

## A Comparative Study to Evaluate Efficacy of Tadalafil, Alfuzosin and Their Combination in Patients Less Than 60 Years Presenting with LUTS Due to BPH

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## Abstract

## Original Research Article

**Background:** Benign prostatic hyperplasia (BPH) is one of the most common disorders seen in elderly men and is associated with lower urinary tract symptoms (LUTS). This study compared the efficacy of tadalafil, alfuzosin and their combination in the treatment of LUTS associated with BPH. **Methods:** This was a randomised open-label, comparative study conducted between April 2018 and March 2019, which included men with <60 years of age diagnosed with LUTS associated with BPH with International Prostate Symptom Score (IPSS) more than 8. Patients were randomised into three groups to receive alfuzosin SR 10 mg once-daily (group A); tadalafil 5mg once-daily (group B) or alfuzosin plus tadalafil (group C). Prostate volume, post-void residual (PVR) volume, IPSS, and maximum urinary flow rate ( $Q_{max}$ ) were evaluated. **Results:** A total of 121 patients were included in the study and 94 patients who completed the study were included in the analysis. Demographics and baseline characteristics were comparable between the groups. Patients from group C showed greater percent change (24.79%) in lowering the mean prostate volume. There was a significant ( $p=0.001$ ) decrease in the IPSS score from baseline at 24 weeks in all three groups; however, the percentage change was higher (35.54%) in group C than group A (24.5%) and B (18.14%). There was a significant improvement in PVR, IIEF in all groups; however, improvements were better in group C. **Conclusion:** The combination therapy has shown improvement in PVR, IIEF score than tadalafil or alfuzosin alone.

**Keywords:** Alpha- Adrenergic Antagonists; Erectile Dysfunction; International Prostate Symptom Score; Phosphodiesterase-5 Inhibitor; Post-Void Residual.

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## INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common disorder seen in elderly men, generally progressive and may lead to lower urinary tract symptoms (LUTS). Erectile dysfunction (ED) is a condition in which a man is unable to maintain a penile erection necessary for vaginal penetration and sexual satisfaction. Prevalence and severity of ED increases with age and is directly associated with LUTS [1,2]. Clinical manifestations of patients with LUTS due to BPH include sleep disturbances, anxiety, changes in leisure, sexual activity; enlarge prostate and acute urinary retention, which may ultimately affect the quality of life [3].

Alpha adrenergic blockers are most commonly used and effective agents in patients with LUTS due to BPH [4]. Various other pharmacological agents include 5- $\alpha$ -reductase inhibitors (5- $\alpha$ RI), anticholinergics and phytotherapeutics[5]. Phosphodiesterase 5 inhibitors (PDE5Is) and combination therapies ( $\alpha$ 1-adrenergic-

receptor antagonists [ARAs] plus 5- $\alpha$ RI or  $\alpha$ 1-ARAs plus antimuscarinics) were effective and well tolerated in some studies[6-8]. A 12-week randomised study demonstrated significant improvement of in uroflowmetry measurements and quality of life in patients treated with combined therapy (alfuzosin plus tadalafil)[9]. Another open label, prospective non-comparative study showed tadalafil 5 mg once a day in combination with  $\alpha$ -blocker was effective with less adverse effects [10]. The aim of the present study was to compare the efficacy of tadalafil, alfuzosin and a combination of these two in the treatment of LUTS associated with BPH in patients less than 60 years of age.

## MATERIALS AND METHODS

This was a randomised open-label comparative study was conducted at tertiary care hospital between April 2018 and March 2019. The study included men with <60 years of age diagnosed with LUTS associated with BPH who had International Prostate Symptom

Score (IPSS) more than 8. Patients with a history of hypersensitivity to PDE5Is or  $\alpha$ -blockers, underwent surgery for ED, received tadalafil or alfuzosin within last three months, patients with acute urinary retention, urethral stricture, neurogenic bladder, and patients with large prostates (>60ml) were excluded from the study. Patients with carcinoma of the prostate were also excluded from the study. The study protocol was approved by Institutional Ethics Committee. Informed consent was obtained from each patient before participation in the study.

The patients were randomly divided into three groups: group A receiving alfuzosin SR 10mg once daily; group B receiving tadalafil 5mg once daily and group C receiving alfuzosin SR 10 mg plus tadalafil 5 mg. The duration of treatment was 6 months. The measurements of systolic and diastolic blood pressures were taken in all patients receiving tadalafil both before and a week after starting the treatment.

