Comparing Monotherapy with Tadalafil or Tamsulosin and Their Combination Therapy in Men with Benign Prostatic Hyperplasia: A Randomized Clinical Trial

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Purpose: To compare monotherapy with tadalafil or tamsulosin and their combination therapy in men with benign prostatic hyperplasia and erectile dysfunction by comparing IPSS score, prostate volume and Qmax and some other outcomes.

Materials and Methods: This randomized, single-blind, paralleled group clinical trial was done in 2013 on patients who had referred to our hospital in Tehran. All patients with lower urinary tract symptoms, benign prostatic hyperplasia and any grade of erectile dysfunction were recruited. They were randomly divided into three groups (61 participants in each group): Group A received 20 mg/daily tadalafil; Group B received 0.4 mg/daily tamsulosin; Group C receieved a combination of 0.4 mg/daily tamsulosin and 20 mg/daily tadalafil. Primary outcomes were prostate volume, prostate specific antigen, post-void residual volume, IPSS score, LUTS severity, Qmax, IIEF and erectile dysfunction severity and secondary outcome was complications.

Results: The mean ± SD of ultrasonographic prostate volume was 61.4 ± 15.1 mL and prostate specific antigen level was 2.4 ± 1.9 ng/dl. Post-void residual level was significantly different before and after the treatment, except for group A. Also, this group had no meaningful difference compared to the other groups in this regard ($P > 0.05$). There were significant differences between pre- and post-treatment international prostate symptom scores in each group ($P < 0.05$).

Conclusion: Combination of tamsulosin and tadalafil can improve international prostate symptom scores, international index of erectile function questionnaire scores and Qmax in patients with lower urinary tract symptoms and benign prostatic hyperplasia to more degrees than their separate use. This combination is recommended because of its synergistic effects, well toleration and safety.

Keywords: benign prostate hyperplasia; erectile dysfunction; tadalafil; tamsulosin

INTRODUCTION

A major difficulty in comparing the prevalence of lower urinary tract symptoms (LUTS) among different groups is lack of a common definition. LUTS because of benign prostate hyperplasia (BPH-LUTS) often interferes with patients' daily activities. Many men with benign prostate hyperplasia LUTS seek treatment to improve their quality of life.

Research on LUTS in men has traditionally focused on the development and testing of treatments for progressive disease.[1] Benign prostate hyperplasia is a histological diagnosis which is identified by nonmalignant hyperplasia of prostatic tissue due to smooth muscle and epithelial cell proliferation in the prostate transition zone.[2] The prevalence of histologically diagnosed prostatic hyperplasia increases from 8% in men aged 31 to 40 years old to 40-50% in men aged 51 to 60 years old. This increases to over 80% in men older than 80 years old.[3] Benign prostate hyperplasia can result in prostate enlargement. This leads to the development of LUTS such as storage, voiding and post-micturition symptoms. An increased smooth muscle tone in the prostate or the vasculature supporting the lower urinary tract may play a contributing role.[4]

LUTS has no common definition. A large population-based study found the prevalence of moderate or severe LUTS for men in the fifth, sixth, seventh, and eighth decades of life to be 26%, 33%, 41%, and 46%, respectively.[5] BPH-LUTS are common in aging men worldwide.[6] Given that BPH-LUTS often interferes with daily activities,[7] many men with BPH-LUTS seek treatment to improve their quality of life.[8]

When pharmacological treatment is required, the most common drugs are a-blockers and 5-alpha reductase inhibitors (5ARIs). The five extensively available alpha-blockers are doxazosin, terazosin, tamsulosin, alfuzosin and silodosin, the last one being the only one that is a1A adrenoreceptor specific. As for 5ARIs, two drugs are available, finasteride and dutasteride. In addition, combining these two classes of drugs has been shown to be more effective in BPH-LUTS than using each separately.[9]

Tadalafil's mechanism as a long-acting phosphodiesterase 5 (PDE5) inhibitor in the treatment of men with BPH-LUTS is associated with increased activity of the nitric oxide/cGMP (Cyclic guanosine monophosphate)/

