

A Comparative Study on Efficacy of Tamsulosin, Finasteride and Combination Therapy in Patients with Benign Prostatic Hyperplasia

KALAIVANI R¹, SARANYA P^{*2}, MANOJKUMAR RAJA M³

¹ – Pharm. D. Alumni, SPS, VISTAS

² – Associate Professor, SPS, VISTAS

³ – Assistant Civil Surgeon, ESIC Hospitals, Ayanavaram

* - corresponding author

Abstract: Context: Benign prostatic hypertrophy (BPH) is a common condition that can result in bothersome lower urinary tract symptoms.

Aims: The study aimed to determine the efficacy of tamsulosin, finasteride and combination therapy in patients with benign prostatic hyperplasia and to observe the quality of life in all the 3 groups.

Settings and Design: A prospective observational study was carried out in the department of surgery of a tertiary care hospital.

Methods and Material: Benign prostatic hyperplasia (BPH) patients who fulfilled the inclusion and exclusion criteria were enrolled into the study and were assigned to any one of the 3 groups randomly, G1-Tamsulosin, G2-finasteride and G3-combination therapy (tamsulosin + dutasteride). Patients were monitored during the hospital stay and followed up until discharge. Severity of symptoms was observed by administering AUA symptom score questionnaire either in English or in tamil.

Statistical analysis used: All statistical analysis was performed using SPSS 17.0 and graph pad prism 7.0. Unpaired student t –test was used to compare two groups and p value less than 0.05 was considered statistically significant throughout the study (95% of confidence interval).

Results: A total of 120 patients, most of the age group ranging from 61-70 yrs (54.16%). There were no significant differences in baseline characteristics. There was significant differences in group wise pre and post drug therapy ($p < 0.0001$) and the treatment efficacy was not similar between the treatment groups ($P < 0.05$).

Conclusion: Combinational therapy was observed to be more efficacious than monotherapy with either tamsulosin or finasteride therapy. Hence it is recommended that combinational therapy can be preferred over monotherapy in the management of BPH in elderly males with or without over active bladder.

Key-words: Benign prostatic hyperplasia, tamsulosin, finasteride, dutasteride, combination therapy, lower urinary tract symptoms

Key Messages: In the current study, combinational therapy was observed to be more efficacious than monotherapy with either tamsulosin or finasteride therapy in the management of BPH in elderly males

with or without over active bladder. Hence it is recommended that combinational therapy can be preferred over monotherapy in patients with BPH.

Introduction:

Benign prostatic hypertrophy (BPH) is a common condition that can result in bothersome lower urinary tract symptoms (LUTS). This condition may arise from anatomic obstruction caused by an enlarged prostate (static component), as well as from an increased smooth muscle tone in the prostate, urethra and bladder neck caused by the sympathetic nervous system-mediated stimulation of α_1 -adrenoreceptors (ARs) (dynamic component)¹. Benign prostatic hyperplasia is the main cause of lower urinary tract symptoms in geriatric male population. These symptoms may adversely affect the quality of life and interfere with daily activities of the patients^{2,3}. BPH is among the most common conditions associated with aging in men, affecting 50% of those between the ages of 50 and 60 years and as many as 90% of those older than 80 years of age. The condition is characterized by cell proliferation in the transition zone of the prostate and increased tone in the smooth muscle of the prostate and bladder neck that can contribute to urethral obstruction⁴. Benign prostatic hyperplasia (BPH) is a common condition in older men that can often result in lower urinary tract symptoms (LUTS). BPH refers to benign prostatic hyperplasia (increase in the number of cells) or hypertrophy (increase in size of cells). BPH is a benign enlargement or growth of the prostate gland. Increase in size of the prostate results in narrowing of the urethra and affects micturition in many ways. Though BPH is not a critical condition, it majorly affects the patient's quality of life. It affects nearly all men at some time in their lives.

Literature states that 14 million men of the United States had lower urinary tract symptoms suggestive of BPH. Although benign prostatic hyperplasia rarely causes symptoms before age 40, the occurrence and symptoms increase with age. Studies reveal that nearly 50% of men between ages of 51 to 60 year and 90% of men older than 80 year are affected by BPH².

