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Single Versus Double Dose Tamsulosin for Patients with Moderate or Severe Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia: Prospective Randomized Study

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ABSTRACT

Background: As men age, the prevalence of lower urinary tract symptoms (LUTS) linked with benign prostatic hyperplasia (BPH) rises. By the time they are 70 years old, almost 80% of men have been found to have BPH-related LUTS. LUTS, such as incomplete urination, frequency, urgency, nocturia, and reduced urine flow, appear in patients with BPH.

Objective: We aimed to evaluate the efficacy and safety of single versus double dose of tamsulosin 0.4 mg for treatments of LUTS/BPH.

Patients and methods: A double-blinded randomized controlled trial was conducted in the Outpatients Clinics for BPH-associated moderate and severe LUTS. Patients were randomized to receive single dose tamsulosin 0.4 mg capsule (1st group n = 33), and double dose tamsulosin 0.4 mg capsule (2nd group n= 32). The primary endpoints were the changes in International Prostate Symptom Score (IPSS), Uroflowmetry and PVR urine volume before starting the study, after one month and after 3 months of the treatment.

Results: Total IPSS was more decreased (improved) in double dose tamsulosin 0.4 mg group than single dose tamsulosin 0.4 mg group, with P-value = 0.005 at one month follow up and 0.007 at three months follow up, which was statistically significant. However, dizziness was more frequent in double dose tamsulosin 0.4 mg group than in single dose tamsulosin 0.4 mg group (with P = 0.03 at one month follow up and P= 0.01 at three months follow up), which was statistically significant.

Conclusion: Tamsulosin single and double doses had equal effects, safe, and well tolerated in the target BPH population. However, tamsulosin double doses was statistically superior to single dose in improving IPSS scoring. On the other hand, tamsulosin double doses had statistically significant adverse effect in the form of dizziness.

Keywords: Benign prostatic hyperplasia, Tamsulosin, Lower urinary tract symptoms.

INTRODUCTION

Men's LUTS is frequently caused by BPH. The pathophysiology of BPH involves both active and passive pressures in the prostatic tissue. Although the adrenergic nerve system has been shown to govern active smooth muscle tone, it is unknown what elements ultimately decide the prostate's passive tone [(1)].

Alpha1-blockers work by preventing endogenously generated noradrenaline from acting on the prostate's smooth muscle cells, which lowers BOO and prostate tone [(2)].

Alpha1-blockers usually result in a 30–40% reduction in IPSS and a 20–25% rise in Qmax. Alpha1-blockers showed up to a 50% improvement in IPSS and a 40% rise in Qmax in another experiment [(3)].

Nonetheless, the preferred medication for LUTS related to BPH (LUTS/BPH) is an α-blocker. Three subtypes of the alpha 1-adrenoceptor exist: α 1a, α 1b, and α 1d. Of these, α 1a is the most common in patients with BPH, accounting for up to 85% of cases. Alpha-blockers relieve LUTS/BPH by relaxing the smooth muscles of the prostate [(4)].

In this trial, we aimed to evaluate the efficacy and safety of single versus double dose of tamsulosin 0.4 mg for treatments of LUTS/BPH.

PATIENTS AND METHODS

Between March 2022 and December 2022, a double-blinded randomized controlled trial was conducted in the Outpatients Clinics of Menoufia University Hospitals.

A total of 65 patients suffering from BPH-associated moderate and severe LUTS, were randomized to receive single dose tamsulosin 0.4 mg capsule (1st group = 33), and double dose tamsulosin 0.4 mg capsule (2nd group = 32). Three and two patients from the first and second group respectively, lost follow up.

Inclusion criteria: Patients suffering from BPH-associated moderate and severe LUTS (IPSS ranging from 8 to 35) and had normal PSA (≤ 4 ng/dl).

Exclusion criteria: Patients with congenital or acquired urethral stricture and neurogenic bladder or bladder cancer. Also, patients with elevated PSA (> 4 ng/dl), history of previous prostate surgery, complicated BPH either with hematuria, stones, diverticulum, refractory urinary retention and patients with upper urinary tract pathology were excluded in this trial.

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All patients were evaluated by history taking (including personal history, complaint, present history), IPSS, past medical and surgical history and body mass index (BMI).

Physical examination was done including abdominal examination and digital rectal examination. Uroflowmetry (Q-max), ultrasonographic assessment of prostate volume, postvoid residual urine volume (PVR) and laboratory evaluation by prostate specific antigen (PSA) were done. Follow up of patients was done after one and after three months of treatment.

Patients were followed up for IPSS, uroflowmetry Q-max, PVR urine volume and the adverse effects of the treatment as retrograde ejaculation, dizziness, nasal congestion, headache, orthostatic hypotension and asthenia.

Ethical approval: Menoufia Faculty of Medicine Ethics Committee gave its approval to this study. All participants gave written consents after receiving all information. The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

SPSS statistics, Version 22.0, was used to code, tabulate, and statistically analyse the data that were gathered. Quantitative data that was normally distributed was expressed as mean ± SD, and it was compared using both paired and independent t-tests (two independent groups and paired data). Numbers and percentages used to express qualitative data that were then compared using the Chi square test. Significant data was defined as a P value ≤ 0.050.