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Table 1. Demographics of the participants

Characteristics	Group A	Group B	Group C	*P* value
Number of participants	60	59	58	-
Age, years (Mean ± SD)	68.2 ± 7.8	68.5±8.9	67.9 ± 8.8	.90
BMI, kg/m^2 (Mean± SD)	27.4 ± 1.2	26.7±2.4	27.1 ± 2.3	.17

protein kinase G pathway via PDE5 isoenzymes' inhibition in different lower urinary tract tissues. These results can be detected in smooth muscle relaxation in the bladder, urethra, prostate, and supporting vasculature, increased blood perfusion to the pelvic area, and finally modulation of sensory stimuli from this area.[10-12]

Epidemiological and pathophysiological links have been found between BPH-LUTS and erectile dysfunction.[7,10] Although the current medical therapy for BPH-LUTS is effective, it has potential side-effects on sexual function.[13] Moreover, PDE5i increases the concentration and activity of intracellular cGMP, thus reducing smooth muscle tone of the detrusor, prostate and urethra.[14] It is believed that these mechanisms may help to treat BPH-LUTS.

This clinical trial has compared monotherapy with tadalafil or tamsulosin and their combination therapy by comparing IPSS score, LUTS severity, IIEF score and some other measurements in men with benign prostatic hyperplasia and erectile dysfunction.

MATERIALS AND METHODS

This randomised, single-blind, paralleled group clinical trial was done in 2013 on patients who had referred to the urology clinic of Shohadaye Tajrish hospital in Tehran. All patients with LUTS, benign prostate hyperplasia and any grade of erectile dysfunction were recruited for this study.

Inclusion and exclusion criteria

We assessed patients with these inclusion criteria: men older than 45 years old, International Prostate Symptom Score (IPSS) ≥ 12, and having a history of erectile dysfunction. Patients with previous benign prostate hyperplasia or erectile dysfunction treatment, history of surgical procedure for their prostatic problem, contraindication for tadalafil (i.e. nitrate consumption) or tamsulosin (i.e. allergic reactions), bladder stone, history of urinary retention, active urinary tract infection, prostate cancer, post-void residual urine test > 200 mL, kidney failure, liver insuficiency, history of pelvic radiation, urethral stricture, ureteral stone in past six months before entering the study, overt hematuria, consumption of finastridie, anti-depressent drugs and beta-adrener

Table 2. Distribution of clinical, laboratory and functional characteristics of the participants before treatment

Characteristics	Group A	Group B	Group C	*P* value
Prostate volume, ml (Mean ±SD)	59.6±14.1	61.1±16.1	63.2±12.1	0.46
PSA, ng/ml (Mean±SD)	2.5±1.8	2.3±1.9	2.1±1.6	0.51
PVR volume, ml (Mean ±SD)	61.6±63.3	57.2±59.7	58.6±60.2	0.78
IPSS (Mean ±SD)				
Total IPSS	19.9±6.3	20.6±7.3	21.2±7.5	0.63
IPSS voiding	14.6±4.0	14.2±4.5	14.9±4.1	0.42
IPSS storage	5.8±2.1	6.5±2.7	6.6±3.2	0.19
IPSS QoL index	3.9±1.3	3.9±1.2	4.1±1.2	0.27
LUTS severity, N (%)				
Moderate	48 (80)	45 (76.2)	44 (75.8)	0.34
Sever	12 (20)	14 (23.8)	14 (24.2)	
Qmax, mL/s (Mean ±SD)	12.6±5.4	12.3±3.8	12.4±4.8	0.33
IIEF (Mean±SD)	10.1±1.8	10.9±1.6	10.6±1.7	0.08
Erectile dysfunction severity, N (%)				
Mild	18 (30)	18 (30.5)	16 (27.6)	
Moderate	33 (55)	31 (52.5)	32 (55.1)	0.29
Severe	9 (15)	10 (17)	10 (17.3)	

