in relation to the beginning of the study, the mean IPSS was 7.66 ± 3.99 and 11.37 ± 3.64 in the treatment and placebo groups, respectively. The mean Q_{max} was 9.99 ± 4.76 mL/s and 8.73 ± 2.22 mL/s in the treatment and placebo groups, respectively. The mean quality of life score was 1.8 ± 0.98, and 2.19 ± 0.53 in the treatment and placebo group, respectively. The mean post voided residual volume was 22.13 ± 21.65 mL and 26.91 ± 23.17 mL in the treatment and placebo group, respectively (Table-4).

The side effects of Tadalafil included orthostatic hypotension, headache or flushing, lumbar pain and the side effects of placebo included gastrointestinal complaints. 9.1% of patients from the treatment group and 6.1% of patients from the placebo group dropped out of study due to drug intolerance.

DISCUSSION

Lower urinary tract symptoms (LUTS) encompass all urinary symptoms such as storage, voiding and postmicturation symptoms. LUTS in men may be related to bladder outlet obstruction (BOO) which is often associated with benign prostatic hyperplasia (BPH) in about 50% of men over 50 year with increasing prevalence up to 90% in those older than 80 year. Moreover, 25 to 50% of men with histologically confirmed BPH have LUTS (3). Likewise, male LUTS may result from bladder dysfunction or overactive bladder (OAB) (9). Epi-

Table 3 - Mean values of variables before and after treatment of the drug group.

	Before	After	P-value
IPSS	13.06 ± (4.38)	7.66 ± (3.99)	0.001
Residual Urine volume	24.53 ± (25.75)	22.13 ± (21.65)	0.002
Quality of life	2.93 ± (0.86)	1.80 ± (0.98)	* 0.001
Q_{max}	8.92 ± (2.96)	9.99 ± (4.76)	0.06

*Wilcoxon Signed Ranks Test

Table 4 - Mean values after treatment of the two groups.

	Placebo n = 62	Drug n = 60	P-value
IPSS	11.37 ± (3.64)	7.66 ± (3.99)	0.001
Residual Urine volume	26.91 ± (23.17)	22.13 ± (21.65)	0.241
Quality of life	2.19 ± (0.53)	1.8 ± (0.98)	* 0.036
Q_{max}	8.73 ± (2.22)	9.99 ± (4.76)	0.066

*Mann-Whitney Test

demiological evidence provides a clear and clinically meaningful association between LUTS and various types of sexual dysfunction in aging men worldwide. The result of a longitudinal population based study of 428 Brazilian men without ED at baseline indicates that the adjusted relative risk of developing ED is 3.67 for those with self-reported BPH after a mean follow up of 2 years (10).

Pathophysiology of LUTS and sexual dysfunction, particularly ED and EjD, has suggested some common components that may be involved. The prostate gland contains both epithelial and stromal components; excessive growth of either or both components, increase smooth muscle tone in the prostate capsule and the bladder neck can also contribute to the LUTS associated with BPH. Although the pathophysiology of LUTS associated with BPH was historically attributed to prostate gland enlargement and bladder outlet obstruction, the weak correlation between LUTS and prostate size (10,11) has resulted in a greater focus on the role of increase muscle tone in the prostate and bladder and highlighted the need to investigate other possible underlying mechanisms. Increase smooth muscle tone in the prostate with BPH is related to the stimulation of α1-adrenergic receptors (12).

Other receptors which have been identified in human prostate tissue may play a role in LUTS associated with BPH, including dopaminergic, muscarinic, serotoninergic and histaminergic receptors (13). Nitric oxide (NO) which is present in the human prostate (14) and modulates prostatic smooth muscle tone (15) may also play a role in the pathophysiology of LUTS associated with BPH. Although the precise mechanism of action by which PDE-5 inhibitors may alleviate LUTS is not completely understood, several putative mechanisms are currently under investigation.

One mechanism focuses on the accumulation of intracellular prostatic and bladder smooth muscle cyclic guanosine monophosphate following PDE-5 inhibition which may decrease tension of the smooth muscle of the prostatic stroma and

capsule. This muscle relaxation results in bladder neck opening and improved voiding function (16).

Another possible mechanism involves pelvic arterial insufficiency and ischemia, which may compromises normal bladder detrusor function that causes a change in prostatic structure (17,18). Increased vascular perfusion of the lower urinary tract especially the prostate or bladder neck can result in a beneficial therapeutic effect and decrease LUTS (19).

Additional theories about PDE-5 inhibition of the lower urinary tract suggest that LUTS decrease via modification of afferent nerve signaling from the bladder and urethra (20).

In the study (21) by McVary et al., following a 4-week period, single-blind, placebo run-in 281 men were randomly assigned (1:1) to 5 mg Tadalafil for 6 weeks, followed by dose titration to 20 mg for 6 weeks, or 12 weeks of placebo. In their study, Tadalafil significantly improved the IPSS at 6 weeks and 12 weeks of the Tadalafil group. No change in post voided residual volume was reported. They concluded that Tadalafil once daily was well tolerated and demonstrated clinically meaningful and statistically significant symptomatic improvement of lower urinary tract symptoms/benign prostatic hyperplasia. Tadalafil also improved erectile function in men with lower urinary tract symptoms and erectile dysfunction. Of the doses studied, 5 mg Tadalafil appeared to provide a positive risk-benefit profile. Treatment adverse side effects included dyspepsia, back pain, headache, nasopharyngitis and upper respiratory tract infection. In the current study, 6 patients experienced adverse side effects such as orthostatic hypotension, headache or lumbar pain in the treatment group and 2 patients experienced the gastrointestinal upsets in the placebo group.