The efficacy of patients with LUTS due to BPH was assessed by evaluating prostate size and post-void residual (PVR) volume, IPSS, and maximum urinary flow rate ( $Q_{max}$ ). Other efficacy variables included International Index of Erectile Function (IIEF) used to assess severity of ED and BPH impact index (BPH-II) used to analyse the patient's daily activities affecting their life. The prostate size and PVR volume were measured by ultrasonography (USG) and uroflowmetry was used for documenting  $Q_{max}$ . Before starting the treatment, all patients completed the IPSS, IIEF and BPH-II questionnaire. The IPSS, prostate volume, PVRU,  $Q_{max}$ , IIEF and BPH-II were recorded at baseline, 6 weeks, 12 weeks and 24 weeks.

Statistical analysis was performed using SPSS version 23. The changes in IPSS, prostate volume, PVR,  $Q_{max}$ , IIEF and BPH-II were expressed using percentage of improvement. The difference between the three groups was analysed using analysis of variance (ANOVA) test. A p-value of <0.05 was considered statistically significant.

## RESULTS

A total of 185 patients were screened and 121 patients were included in the study (group A, n=38; group B, n=35; and group C, n=48). Seven patients from group a, nine from group B and 11 from group C were lost in follow up or withdrew from the study,

hence excluded from the analysis. Finally, 94 patients who completed the study were included in the analysis (Figure 1). Demographics and baseline characteristics were comparable between the groups. The majority (n=60, 63.83%) of the patients were between 45 and 60 age group and the remaining (n=34, 36.17%) were <45 years of age.

There was a significant ( $p=0.001$ ) decrease in the IPSS score from baseline to 24 weeks in all three groups; however, the percentage change was higher (35.54%) in patients with combination therapy to that of alfuzosin (24.5%) and tadalafil (18.14%) (Table 1 and Figure 2A).

The mean prostate volume in patients receiving alfuzosin, tadalafil and combination at baseline was 34.8, 33.2 and 36.7, respectively. The patients receiving combination therapy showed greater lowering of the mean prostate volume (24.79%) (Table 1 and Figure 2B). Alfuzosin and tadalafil also had decrease in prostate volume with a percent change of 17.91% and 12.95%, respectively. The mean PVRU volume was significantly ( $p=0.001$ ) reduced from baseline in all the groups. The percentage change with combination therapy was 67.2% while that of alfuzosin and tadalafil was 49.42% and 35.78%, respectively (Table 1 and Figure 2C).