Table 3. Comparison of functional tests and their changes before treatment and in follow up sessions in the three studied groups

PSA, ng/ml (Mean ± SD)				
Before	2.5±1.8	2.3±1.9	2.1±1.6	0.58
3 Month Follow-Up	2.5±1.7	2.2 ± 2.0	2.1±1.5	0.37
P value	NS	NS	NS	
Change	0.0 ± 0.1	0.0 ± 0.3	0.0 ± 0.2	NS
PVR, ml (Mean ± SD)				
Before	61.6 ± 63.3	57.2±59.7	58.6 ± 60.2	0.74
3 Month Follow-Up	49.8 ± 25.9	38.9±21.6	35.4 ± 20.9	0.06
P value	0.06	0.0009	0.0001	
Change	-11.9 ± 37.1	-19.1±36.2	-23.4 ± 40.1	0.32
IPSS total (Mean ± SD)				
Before	19.9 ± 6.3	20.6±7.3	21.2 ± 7.5	0.52
3 Month Follow-Up	11.4 ±3.6	10.6±3.5	10.1 ± 3.2	0.22
P value	0.0001	0.0001	0.0001	
Change	-8.6 ± 2.8	-10.1 ± 3.9	-11.1 ± 4.4	0.01
IPSS storage (Mean ± SD)				
Before	5.8 ± 2.1	6.5 ± 2.7	6.6 ± 3.2	0.36
3 Month Follow-Up	3.7 ± 1.9	3.6 ± 1.8	3.4 ± 2.1	0.54
P value	0.0001	0.0001	0.0001	
Change	-2.1±1.2	-2.9 ± 1.1	-3.3 ± 1.0	0.0004
IPSS voiding (Mean ± SD)				
Before	14.6 ± 4.0	14.2 ± 4.5	14.9 ± 4.1	0.49
3 Month Follow-Up	7.6 ± 2.5	7.1 ± 1.7	6.9±1.5	0.18
P value	0.0001	0.0001	0.0001	
Change	-7.1 ± 1.3	-7.1± 2.7	8.0±2.5	0.03
Qmax, mL/s (Mean±SD)				
Before	12.6 ± 5.4	12.3 ± 3.8	12.4 ± 4.8	0.78
3 Month Follow-Up	13.9 ± 4.4	15.6 ± 3.1	15.9 ± 2.1	0.001
P value	0.06	0.0001	0.0001	
Change	1.5 ± 1.5	3.3 ± 2.1	3.5±2.7	0.0002
IIEF (Mean ± SD)				
Before	10.1 ± 1.8	10.9 ± 1.6	10.6 ± 1.7	0.09
3 Month Follow-Up	17.7 ± 2.3	12.1± 5.1	17.2 ± 3.2	0.0001
P value	0.0001	0.06	0.0001	
Change	7.8 ± 1.7	4.6 ± 2.1	7.6 ± 1.9	0.0001

gic blockers and history of substance addiction were excluded from the study.

Randomization

A number of 200 patients with LUTS were candidates to particpate in this study. Seventeen patients were excluded for not having the inclusion criteria and not consenting to participate. So, 183 participants were randomly divided into three groups with a sample randomization chart (61 participants in each group): Group A received 20 mg/daily tadalafil; Group B received 0.4 mg/daily tamsulosin; Group C receieved a combination of 0.4 mg/daily tamsulosin and 20 mg/daily tadalafil. Two patients of group B, one of group A and three of group C were lost in the follow-up process because of discontining their drugs. So, 59 participants in group B, 60 participants in group A and 58 participants in group C were evaluated until the end of follow-up. (**Figure 1**)