In addition, other factors such as central nervous system disorders and/or bladder disorders may be involved. Although voiding ('obstructive') symptoms (i.e weak stream, hesitancy, intermittency, dribbling, abdominal straining and incomplete bladder emptying) are most prevalent, storage ('irritative') symptoms (i.e. nocturia, urgency, frequency and urge incontinence) seem to be the most bothersome for the patient. An increased urinary frequency, urgency, trouble in starting a urine stream, a weak/interrupted urine stream, dribbling at the end of micturition, nocturia, urinary retention/incontinence, pain after ejaculation/during micturition and an unusual color/smell of urine are the LUTS suggestive of BPH. The severity of obstruction/symptoms is independent of the prostate size; a patient with a larger prostate may have minimal symptoms and a patient with minimally enlarged prostate may have severe blockage/symptoms. Less than half of all men with benign prostatic hyperplasia have lower urinary tract symptoms⁵⁻⁸.

The cause of benign prostatic hyperplasia is not well understood. As age increases, level of testosterone circulating in blood decreases leaving an increased estrogen level in men. Some studies state that an increased proportion of estrogen in the prostate can increase the prostate cell growth. Men of age >40 year, with a family history of BPH, lack of physical activities, erectile dysfunction and known case of diabetes, cardiovascular diseases are at greater risk to develop benign prostatic hyperplasia.

Selective α_1 -blockers, such as doxazosin, terazosin, and tamsulosin, block α_1 -adrenoceptors in the prostate and bladder neck, inhibiting sympathetic stimulation of prostatic smooth muscle, thereby reducing prostatic tone and relieving urinary obstruction in men with BPH. These agents improve

obstructive and irritative BPH symptoms and improve urinary flow, usually within 1 to 2 weeks of treatment. Finasteride is a 5-alpha-reductase inhibitor that interrupts the conversion of testosterone into 5-alpha-dihydrotestosterone⁹⁻¹⁵.

Subjects and Methods:

The study protocol was submitted to the institutional ethics committee for its review and approval. The patients were enrolled into the study after obtaining written informed consent from each, either in English or in the local language (tamil) whichever the participant felt comfortable. BPH patients who fulfilled the inclusion and exclusion criteria were enrolled into the study and were assigned to any one of the 3 groups randomly: G1-Tamsulosin, G2-finasteride and G3-combination therapy (tamsulosin + dutasteride). Patients were monitored during the hospital stay and followed up for until discharge. On the day of admission American Urological Association (AUA) symptom score as well as vital signs (blood pressure and heart rate) were documented along with laboratory investigations (routine biochemistry, urinalysis and PSA levels) performed at the screening visit, history of recent or concomitant medication taken, the size of prostate estimated by rectal palpitation and abdominal ultrasound were recorded. Severity and symptoms was observed by using AUA symptom score (AUASS). If there is any ADR noticed, will be documented and reported to the physician. Patient's clinical data post intervention will be documented and assessed statistically. All statistical analysis was performed using SPSS 17.0 and graph pad prism 7.0. Unpaired student t –test was used to compare two groups and p value less than 0.05 was considered statistically significant throughout the study (95% of confidence interval).

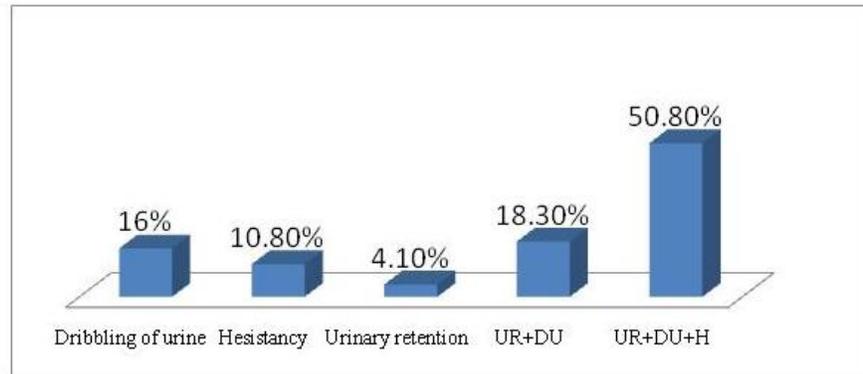
Results:

Around 120 men were randomized into three groups according to the therapy they received for BPH. About 40 study participants were assigned in each group based on the drug therapy they received; group 1, group2 and group 3, that received tamsulosin, finasteride and combinational therapy (tamsulosin+dutasteride) respectively.

