Original Article

Effect of dose reduction of dutasteride in combination with alpha-blockers in patients with lower urinary tract symptoms/benign prostatic enlargement

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Abstract

Context: Dutasteride is used in the treatment of benign prostate enlargement with reported many side effects.

Aims: The purpose of this study is to examine how different doses of dutasteride (0.5 mg) in combination with tamsulosin affect the outcome of treatment of benign prostatic enlargement (BPE).

Settings and Design: Prospective study (phase III trial).

Subjects and Methods: Between April 2017 and March 2020, this randomized study was conducted on 300 patients with moderate-to-severe lower urinary tract symptoms attributable to BPE and a prostate volume of more than 40 cc. The patients were divided into three therapy groups at random (one-to-one randomization), each with 100 patients: (Group I) daily tamsulosin 0.4 mg plus dutasteride (0.5 mg). (Group II) every other day tamsulosin 0.4 mg plus dutasteride 0.5 mg. (Group III) once a week tamsulosin 0.4 mg plus dutasteride 0.5 mg.

Statistical Analysis: Statistical analysis was carried out with the help of the SPSS program 22. (IBM, Armonk, NY, USA). The mean and standard deviation (SD) are used to express quantitative data (SD). When comparing two means, an independent-samples *t*-test of significance was used. To compare more than two means, a one-way analysis of variance was utilized. For multiple comparisons between distinct variables, a *post hoc* test was performed.

Results: Patients were followed up every 3 months, with a 1-year follow-up to examine the medications' efficacy, prostate size reduction, and erectile function. After 1 year of treatment, all groups showed significant improvement in their symptom scores. However, Groups I and II experienced a considerable reduction in prostate size after therapy, but Group III experienced no meaningful reduction. In terms of sexual dysfunction, there was a considerable shift in Group I after 12 months.

Conclusions: Dutasteride treatment on the other day schedule has the same efficacy as the daily dose on prostate size at the same time; the other day scheduled dose has better preservation of sexual function.

Keywords: Benign prostatic enlargement, dutasteride, quality of life

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INTRODUCTION

Benign prostatic enlargement (BPE) is one of the most frequent disorders in aging men, affecting more than half of men in their sixth decade and reaching 90% by the age of 80 years.[1,2] BPE is mostly caused by benign prostatic hyperplasia (BPH), which is defined by hyperplasia of the prostatic stroma and epithelial cells and is clinically manifested by lower urinary tract symptoms (LUTS) that negatively impact patients' quality of life.[3] The major hormone responsible for prostate growth is dihydrotestosterone (DHT), which is created by converting testosterone (T) to DHT through the 5-alpha reductase enzyme (5-R).[4] There are two isoforms of 5-reductase (Type I and Type II). Finasteride inhibits Type II enzymes, whereas dutasteride inhibits both Type I and type II enzymes.[5] A lot of differences between finasteride and dutasteride are present; finasteride decreases serum DHT by about 70%, while dutasteride reduces serum DHT by more than 90%. In addition, dutasteride has a long half-life of 5 weeks and can be detected in serum 4–6 months after discontinuation.[4] The main adverse effects of both drugs are sexual problems (decreased libido and erectile dysfunction [ED]).[6] Guidelines show that combination therapy (Alpha-blockers [AB] and 5-α reductase inhibitors) is better than monotherapy in the treatment of BPH in patients with a large prostate (over 40cc) and the prevention of disease progression.[7] The aim of this study was to examine the effect of using different scheduled doses of dutasteride (0.5 mg) in combination with tamsulosin for the treatment of BPE.

SUBJECTS AND METHODS

Between April 2017 and March 2020, this randomized study was conducted on 300 patients with moderate-to-severe LUTS attributable to BPE and a prostate volume of more than 40 cc. All patients underwent a history and symptom assessment, which included sexual history, the International Prostate Symptom Score (IPSS), and the International Index of Erectile Function (IIEF-5), as well as a physical examination, which included digital rectal examination, laboratory investigations (urine analysis and renal function assessment), and ultrasound (abdominal and transrectal). Prostate volume was assessed using transrectal ultrasound (TRUS).

Exclusion criteria

Patients with prostate <40cc, prostate cancer, neurologic disease, history of radiation therapy, and hepatic and renal disease.

Patients who had follow-up <1 year.

Randomization

Patients were randomly divided into three treatment groups (one-to-one randomization), and each group had 100 patients:

- (Group I) received a daily dose of tamsulosin 0.4 mg plus dutasteride (0.5 mg) daily
- (Group II) received daily tamsulosin 0.4 mg plus dutasteride 0.5 mg every other day
- (Group III) received daily tamsulosin 0.4 mg plus dutasteride 0.5 mg once a week.

Patients were evaluated every 3 months for the 1st year of treatment to measure medication efficacy, prostate size reduction, and erectile function; re-evaluation was done using symptom scores and TRUS ultrasonography.

Primary outcome

Primary outcome was the sexual dysfunction measured by the IIEF-5 score, while the secondary outcome was the change in prostate size.