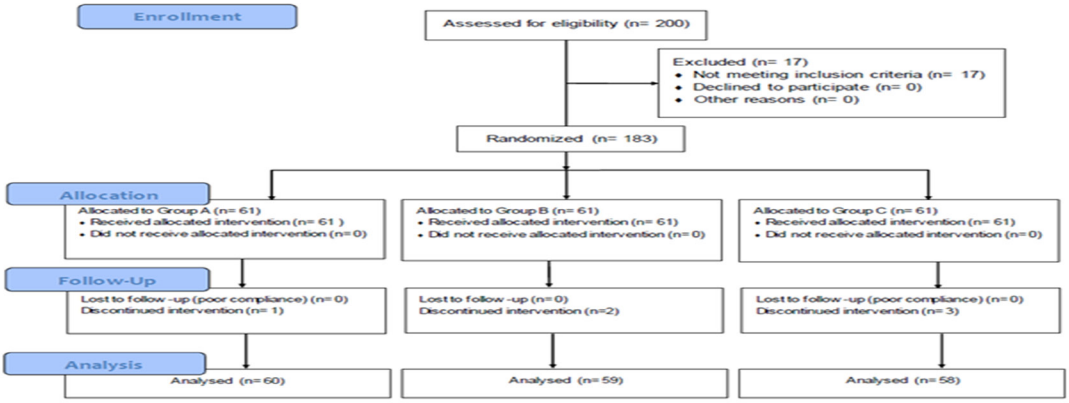

Figure 1: Flow chart of study design; Group A: Patients received only Tadalafil, Group B: patients received only Tamsulosin, Group C: Patients received both Tadalafil and Tamsulosin

The participants' medical history and drug use were taken at the fisrt visit. Then complete systemic and rectal examination of prostate was done. Laboratary blood samples were taken to measure blood urea nitrogen, creatinine and prostate specific antigen. Urine analysis was done as well. Ultrasound of kidneys and bladder including determining residual urine volume and uroflometric test were done for each patients. We also completed the IPSS and International Index of Erectile Function (IIEF) Questionnaire for the participants. We repeated these assessments three months after the first visit and compared the three study groups' IPSS, Qmax and post-void residual results.

Statistical analysis

The data analysis was performed with the Statistical Package for Social Sciences (SPSS) software version 19 (Chicago, IL, USA). Descriptive statistics (mean ± standard deviation) and Student t-test were used show and analyze the quantitative outcomes. The qualitative data were presented with frequency and percentage and their analysis was done with Chi-square test and Fisher's exact test. Correlational analysis was done by Pearson or Spearman correlation coefficients. We used One-Way ANOVA test for comparison of indexes between groups. P-value less than 0.05 was considered significant.

Ethics

All participants signed an informed consent and benefits and complications were explained to them before entering the study. The study protocol was approved by ethics committee of Shahid Beheshti University of Medical Sciences.

RESULTS

The participants' mean age was 68.40 ± 8.80 years and the mean time of symptoms' existence was 4.8 ± 12.6 months. The mean ± SD of body mass index mean was 27.1 ± 2.3 kg/m^2. (**Table 1**)

The mean±SD of ultrasonographic prostate volume was 61.4 ± 15.1 mL and prostate specific antigen level was 2.4 ± 1.9 ng/dl. The mean of prostate functional scores were 59.4 ± 61.3 for post-void residual level based on trans-abdominal ultrasound, 12.5 ± 4.8 for Qmax and 20.6 ± 7.8 for IPSS in all patients. 137 participants had moderate and 40 participants had severe IPSS scores. Mild, moderate and severe erectile dysfunctions were seen in 52, 96 and 29 participants, respectively (**Table 2**). There were no significant differences between prostate volume, prostate specific antigen, post-void residual volume, IPSS score (also in its three components; voiding, storage, quality of life indexes), LUTS severity, Qmax, IIEF and erectile dysfunction severity between the three groups ($P > 0.05$).