The mean \pm (S.D) age of study participants was $67.89 \pm (7.04)$ years. Most of the patients were in the age group ranging from 61-70yrs (54.16%) followed by 71-80yrs (29.16%). A majority of the patients were smokers in group1 (35%) and group2 (52.5%) and alcoholic in group3 (57.5%). Overall 60% of the study population suffered from a co-morbid condition. Most of the patients had hypertension (HTN) in group1 (54%), whereas diabetes mellitus (DM) in group2 (43.4%) and group 3 (51.4%).

About 52.5% and 65% of the study participants had less than 4ng/ml of serum prostate antigen (PSA) whereas 60% in group2 had more than 4ng/ml. A majority of patients were observed to have normal prostate volume (G1=87.5%, G2=77.5% and G3=90%), but their post void volume was more than 50ml in most of the patients of all the three groups. A majority of patients came with chief complaints of urinary retention, dribbling of urine and hesitancy in 50%, 45%, 50.8% of study participants in group1, 2 &3 respectively, followed by 30%, 25% and 18.3% in group1,2,3 with only urinary retention & dribbling of urine (Fig1).

FIG 1: DISTRIBUTION OF SYMPTOMS



AUA symptom score assessment on the day of admission

About 40% and 52.5% of study participants in group1 and group3 reported that more than half the time they had sensation of not emptying their bladder completely after they finished urinating and 37.5% in group2 reported that about half the time they had the same sensation.

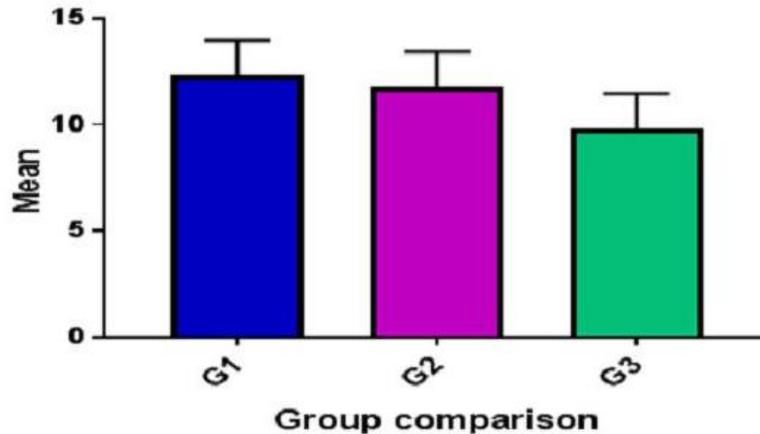
A majority of patients in group1, 2 & 3 (42.5%, 30% &35% respectively) have reported that more than half the time, about half time and almost always had to urinate less than 2hours after they finished urinating respectively. Most of the patients often had to stop and start again several times when they urinated more than half the time in group1(45%), group 2(45%) and almost always in group 3(40%).

A majority of patients in group1 (47.5%), group 2 (40%) & group 3 (37.5%) reported that they had difficulty to postpone urination more than half the time. When asked for how often they had weak urinary stream during the past month, the majority of patients in group1 (45.5%), group 2 (37.5%) and group 3(40%) reported that they had it more than half the time. About 47.5% & 32.5% patients in group1 & group 3 reported that more than half the time in the past month they had to push or strain to begin urination whereas, 37.5%in group2 had to do it less than half the time. A majority of patients in group1 (52.5%), group 2 (35%) & group 3 (27.5%) reported that they had to getup 4times per night to urinate from the time they went to bed at time until the night they got up at the morning.

AUA symptom score assessment on the day of discharge

The AUA Symptom Score was observed to improve after tamsulosin or finasteride or combination therapy on the day of discharge when compared to the day of admission. A majority of the patients in group1, 2 and 3 (90%, 95%, 92.5% respectively) have reported that they had a sensation of not emptying their bladder after they finished urinating less than 1 time in 5 on the day of discharge. From more than half, about half the time & almost always to urinate again less than 2 hrs after finishing urinating on the day of admission, their symptoms improved to less than half the time (52.5% in group1) & less than 1 time in 5 (group 2 =45% & group 3=52.5%) during discharge (Fig 2).