In another study (22), during a 12 week study period, 369 men with ED and LUTS (IPSS > 12, mean age of 50 years) received Sildenafil 50 mg daily or placebo. Results showed that Sildenafil significantly improved IPSS and quality of life scores. Interestingly, there was no change in maximum flow rate.

In the study by Stief et al. (23), men aged 45-64 years with BPH/LUTS and an IPSS > 12 were randomized to receive either 10 mg Vardenafil or placebo twice daily. After 8 weeks of treatment, there was a significant improvement in the IPSS total score in the Vardenafil group compared to placebo (-5.9 and -3.6, respectively; $p = 0.0013$). Nominally significant improvements in irritative and obstructive IPSS subscores ($p = 0.0017$ and $p = 0.0081$, respectively), EF (Erectile function) ($p = 0.0001$), and Urolife QoL-9 ($p < 0.0001$) were also associated with Vardenafil treatment. Q_{max} and PVR urine volume did not change significantly with treatment, although baseline values were already considered close to normal. Vardenafil was generally well tolerated, with most adverse events considered mild or moderate in severity. They concluded that Vardenafil treatment significantly improved LUTS, EF, and QoL in men with BPH/LUTS and Vardenafil may be considered a promising treatment option for men with symptoms secondary to BPH.

In the study by Broderick et al. (24), men with moderate-to-severe BPH-LUTS who received placebo for 4 weeks, were randomized to placebo or Tadalafil 2.5, 5, 10, or 20 mg once daily for 12 weeks. At the end of treatment, changes in IPSS in men with ED and without ED were evaluated and were not significantly different. Changes in IPSS, quality of life and BPH Impact Index were similar in 2 groups. Tadalafil was generally well tolerated in men with or without ED. They concluded that changes in BPH-LUTS in placebo and Tadalafil groups were similar in men with or without comorbid ED.

In another study by Kim et al. (25), men with an International Index of Erectile Function-5 (IIEF-5) score of less than 11 and with an IPSS of more than 8 were included for treatment with 20 mg Tadalafil (once every 3 days) for 12 weeks. Changes in IPSS and IIEF-5 scores were significant different between baseline and end of treatment. Furthermore, the differences of these scores were significant between baseline and week 20 after treatment. However, except for IIEF-5 scores, there were no significant differences between week 12 and week 20. They concluded that treatment with tadalafil were effective on LUTS and ED in patients with moderate-to-severe ED and LUTS.

Mirone et al. (26) reported the first comparative trial of alternative dosing, investigating treatment efficacy and patient preference for 20

mg Tadalafil taken on-demand versus 3 times per week, over a 6-weeks study period for the treatment of ED. This study demonstrated that 42.2% of men preferred scheduled dosing versus 57.8% for on-demand; both treatment regimens were well tolerated and successful.

More recent studies have demonstrated that constant doses may be advantageous versus on-demand regimens, offering a valuable treatment option for ED.

McMahon (27) reported upon the efficacy, safety, and tolerability of on-demand 20 mg versus daily dosed 10 mg Tadalafil in 145 men with mild to severe ED of various etiologies in a 26 weeks study period. Patients receiving on-demand and daily Tadalafil experienced a significant mean improvement of 8.3 and 11.9 points in the IIEF, respectively ($p < 0.001$), with daily-dose mean changes significantly higher versus on-demand Tadalafil ($p < 0.05$). Successful completion of sexual intercourse was also statistically higher for daily Tadalafil than for on-demand Tadalafil ($p < 0.05$). Also, both treatments were well tolerated. The authors concluded that treatment with daily Tadalafil was associated with a significantly higher IIEF erectile function domain score and completion of successful intercourse compared with on-demand Tadalafil (28).

In the current study, although Tadafil effect on ED and quality of erection was not assessed, the addition of 10 mg Tadalafil once nightly for 3 months in patients whose symptoms had reached the plateau level with previous treatment with an α1-blocker and/or Finasteride was superior to placebo in improvement of IPSS and QoL. Although post void residual urine decreased and Q_{max} increased with 10 mg Tadalafil once nightly, the difference was not statistically significant. The lack of a significant peak flow improvement in men with LUTS suggestive of BPH treated with Tadalafil confirms the previous reports of PDE-5 inhibitors compounds on Q_{max} as mentioned above.

CONCLUSIONS

Tadalafil improves quality of life and urinary symptoms subjectively in BPH patients but does not have significant effect on Q_{max}. Therefore, considering the high prevalence of ED in this age group, this drug may be used in combination with standard medical therapies of BPH. However, further studies with larger samples are needed to document these findings.

CONFLICT OF INTEREST

None declared.

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