RESULTS

Regarding patient demographics and baseline assessment of both groups before starting the study, there was no statistically significant difference between the two groups regarding prostate size, total PSA, total IPSS, uroflowmetry and PVR urine (Table 1).

Table (1): Patient demographics and baseline assessment of both groups before starting the study.

Variable	Single dose (N=30)	Double dose (N=30)	P – Value
Age (years) (Mean ± SD)	63.8 ± 10.7	60 ± 9.3	0.83
BMI (Kg/m^2) (Mean ± SD)	26.6 ± 2.46	26.6 ± 2.93	0.99
Smoking	10/30 (33.3 %)	13/30 (43.3 %)	0.426
Hypertension	20/30 (66.7%)	14/30 (46.7 %)	,0.192
Diabetes Mellitus	12/30 (40 %)	7/30 (23.3 %)	0.165
Prostate Size (gm) Median (IQR)	94.5 (75 , 128)	81 (70 , 120)	0.27
Total PSA (ng/dl) (Mean ± SD)	3.19 ± 0.68	3.05 ± 0.89	0.49
Total IPSS, Median (IQR)	17 (13 , 25)	15.5 (12 , 23)	0.64
Uroflowmetry (ml/sec) (Mean ± SD)	9.53 ± 2.81	9.93 ± 2.89	0.59
PVR (ml) (Mean ± SD)	76.66 ± 15.44	73.33 ± 14.64	0.39

Regarding follow up assessment of both groups at one and three months follow up, total IPSS was more decreased (improved) in double dose tamsulosin 0.4 mg group than single dose tamsulosin 0.4 mg group, which showed statistical significant difference. Uroflowmetry was greater (improved) in double dose tamsulosin 0.4 mg group than single dose tamsulosin 0.4 mg group, which showed statistical insignificant difference. PVR urine was more decreased (improved) in double dose tamsulosin 0.4 mg group than single dose tamsulosin 0.4 mg group, which showed statistical insignificant difference (Table 2).

Table (2): Follow up assessment and adverse effects of both groups at one month follow up

Variable	Single dose (N=30)	Double dose (N=30)	P – Value
Total IPSS, Median (IQR)	11 (8 , 15)	7 (4 , 12)	**0.005**
Uroflowmetry (ml/sec) (Mean ± SD)	15.73 ± 4.59	16.73 ± 5.95	0.47
PVR (ml), Median (IQR)	47 (20 , 60)	40 (20 , 60)	0.32
Retrograde Ejaculation	7/30 (23.3 %)	11/30 (36.7 %)	0.26
Dizziness	2/30 (6.7 %)	8/30 (26.7 %)	**0.03**
Nasal congestion	3/30 (10 %)	6/30 (20 %)	0.27
Orthostatic hypotension	5/30 (16.7 %)	9/30 (30 %)	0.22
Headache	1/30 (3.3 %)	5/30 (16.7 %)	0.08
Asthenia	1/30 (3.3 %)	4/30 (13.3 %)	0.16

Regarding adverse effects of different doses at one and three months follow up, retrograde ejaculation, nasal congestion, orthostatic hypotension, headache and asthenia were more frequent in double dose tamsulosin group than in single dose tamsulosin group, with statistically insignificant difference. However, dizziness was more frequent in double dose tamsulosin 0.4 mg group than single dose tamsulosin 0.4 mg group, which showed statistically significant difference (Table 3).

Table (3): Follow up assessment and adverse effects of both groups at three months follow up

Variable	Single dose (N=30)	Double dose (N=30)	P – Value
Total IPSS, Median (IQR)	7 (4 , 12)	3.5 (2 , 6)	**0.007**
Uroflowmetry (ml/sec) (Mean ± SD)	18.93 ± 5.81	19.63 ± 5.72	0.64
PVR (ml), Median (IQR)	20 (0 , 40)	25 (0 , 40)	0.54
Retrograde Ejaculation	7/30 (23.3 %)	14/30 (46.7 %)	0.05
Dizziness	2/30 (6.7 %)	13/30 (43.3 %)	**0.01**
Nasal congestion	4/30 (13.3 %)	8/30 (26.7 %)	0.19
Orthostatic hypotension	6/30 (20 %)	11/30 (36.7 %)	0.15
Headache	2/30 (6.7 %)	7/30 (23.3 %)	0.07
Asthenia	1/30 (3.3 %)	5/30 (16.7 %)	0.08

DISCUSSION

Age-related increases in the prevalence of BPH-associated LUTS have been documented. By time, at 70 years of age, almost 80% of men have BPH-associated LUTS [5]. BPH patients have symptoms, including as incomplete urination, frequency, urgency, nocturia, and reduced urine flow, which can contribute to LUTS [6].

Medical therapy such as α1-Adrenoceptor antagonists, 5alpha-reductase inhibitors, or their combination, can be employed to treat BPH [4]. Nonetheless, the preferred medication for LUTS related to BPH (LUTS/BPH) is an alpha-blocker. Three subtypes of the alpha 1-adrenoceptor exist: alpha1a, alpha1b, and alpha1d. Of these, alpha1a is the most common in patients with BPH, accounting for up to 85% of cases. Alpha-blockers relieve LUTS/BPH by relaxing the smooth muscles of the prostate [4].