Ethical consideration

Ethical approval was obtained from the local ethical committee before the start of this study. The study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. The procedures and its possible complications were discussed with all patients, and informed consent was obtained from the subjects of this study before the beginning of the procedures. Patients' confidentiality was respected and maintained throughout this study.

Sample size calculation

the sample size and power analysis were calculated using Epi-Info software statistical package created by the World Health Organization and Center for Disease Control and Prevention, Atlanta, Georgia, USA version 2002. The hypothesized power of the study is 88% with a 95% confidence limit, an alpha of 0.05, and the percentage of improvement of ED between cases at 15%, thus at least 95 patients should be included in the study.[2]

Statistical analyses

Statistical analyses were carried out with the help of the SPSS program 22 (IBM, Armonk, NY, USA). The mean and standard deviation (SD) are used to express quantitative data (SD). When comparing two means, an independent-samples *t*-test of significance was used. To compare more than two means, a one-way analysis of variance was utilized. For multiple comparisons between distinct variables, a *post hoc* test was performed.

RESULTS

we enrolled 332 patients with LUTS secondary to BPE in this study. At 12 months, 300 patients completed the study. Nineteen patients lost follow-up. Thirteen patients discontinued medical treatment, and seven of them had endoscopic treatment. At the start of the trial, there were no statistical differences between the three therapy groups in terms of age, IPSS score, IIEF-5, or prostate volume) [Table 1]. Before therapy, all of the patients had a prostate size of more than 40cc. After 1 year of treatment, all groups showed a significant improvement in their symptom score (IPSS) [Table 2]. However, Groups I and II experienced a considerable reduction in prostate size after therapy, while Group III experienced no significant reduction in prostate size [Table 3]. In terms of sexual dysfunction, there was a considerable change in Group I after 12 months; however, there was no change in IIEF-5 in Groups II and III [Table 4].

Table 1: Age distribution in the three treatment groups

Age	Group I	Group II	Group III
Range	58-75	60-76	60-75
Mean±SD	67.14±3.90	67.37±4.16	67.53±4.29
t		0.227	
P		0.797	

SD: Standard deviation

Table 2: International Prostate Symptom Score before and after treatment

IPSS	Pre	Post	*t*	*P*
Group I				
Range	9–30	7–22	8.885	0.05
Mean±SD	20.25±5.09	14.39±4.19		
Group II				
Range	8-29	6-21	11.819	0.001*
Mean±SD	20.20±3.81	14.36±3.14		
Group III				
Range	9-30	7-23	8.255	0.001*
Mean±SD	19.83±4.79	15.01±3.34		
F	0.294	1.047		
P	0.780	0.352		
Group I and Group II	0.939	0.953		
Group I and Group III	0.519	0.223		
Group II and Group III	0.570	0.201		

IPSS: International Prostate Symptom Score, SD: Standard deviation

Table 3: Size of the prostate before and after treatment

Size	Pre	Post	*t*	*P*
Group I				
Range	45-85	40-72	11.304	0.05
Mean±SD	63.71±9.77	50.29±6.74		
Group II				
Range	46–83	39-70	10.271	0.001*
Mean±SD	65.25±9.55	51.63±9.20		
Group III				
Range	41-86	40-83	1.566	0.119
Mean±SD	63.12±10.43	60.94±9.22		
F	1.228	46.907		
P	0.294	0.001*		
Group I and Group II	0.273	0.264		
Group I and Group III	0.674	0.001*		
Group II and Group III	0.130	0.001*		

SD: Standard deviation

Table 4: International Index of Erectile Function-5 score before and after treatment

IIEF	Pre	Post	*t*	*P*
Group I				
Range	7–22	5-19	6.487	0.05
Mean±SD	14.60±3.85	11.14±3.70		
Group II				
Range	7-23	6-22	1.294	0.197
Mean±SD	14.46±3.46	13.81±3.64		
Group III				
Range	7-23	7-22	1.075	0.284
Mean±SD	14.85±3.31	14.35±3.27		
F	0.310	23.597		
P	0.734	0.05		
Group I and Group II	0.780	0.001*		
Group I and Group III	0.619	0.001*		
Group II and Group III	0.438	0.281		

SD: Standard deviation, IIEF: International Index of Erectile Function

DISCUSSION

BPH is a disorder that progresses over time and is characterized by prostate enlargement, LUTS, and sexual dysfunction.[3] Treatment for BPH with 5ARIs and/or 1-blockers is first-line therapy, and the two medications have different mechanisms of action for influencing prostate development.[6] After 6 months of treatment, both medications result in a reduction in prostate size (18%–28% reduction) and a 50% reduction in prostate-specific antigen levels.[5] AB and 5ARIs have been shown to improve LUTS and urine flow in a substantial body of research.[8,9] The usage of these drugs, on the other hand, has been linked to a worsening of sexual function. AB cause ejaculation to be dry. Ejaculatory difficulties have also been linked to the usage of 5ARIs.[10] Furthermore, there has been an increase in concern in recent years about the likelihood that 5ARIs can cause ED and hypoactive sexual desire (HSD) in BPH patients. which can last even after stopping the medicine.[11,12] Finasteride and dutasteride have both been used to treat androgenetic alopecia with similar results.[2] According to Zhou *et al*.,[6] the combination of tamsulosin and dutasteride provides a preferable therapeutic effect for BPE with a higher incidence of sexual side effects, but it can significantly reduce the risk of BPE-related symptom progression and acute urinary retention when compared to tamsulosin monotherapy. Furthermore, Corona *et al*.[13] found that using 5ARIs increases the incidence of ED and HSD in people with BPE, especially when obstructive symptoms are present, even though some of the sexual side effects