FIG2 : COMPARISON OF AUA SYMPTOM SCORE



Most of the patients had to often stop and start again several times when they urinated more than half the time and almost always during admission whereas after a-blocker drug therapy they had the same less than half the time (55% in group1) & less than 1 time in 5(55% group 2 and group 3=52.5%) on the day of discharge. About 50% each in group1 reported that they not all or less than 1 time in 5 felt difficult to postpone urination. A majority (55% in group 2 & 52.5% in group 3) had mentioned that less than half the time and not at all respectively for the same symptom after drug therapy. From more than half the time on the day of admission the symptom of having a weak urinary stream often have come down to less than half the time in a majority of the study participants (45% in group1, 60% in group 2 &55% in group3) during discharge.

A majority of the patients reported that either less than half the time (G1=50%, G2=40%) or less than 1 time in 5 (G3=42.5%) they had to push or strain to begin urination. From getting up 4 times per night to urinate from the time, they went to bed at night until the time they got up at the morning, majority of participants (G1=62.5%, G2=45% &G3=57.5%) reported that they had to wake up only 3 times after drug therapy. The overall symptom score on the day of admission was calculated and observed that 95%, 85% & 85% of group 1, 2 & 3 patients respectively had severe urological symptoms as per the AUA symptom score. The distribution of overall symptom score on the day of admission and discharge. A statistically significant difference ($p<0.0001$) in AUASS was observed between pre and post tamsulosin therapy in group1(Fig 3) , pre & post finasteride therapy in group2 patients (Fig 4), pre & post combinational therapy in group 3 patients and between the groups(G1,G2&G3) post drug therapy the day of discharge (Fig 5).

FIG 3: COMPARISON OF AUASS PRE AND POST-TAMSULOSIN THERAPY

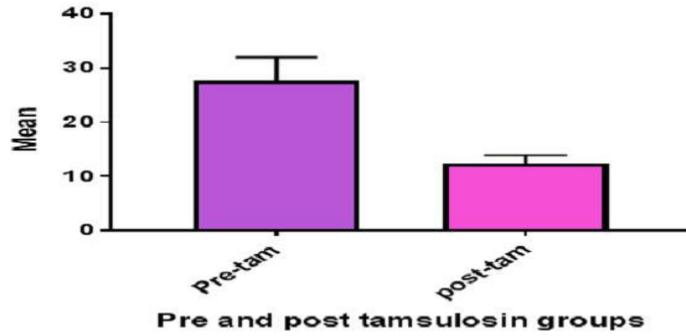


FIG 4: COMPARISON OF AUASS PRE AND POST-FINASTERIDE THERAPY

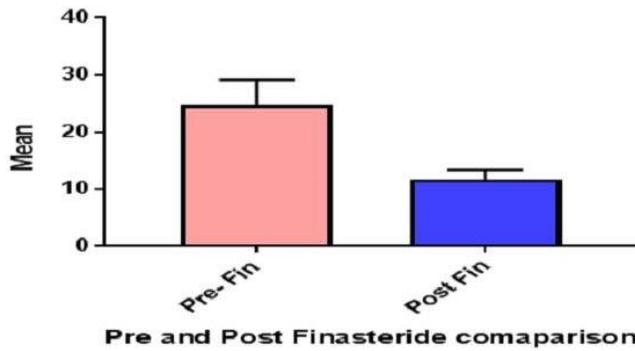
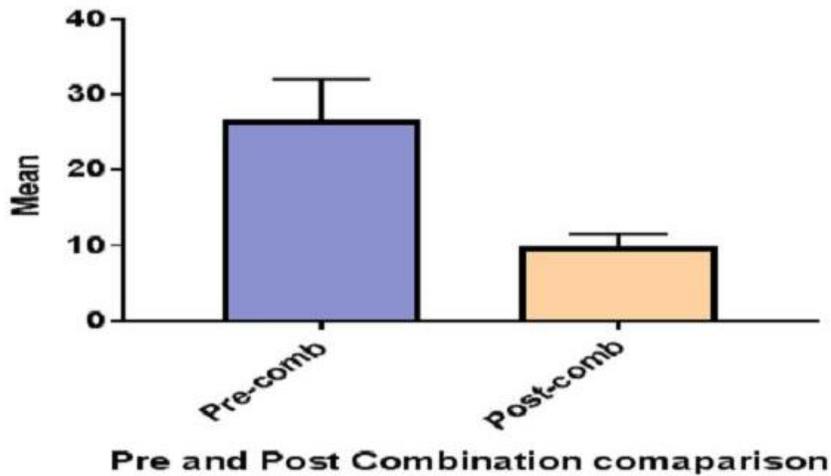
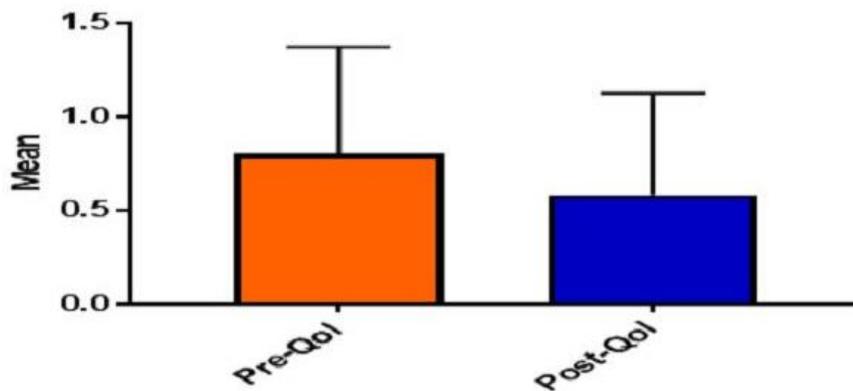