Song *et al.* [7], evaluated the effect of tamsulosin 0.2 mg on ejaculatory function in BPH/LUTS, they found improvement of IPSS mean from baseline 16.35 ± 7.14 to 13.71 ± 7.05 at 4-weeks and 12.09 ± 6.14 at 12 -weeks.

in our trial, the baseline total IPSS median (IQR) were 17 (13 , 25) and 15.5 (12 , 23) improved at 4-weeks to 11 (8 , 15) and 7 (4 , 12) in single and double dose respectively, with better improvement in double dose (p= 0.005). At 12-weeks follow up the total IPSS median (IQR) were 7 (4 , 12) and 3.5 (2 , 6) in single and double dose with P-value = 0.007. The better results of our trial might be attributed to the escalating dose effect with better effect with 0.8 mg than 0.4 mg than 0.2 mg tamsulosin.

In **Lepor *et al.*** [8] study, tamsulosin 0.8 mg, tamsulosin 0.4 mg, and placebo were given to individuals with BPH. The mean change in IPSS was considerably larger in both tamsulosin groups than in the placebo group (P < 0.001), with tamsulosin 0.8 mg outperforming tamsulosin 0.4 mg in voiding subscores (P = 0.007).

In study by **Yang *et al.* [9],** transferred male patients who were unsatisfied with 0.2 mg tamsulosin medication to 0.4 mg tamsulosin. Total IPSS scores improved statistically significantly from baseline (14.94 ± 7.41) to 12 weeks (7.36 ± 5.77) in participants who were moved from 0.2 to 0.4 mg tamsulosin (P<0.001).

Conversely, in the research done by **Narayan and Tewari [10],** there was no statistically significant difference in the mean change in IPSS from baseline to endpoint between tamsulosin 0.4 mg and tamsulosin 0.8 mg (-5.09 ± 0.41 and -5.76 ± 0.41 respectively). In addition, **Chapple *et al.*** [11] discovered no statistically significant difference in IPSS between tamsulosin 0.4 mg and tamsulosin 0.8 mg.

In our study, Q-max was improved in double dose tamsulosin 0.4 mg group than in single dose tamsulosin 0.4 mg group at 4 and 12-weeks follow-up, which was statistically insignificant. This is similar to **Lepor** [8] study, as there was no statistically significant difference in the mean change between tamsulosin 0.4 mg and 0.8 mg (1.75 ± 3.5 and 1.78 ± 3.3 ml/sec respectively). The same occurred in **Narayan and Tewari's** [10] trial, and the Q-max did not significantly change between 0.4 mg and 0.8 mg of tamsulosin. On the contrary, **Yang *et al.*** [9] found that in patients switched from 0.2 mg to 0.4 mg of tamsulosin, Q-max rose considerably from baseline (11.37 ± 6.04 ml/sec.) to week 12 (13.06 ± 6.18 ml/sec.) (P = 0.0037).

Kim *et al.* [12] showed that tamsulosin 0.4 mg significantly improved Q-max at 12 weeks (P < 0.001) when compared to tamsulosin 0.2 mg treatment. The mean change in Q-max for tamsulosin 0.2 mg was -0.25 ± 0.3 ml/sec., and for tamsulosin 0.4 mg, it was 3.0 ± 0.48 ml/sec (P < 0.001).

In our research, we discovered statistically insignificant difference in PVR in double dose tamsulosin 0.4 mg group than in single dose tamsulosin 0.4 mg group at 4 and 12-weeks follow up. This is similar to studies performed by **Yang *at al.*** [9] and **Kim *et al.*** [12].

In our study, we found that retrograde ejaculation, nasal congestion, orthostatic hypotension, headache and asthenia were more frequent in double dose tamsulosin group than single dose tamsulosin group, after one month and 3 months of treatment, which showed statistically insignificant difference. However, dizziness was more frequent in double dose tamsulosin 0.4 mg group than in single dose tamsulosin 0.4 mg group, which showed statistically significant difference. The occurrence of vertigo was similar for both the placebo (1.4%), and the 0.4 mg dosage (1.4%). But there was a more noticeable rise in the frequency of abnormal ejaculation from tamsulosin 0.4 mg (1.9%) to tamsulosin 0.8 mg (5.3%) [11]. Abnormal ejaculation was significantly frequent with tamsulosin 0.8 mg (18%) versus 0.4 mg (6%) with p<0.001 in the study done by **Lepor** [8]. However, there were insignificant difference in the other side effect between 0.4 and 0.8 mg tamsulosin doses [8].

Limitations: The current study was a short-term study and with small sample size.

CONCLUSION

Tamsulosin single and double doses had equal effects, safe, and well tolerated in the target BPH population. However, tamsulosin double doses was statistically superior to single dose in improving IPSS scoring. On the other hand, tamsulosin double doses had statistically significant adverse effect in the form of dizziness.

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- **Conflict of Interest:** Nil.

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