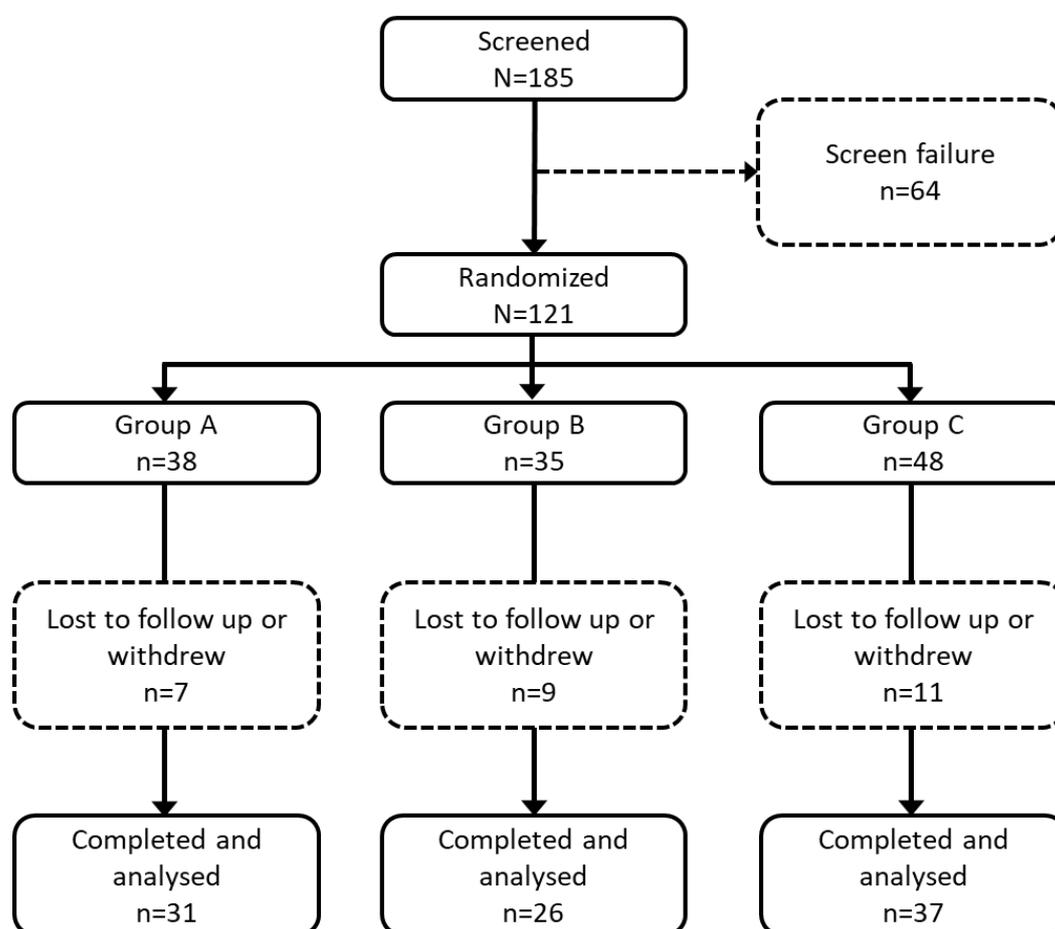
Improvement in peak flow rate ( $Q_{max}$ ) was observed in all patients; however, patients receiving combination therapy had greater improvement (67.2%) over the period of time than that by alfuzosin (49.42%) and tadalafil (35.78%). In group C, the mean  $Q_{max}$  at 24 weeks was increased to 19.72 from 12.72 at baseline (Table 1 and Figure 2D).

The mean IIEF score at baseline in patients receiving alfuzosin, tadalafil and combination was 17.38, 16.85 and 17.35, respectively. There was a significant improvement in IIEF from baseline to week 24 in all groups; however, at 24 weeks, patients receiving combination therapy showed highest improvement (6.05) compared to alfuzosin (0.93) and tadalafil (5.95) (Table 1 and Figure 2E). The mean BPH-II score at baseline was 10.87, 11.39, and 12.47 for alfuzosin, tadalafil and combination, respectively. At week 24, these scores were reduced to 7.63, 7.94, and 7.36, respectively ( $p<0.001$ ) (Table 1 and Figure 2F).