FIG 5: COMPARISON OF AUASS PRE AND POST-COMBINATION (TAMSULOSIN+DUTASTERIDE) THERAPY



The QOL post drug therapy was observed to improve on the day of admission. A statistically significant difference ($P < 0.004$) in QOL was observed between pre & post drug therapy (Fig 6). The QOL was assessed based on how the participants felt if they had to live with their urinary condition the way it is now, no better, no worse for the rest of their life and it was observed that most of patients were pleased for the same in group1 (60%), group 2 (67%) and group 3(37.5%). A majority of patients did not experience any ADR (group1=87.5%, group 2= 82.5%, group3=95%). The common adverse effects observed were headache (85% in group1& 75 in group3) and dizziness (90% in group 2).

FIG 6: COMPARISON OF QUALITY OF LIFE (QOL) PRE AND POST-DRUG THERAPY



Discussion:

Benign prostatic hyperplasia can cause acute urinary retention, a need for surgery, urinary incontinence, urinary tract infections and other complications. Treatment with an alpha blocker or a 5 α -reductase inhibitor can ameliorate symptoms and improve urinary flow rate. Finasteride substantially reduces the risk of acute urinary retention and the need for surgical treatment. Benign prostatic hyperplasia and lower urinary tract symptoms can affect the quality of life in older men.

BPH and LUTS is more commonly associated with older men, affecting 50% of those between the age of 50 and 60 years and as many as 90% of those older than 80years of age¹⁸. The mean age(SD) of BPH patients in our study was 67.89 (± 7.04 , range; 51-80yrs) which is similar to the study population of Singh et al (67.28 ± 7.99), closer to Ong et al (72.9 ± 9.0 , range;40-97yrs), in line with that of Kirby et al (64yrs) and Rigatti P et al (69 ± 7.1 yrs). The mean prostate volume of the study population was 33.88 ± 0.94 ml which is similar to that reported by Singh *et al* (36.28 ± 24.67 & 45.20 ± 22.16) and McConnell JD et al (36.9 ± 20.60). The current study mean serum PSA was 4.61 ± 0.94 ng/ml which is higher than (2.4 ± 2.1 ng/ml) that reported by McConnell. The observed mean postvoid volume among the study participants was 71.5 ± 13.10 ml which is similar to that reported by Gormley GJ *et al* 1992, (73 ± 89) and that reported by Mcconnell *et al* 2003(69.6 ± 82).The renal function of the study population was apparently normal, when assessed by serum creatinine levels. The mean serum creatinine was observed to be 0.77 ± 0.25 which is closer to that reported by McConnell *et al* (1.1 ± 0.1).