There was no significant difference in prostate specific antigen before and after the treatment in all groups and

Table 4. Drug complications in the three studied groups

Complications	Group A	Group B	Group C	Total
Myalgia, N (%)	3 (5)	0 (0)	4 (6.7)	7 (3.9)
Headache, N (%)	3 (5)	1 (1.6)	3 (5)	7 (3.9)
Back pain, N (%)	4 (6.6)	1 (1.6)	3 (5)	8 (4.5)
Nasopharyngitis, N (%)	2 (3.3)	1 (1.6)	3 (5)	6 (3.3)
Dizziness, N (%)	1 (1.6)	2 (3.3)	2 (3.3)	5 (2.8)
Discontinuation because of an AE, N (%)	1 (1.6)	2 (3.3)	3 (5)	7 (3.9)
Total, N (%)	14 (23.3)	7 (11.8)	18 (31.03)	39 (22.03)

between them ($P > 0.05$). Post-void residual level was significantly different before and after the treatment, except for group A. Also, this group had no meaningful difference compared to the other groups in this regard ($P > 0.05$). There were significant differences between pre- and post-treatment IPSS in each group ($P < 0.05$) (**Table 3**).

Complications

The most frequent complications in all of participants were back pain (4.5%) and myalgia, headache and discontinuation because of adverse side-effects (3.9% for each). Despite of higher complication rate in group C, there was no significant difference between the three groups in this regard (**Table 4**).

DISCUSSION

Both erectile dysfunction and BPH-LUTS are common in men and their prevalence increases with aging.[15-17] Several studies have studied the efficacy of monotherapy with tadalafil[8,18-23] and tamsulosin.[24-26] Also, there are studies on their combination with other drugs or comparing them with each other. [27-29] However, to our knowledge no study has evaluated the effect of each of these drugs with their combination. Also, there was no study with these drugs in an Iranian population. In our study we found out that increase of weight is a risk factor for benign prostate hyperplasia. The mean of body mass index was 27.1 ± 2.3 kg/m^2 in our study.

Our analyses explored the relationships between total IPSS and storage and voiding sub-scores of the IPSS, before the treatment and at the end of follow up (after 3 months). These relationships have not been studied in detail before. It is now well recognized that storage LUTS are the most troublesome for symptomatic patients. However, algorithms for the management of patients with predominantly storage LUTS or predominantly voiding LUTS offer generic guidance to clinicians with respect to the relative proportions of storage to voiding LUTS and their severity. This reflects the lack of published information on this subject.

We can emphasize the importance of our analysis, which offers reassurance that the IPSS storage and voiding sub-scores maintain a tight, fixed ratio to each other similar to Chapple and colleagues' results.[12] However, we did new comparisons of our three groups unlike them. Although this could be predicted from the IPSS design and by bearing in mind that only three of the seven questions in the IPSS consider storage symptoms, it is important to emphasize that separate analysis of IPSS storage and voiding sub-scores is not validated. (30) In other monotherapy studies with these drugs, the IPSS results are in line with our results. Double-blind, randomized, placebo-controlled studies of 5 mg tadalafil once-daily in Japanese men,[19] Japanese, Korean and Taiwanese men,[8] and Japanese and Korean men[20] has demonstrated greater improvement in the change from baseline to endpoint in total IPSS for monotherapy with 5 mg tadalafil compared to placebo.

These improvements were significantly greater in two of these studies ($P < 0.05$),[8,20] whereas in the third study[19] the magnitude of symptom improvement (IPSS) was only greater numerically ($P = 0.062$). Although these results are consistent with our outcomes, IPSS improvement in our study was greater and this is related to combination therapy of tadalafil/α-blocker treatment.

Still, there is no large, double-blind, placebo-controlled study on the efficacy of tadalafil/α-blocker combination therapy. There are just several small sampled clinical trials that have reported tadalafil/α-blocker combination therapy may have better effect on total IPSS than α-blocker[28,29,31] or tadalafil monotherapies[29,32] in men with BPH-LUTS. However, these studies either had a small number of participants, involved tadalafil dosages > 5 mg once-daily, or were not placebo controlled. In our clinical trial, we have corrected these issues. So, based on our findings combination therapy could better improve IPSS score in patients with BPH-LUTS and is recommended for them because of its synergistic effects. This can be concluded from the results of our single groups in comparison with combined therapy that showed improvement in IPSS score in both single groups separately and more IPSS score in combined therapy group rather than each of them.