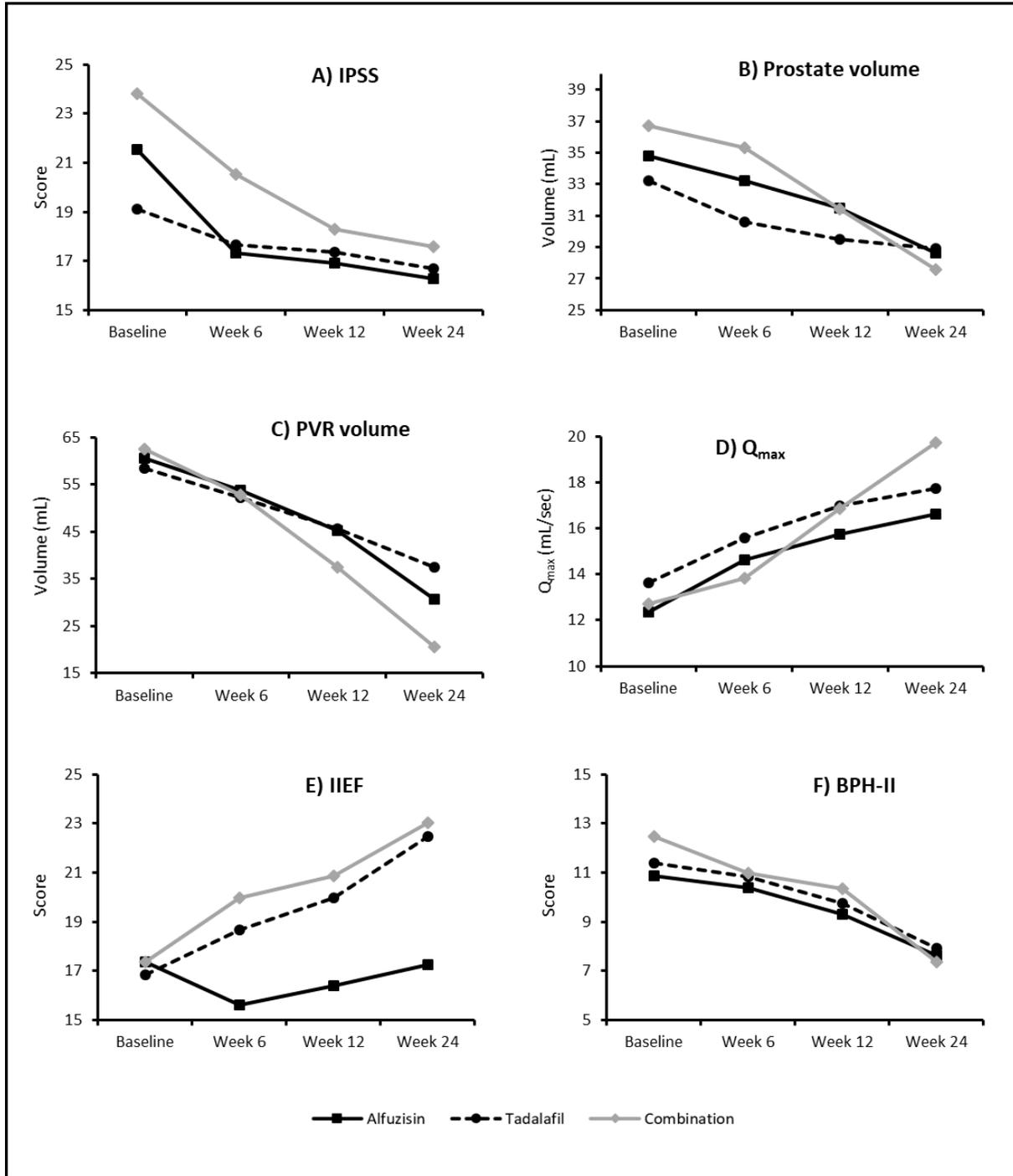
**Table-1: Summary of outcomes**

Variable	Alfuzosin (n=31)	Tadalafil (n=26)	Combination (n=37)	P value
<b>IPSS</b>				0.001
24 weeks	4.74 (2.3)	3.03 (1.3)	6.24 (2.8)	
% change	-24.5	-18.14	-35.51	
<b>Prostate volume</b>				0.079
24 weeks	6.2 (2.6)	4.3 (1.9)	8.1 (2.9)	
% change	-17.91	-12.95	-24.79	
<b>PVRU</b>				0.001
24 weeks	29.9 (12.89)	20.9 (8.96)	42.1 (18.37)	
% change	-49.42	-35.78	-67.2	
<b>PFR (Q<sub>max</sub>)</b>				0.001
24 weeks	29.9 (12.89)	20.9 (8.96)	42.1 (18.37)	
% change	49.42	35.78	67.2	
<b>IIEF</b>				0.0023
24 weeks	0.93 (0.817)	5.95 (2.36)	6.05 (2.35)	
% change	-0.0074	33.31	32.75	
<b>BPH-impact index</b>				0.001
24 weeks	3.23 (1.42)	3.46 (1.52)	5.11 (2.14)	
% change	-29.74	-30.37	-40.98	

Data represented as mean (SD) unless otherwise specified. BPH, benign prostatic hyperplasia; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; PFR peak flow rate; PVRU, post-void residual urine.



**Fig-1: Patient disposition**



**Fig-2: Efficacy outcomes**

BPH-II, benign prostatic hyperplasia impact index; IIEF, International Index of Erectile Function; IIPS, International Prostate Symptom Score; PVR, post-void residual; Q<sub>max</sub>, maximum urinary flow rate.

## DISCUSSION

A wide range of drug modalities are available for management of LUTS associated with BPH, however adverse events associated with each treatment makes it a difficult choice. Present study compared the effectiveness of tadalafil, alfuzosin and a combination

of these two in the treatment of LUTS associated with BPH in patients less than 60 years of age. The salient features of this study are significant improvements observed in LUTS and ED in patients with BPH receiving combination therapy as compared to tadalafil or alfuzosin, alone.