We assessed the changes in AUA symptom score in BPH patients receiving tamsulosin vs finasteride vs combination therapy pre & post drug therapy. Our study demonstrated that tamsulosin, finasteride and

combination therapy reduced the overall AUA symptom score and improved the quality of life in BPH patients.

The overall AUA Symptom score improved from severe to moderate post drug therapy in a majority of patients overall (88.3-severe to 60% moderate) and group wise (severe-G1=95%, G2=75% &G3=60% and moderate G1=87.5 %, G2=75% &G3= 60%). A statistically significant difference ($p<0.0001$) in AUASS was observed between pre and post-tamsulosin therapy in group1, pre and post-finasteride therapy in group2 patients, pre and post-combinational therapy in group 3 patients and between the groups(G1,G2&G3) post drug therapy the day of discharge.

Barry *et al*²⁴ demonstrated that an average 3-point reduction in American Urological Association symptom score was perceived by patients as “slight” improvement, and an average 8.8-point reduction were perceived as “marked” improvement. In our study participants who received tamsulosin had an average perceived improvement in symptom score that can be considered as “markedly improved”. In the current study, BPH patients on tamsulosin, finasteride and combination therapy (G1, G2 &G3) had an average point reduction in the AUA symptom score. Thus AUA symptom score was perceived by tamsulosin therapy, patients as “marked”, finasteride as “marked” and combination therapy patient as “markedly”

The Symptom prostate index (SPI) questionnaire was selected as the primary outcome parameter because the patient’s quality of life (QOL) and its interference with daily life activities are more affected by the extent to which he is bothered by his urinary symptoms, than solely by the frequency of these symptoms. As the SPI captures information on the bother associated with the seven questions included in the AUA Symptom score questionnaire, which is generally accepted for obtaining data on the frequency of urinary symptoms, this questionnaire was selected for measuring the bothersomeness associated with urinary symptoms. In the present study tamsulosin 0.4mg significantly improved total and individual symptom score and there was reduction in AUA symptom score was 87.5% in the tamsulosin treated group which is in line with Singh *et al* and in contrast to Nordling *et al* study reports.

In the present study, only 14 patients were associated with headache, dizziness, and nausea and vomiting. Erectile dysfunction, Dizziness, Dyspnoea, peripheral edema, decreased libido, postural hypotension were the common adverse effects reported in previous study by McConnell *et al*²³. In a study reported by Singh *et al*¹⁹, headache, dizziness, abdominal distension were the common adverse effects. Whereas P Rigatti *et al*²⁵ reported that influenza flu like symptoms, impotence, abdominal pain, ejaculation disorder were the common adverse effects. McConnell *et al* have stated that lower urinary tract symptoms and BPH are not clinically significant risk factors for UTI &have also mentioned that their trial didn’t substantiate the concern that untreated BPH may lead to renal sufficiency. This is par with the current study, in which none of the patients had urinary tract infections (UTI) or renal insufficiency.

Combination therapy with tamsulosin and dutasteride significantly reduce the risk of overall progression of benign prostatic hyperplasia more than did either drug alone. This is in line with that reported by McConnell *et al*.

In order to determine difference in post-treatment AUA symptom score within treatment groups, non-parametric post-hoc analysis was carried out (bonferroni corrections). Statistically significant differences was found between the groups compared ($P<0.05$), suggesting that the treatment efficacy was not similar between the treatment groups ($P<0.005$).These findings are on par with that reported by Mcconnel *et al*.

The incidence of BPH in men of india is high. Tamsulosin or 5-alpha reductase inhibitor monotherapy is considered as gold standard in BPH management. In the current study, combinational therapy was

observed to be more efficacious than monotherapy with either tamsulosin or finasteride therapy. Hence it is recommended that combinational therapy can be preferred over monotherapy in the management of BPH in elderly males with or without over active bladder.

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FIGURE LEGENDS

1. **FIG 1: Distribution of symptoms**
2. **FIG 2 : Comparison of AUA symptom score**
3. **FIG 3 : Comparison of AUASS pre and post-tamsulosin therapy**
4. **FIG 4 : Comparison of AUASS pre and post-finasteride therapy**
5. **FIG 5: Comparison of AUASS pre and post-combination (tamsulosin+finasteride) therapy**
6. **FIG 6: Comparison of quality of life (QOL) pre and post-drug therapy**