fade away after a few months. Furthermore, Zhou *et al*.[6] found that dutasteride (0.5 mg) and finasteride (0.5 mg) reduced libido and potency (5 mg).[14] Favilla *et al*. the researchers found that the overall prevalence of ED and libido changes was significantly higher in the 5-R plus AB group than in the AB group (7.93% vs. 4.66%; odds ratio [OR] 1.81; p50.0001 and 3.69% vs. 2.36%; OR 1.58; p1 40.003, respectively). In our research, we found that when AB and 5-ARIs were used together, the risk of ED and libido changes was much higher than when they were used alone. The likelihood of libido changes was similar in combination therapy and 5-ARI monotherapy. Miller and Tarter[15] also stated that dutasteride is the only dual 5-R inhibitor licensed for the treatment of men with symptomatic BPE only a few drug interactions have been documented in the literature. Due to the potential for harmful effects on the normal development of the male reproductive tract, this medicine is contraindicated in men and women under the age of 18. Impotence, loss of libido, ejaculatory dysfunction, and gynecomastia are all side effects that occur in <5% of patients. Gubelin Harcha *et al*.[16] evaluated the efficacy and safety of dutasteride (Type 1 and 2 5-alpha reductase inhibitor) with finasteride (Type 2 5-alpha reductase inhibitor) and placebo in males with androgenetic alopecia, using the same premise as our trial on dose decrease of dutasteride. Men with androgenetic alopecia aged 20–50 years were randomly assigned to receive dutasteride (0.02, 0.1, or 0.5 mg), finasteride (1 mg/day), or placebo, or a placebo over a period of 24 weeks. They came to the conclusion that dutasteride increased hair growth and restoration in men with androgenetic alopecia, with no difference in hair growth and restoration across all dutasteride doses and fewer side effects at low doses. In a similar vein, Lee *et al*.[17] conducted a meta-analysis to assess the adverse sexual effects of finasteride or dutasteride treatment for male androgenetic alopecia and found that dutasteride 0.5 mg/day was associated with a 1.57-fold increased risk of sexual dysfunction. As a result, dutasteride dose decrease could have the same therapeutic efficacy in diverse diseases. Tsai *et al*.[18] looked studied the prevalence, duration, persistence, and treatment discontinuation of adverse events related to sexual function in men using dutasteride for androgenetic alopecia. For 24 weeks, participants were randomly assigned to receive either dutasteride (0.5 mg) or a placebo once daily, After that, open-label dutasteride (0.5 mg) was used for another 24 weeks. Sexual side effects were tracked for up to 24 weeks following the last treatment, or until they disappeared. In the dutasteride group, the rate of adverse sexual events was roughly two-fold higher than in the placebo group (16% vs. 8%). The total incidence of adverse sexual events was lower (5%) during the double-blind period than during the open-label period. All of the adverse effects were mild to moderate in intensity and were thought to be connected to the treatment. Corona *et al*.[13] looked at the rate of sexual adverse effects in men who were given 5-R. They conducted a thorough investigation using the terms "finasteride," "dutasteride," and "BPH." Only placebo-controlled randomized clinical trials investigating the effects of 5-R in men with BPH were taken into account. Corona *et al*. included 17 studies from 383 publications found through Medline and Cochrane searches. They came to the conclusion that using 5-R considerably raises the risk of ED and HSD in people who have BPE. Chi and Kim[19] looked at the effects of dutasteride treatment on sexual function. They found that after a month of medication, all of the participants tested had a significant decline in sexual function. Overall, sexual function improved after 3 months, but orgasmic function and sexual desire returned to baseline after 6 months. After 1 year of treatment, all groups showed significant improvement in their symptom score (IPSS). However, Groups I and II saw significant reductions in prostate size after therapy, but Group III saw no significant reduction in prostate size. Furthermore, there was a considerable change in Group I; however, no change in IIEF-5 was seen in Groups II and III. In comparison to daily dutasteride, alternate day dose reduction of dutasteride resulted in less adverse effects, primarily sexual dysfunction, and the same improved voiding results in combination therapy with AB. Furthermore, increased dutasteride dose decrease (Group III) improved sexual function but had no effect on prostate size. This is the only study that we are aware of that looks at the influence of dutasteride dose reduction on both IPSS and sexual function.

CONCLUSIONS

Dutasteride treatment on the other day schedule has the same efficacy as the daily dose on prostate size at the same time; the other day scheduled dose has better preservation of sexual function.

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Conflicts of interest
There are no conflicts of interest.

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