Our results showed that although Qmax was significantly improved in the three studied groups, its improvement was greater in the combination therapy group than the other groups. We also showed that post-void residual level was significantly different before and after treatment in each group, but there was no meaningful difference between the three groups ($P > 0.05$). Other studies have also demonstrated the same greater improvements in Qmax index with 5 mg tadalafil compared with placebo in men with BPH-LUTS. The improvements at 12 weeks were maintained for 42 weeks, demonstrating the long-term efficacy of 5 mg tadalafil.[2,8,12,19,21,23,32] Singh and colleagues showed that a significant increase in Qmax and decrease in post-void residual level were observed in combination therapy (33.99%, $P < 0.05$; 29.78%, $P < 0.05$; and 37.04%, $P < 0.05$) and monotherapy with tadalafil (-60.90%, $P < 0.05$; -49.45%, $P < 0.05$; and -62.97%, $P < 0.05$, respectively).[32]

The complications of combination therapy in our study were myalgia, headache, back pain, nasopharyngitis, dizziness and discontinuation because of adverse effects. Although the complication rate was higher in combination therapy group compared to monotherapy groups, it was not significant. In Singh and colleagues study the side effects of combination therapy were dyspepsia, heartburn, headache, flushing, myalgia, and backache and adverse effect dropout and no participant experienced any severe or serious adverse events.[32]

Other randomized, controlled studies such as Bechara and colleagues, Liguori and colleagues, Goldfischer and colleagues and Kim and colleagues[21,28,29,32,33] have investigated the safety and tolerability of 5 mg tadalafil once-daily in three months as a treatment for BPH-LUTS in men, and had a safety profile consistent with the known safety profile of tadalafil as per the current package insert for 5 mg to 20 mg tadalafil as needed for erectile dysfunction.[8]

Integrated analysis of safety data from these studies demonstrated that the most common treatment-emergent adverse events were nasopharyngitis, dyspepsia and headache and few participants experienced serious adverse events.[21,28,29,33] The safety of 5 mg tadalafil in combination with α-blockers (alfuzosin, silodosin, tamsulosin, doxazosin or terazosin) was investigated in a double-blind, randomized, placebo-controlled trial on men with BPH-LUTS in the United States (tadala-

fil/α-blocker, n = 158; placebo, n = 160).[33] This study was not designed to assess efficacy. No new safety concerns were identified for tadalafil/α-blocker combination therapy in this study. Furthermore, the proportion of participants reporting treatment-emergent dizziness or with a positive orthostatic test was similar between the tadalafil/α-blocker combination therapy group and the placebo/α-blocker combination therapy group.[33] So, it can be concluded that the safety of combination therapy is nearly good and its short-term outcomes should be considered for patients and told to them. However, these complications are not serious and threatening.

We investigated the IIEF score and showed that there were significant improvements in each group and between the groups in this regard. These improvements were higher in tamsulosin and combination groups, respectively. Similarly, Singh and colleagues showed that IIEF score increases significantly in the same three groups (+39.28%, $P<0.05$; +45.96%, $P<0.05$; and +60.23%, $P<0.05$, respectively).[32] In another study Bechara and colleagues showed that the IIEF improved in tamsulosin plus tadalafil group ($P < 0.001$), but not in tamsulosin alone group ($P > 0.05$).[28] Based on these results, combination therapy with tadalafil and tamsulosin is recommended because of its good outcomes in erectile dysfunction. The limitation of this study was that some patients lost the follow ups and excluded from study and study period prolonged.

CONCLUSION

Combination therapy can better improve the IPSS score, IIEF score and Qmax in patients with BPH-LUTS than monotherapy with tamsulosin or tadalafil. It is recommended because of its synergistic effects, well toleration and its safety. Although we designed this study to investigate the previous studies' problems, large-scale, multi-centered, randomized, placebo-controlled studies are needed to further assess the long-term safety and effectiveness of these agents in treating BPH-LUTS and erectile dysfunction.

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CONFLICT OF INTERESTS

None declared.

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