In the present study, the mean IPSS scores were significantly improved at week 24 from baseline values for all the three treatments with highest percentage change in combination therapy (p=0.001).

These observations are parallel with the studies by Kumar *et al.* and Lee *et al.* who reported significant improvement in IPSS scores with highest percentage change in combination therapy followed by alfuzosin and tadalafil [7, 10]. A recent study by Das *et al.* comparing the efficacy of tadalafil and alfuzosin regimens in patients of BPH showed that alfuzosin was responsible for improving the level of IPSS much more efficiently than tadalafil[11].

The mean PVRU volume was significantly reduced from baseline in all the groups of the current study ( $p=0.001$ ). The percentage change was higher in patients treated with combination therapy (67.2%) compared to that of alfuzosin (49.42%) and tadalafil (35.78%) group. These results are in concordance with the recent study by Kumar S *et al.* who reported similar observations (combination therapy - 56.1%, alfuzosin - 22.8% and tadalafil - 14.6%)[7]. On the contrary, the results of a previous study by Lee *et al.* did not show any significant decrease in PVRU volume from baseline in patients receiving combination therapy for BPH [10].

In the present study, percentage change in mean prostate volume from baseline to week 24 among patients of all the three groups was comparable (combination therapy- 24.79%; alfuzosin- 17.91% and tadalafil- 12.95%). There is no study in the literature comparing mean prostate volume in BPH patients receiving different treatments.

Further, the present study also demonstrated improvement in  $Q_{max}$  in all patients; however, patients receiving combination therapy had greater improvement (67.2%) over the period of time than alfuzosin (49.42%) and tadalafil (35.78%). Previous studies have reported similar results Kumar S *et al.*[7,10] showed that combination therapy was superior to monotherapy with either alfuzosin or tadalafil for treating BPH with LUTS. They reported efficacy of combination therapy on  $Q_{max}$  was similar to that of alfuzosin but better than that of tadalafil [7]. The network meta-analysis by Yuan *et al.* comparing effectiveness and safety of monodrug therapies for LUTS associated with BPH reported that all monotherapies with doxazosin, dutasteride, terazosin, alfuzosin, tamsulosin, naftopidil, and silodosin had significantly higher post treatment  $Q_{max}$ [12].

The overall observations from LUTS assessments in the present study demonstrated significant improvement in IPSS, PVRU volume, and uroflowmetry measurements ( $Q_{max}$ ) in patients on combination therapy compared to alfuzosin alone or tadalafil alone.

In addition, there was a significant improvement in IIEF at week 24 from baseline in all groups; however, at 24 weeks, patients receiving combination therapy showed highest improvement

(6.05) compared to alfuzosin (0.93) and tadalafil (5.95). These observations suggest a significant improvement in ED of patients receiving combination therapy compared to alfuzosin, but slight improvement compared to tadalafil. Similar results were reported by Liguori *et al.*[9] In a retrospective open-label study, Yassin *et al.* studied 42 BPH patients with comorbid ED who were non-responders to tadalafil 20 mg, and reported that an addition of alfuzosin 10 mg once daily to tadalafil improved ED in 71% of cases[13]. These observations can be based on the fact that the combination of alfuzosin and tadalafil exerts in vitro an additive relaxant effect on human corpora cavernosa compared to each drug alone[14].

The present study also demonstrated a reduction in the mean BPH-II score at week 24 in all the three groups; however, the percentage of change was significantly higher in combination therapy (40.9%) as compared to alfuzosin (29.7%) and tadalafil (30.4%). This result suggests reduced impact of BPH symptoms on health and functioning of patients receiving combination therapy compared to other monotherapy groups. In a study by Angalakuditi *et al.* the BPH-II was suggested as a valid tool to assess the impact of BPH symptoms on health and functioning in clinical trial settings [3].

The chief limitations of the present study are small sample size and shorter follow-up period. Additionally, the present study did not include placebo group.

## CONCLUSION

The observations in present study showed significant improvement in LUTS and ED associated with patients of BPH receiving combination of tadalafil (5mg) and alfuzosin (10mg) compared to tadalafil (5mg) or alfuzosin (10mg), alone. Therefore, combination therapy of these two drugs was more efficacious than monotherapies for the treatment of LUTS associated with BPH in patients younger than 60 years of age.

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