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PROSTATIC DISORDERS
ORIGINAL ARTICLE

Sildenafil citrate in combination with tamsulosin versus tamsulosin monotherapy for management of male lower urinary tract symptoms due to benign prostatic hyperplasia: A randomised, double-blind, placebo-controlled trial

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KEYWORDS

Tamsulosin;
Sildenafil;
Lower urinary tract symptoms (LUTS);
Benign prostatic hyperplasia (BPH)

ABBREVIATIONS

BMI, body mass index;
CONSORT, Consolidated Standards of Reporting Trials;
ED, erectile dysfunction;

Abstract ***Objective:*** To assess the additive effect of sildenafil citrate to tamsulosin in the treatment of lower urinary tract symptoms due to benign prostatic hyperplasia (LUTS/BPH) in men with or without erectile dysfunction (ED).

Patients and methods: In all, 150 men with untreated LUTS/BPH with or without ED were randomised to receive sildenafil 25 mg once daily (OD) or placebo OD (night time) combined with tamsulosin 0.4 mg OD (day time) for 6 months. Changes from pre-treatment scores in International Prostate Symptom Score (IPSS), IPSS-quality of life (QoL) score, maximum urinary flow rate (Q_{max}), and the five-item version of the International Index of Erectile Function questionnaire (IIEF-5) were assessed at 3 and 6 months. Safety profiles were assessed by physical examination and monitoring clinical adverse events.

Results: Group A comprised of men who received tamsulosin and sildenafil (75 men), whilst those in Group B received tamsulosin and placebo (75). The IPSS was significantly improved in Group A compared to Group B, at −29.3% vs −13.7% ($P = 0.039$) at 3 months and −37% vs −19.6% ($P = 0.043$) at 6 months

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after treatment. Q_{max} significantly improved in both groups compared with before treatment ($P < 0.001$). The IIEF-5 scores improved more in Group A than in Group B, at 58.7% vs 11.7% at 3 months and 62.4% vs 12.4% at 6 months after treatment (both $P < 0.001$).

Conclusion: Sildenafil citrate combined with tamsulosin improved LUTS, erectile function, and patient QoL more than tamsulosin monotherapy with the merit of a comparable safety profile in patients with LUTS/BPH.

IIEF-5, five-item version of the International Index of Erectile Function questionnaire;
NO, nitric oxide;
OD, once daily;
PDE5-I, phosphodiesterase type 5 inhibitor;
Q_{max}, maximum urinary flow rate;
QoL, quality of life;
RCT, randomised controlled trial;
SMD, standardised mean difference

Introduction

BPH is the most common and important pathology that contributes to male LUTS [1]. There is a direct relationship between LUTS and age, with an overall prevalence of >50% in men aged ⩾50 years [2,3]. The prevalence of erectile dysfunction (ED) is also similarly high and increases with age. About 35% of men aged 40–70 years have moderate to complete ED, which is strongly related to age and other co-morbidities such as cardiovascular disease, diabetes, and depression [4]. LUTS due to BPH (LUTS/BPH) and ED are common disorders among ageing men, with a striking relationship. In addition, both have a significant negative impact on quality of life (QoL) [5]. In their meta-analysis of 12 randomised controlled trials (RCTs), Gacci et al. [6] reported that the combination of phosphodiesterase type 5 inhibitors (PDE5-Is) and α_1-adrenergic receptor blockers significantly improved the IPSS [standardised mean difference (SMD) −1.8, 95% CI −3.7 to 0.0; $P = 0.05$] and International Erectile Function score (SMD +3.6, 95% CI +3.1 to +4.1; $P < 0.001$), as well as Q_{max} (SMD +1.5 mL/s, 95% CI +0.9 to +2.2; $P < 0.001$) when compared with the use of α_1-adrenergic receptor blockers alone.

Our aim in the present study was to assess the additive effect of sildenafil citrate to tamsulosin in the treatment of LUTS/BPH in men with or without ED in a prospective, randomised, placebo-controlled, double-blind study.

Patients and methods

Patient enrolment

This study was conducted between May 2013 and May 2014. Approval from our ethics committee was obtained and a written consent was signed by each patient before the study. In all, 150 patients who were diagnosed with LUTS/BPH were enrolled. The inclusion criteria were: (i) patients who were recently diagnosed LUTS/BPH without any history of medical or surgical intervention for BPH, (ii) no absolute indication for surgical intervention, (iii) patients with or without ED, (4) a PSA level of <4 ng/dL, and (v) a body mass index (BMI) of ⩽30 kg/m^2, as obesity is a risk factor for both ED and male LUTS. The exclusion criteria were: (i) patients with significant cardiovascular disease, neurological, and psychiatric disorders, (ii) history of hypersensitivity and contraindication to one of the study drugs, (iii) patients with confirmed prostatic malignancy or any other active urinary tract disease, (iv) participation in another clinical trial in the 3 months prior to the study.

Study design

This study was a prospective, two-armed, randomised, double-blind (was carried out by relevant outpatient clinic pharmacist who provided us with a sealed randomisation list that was unblinded at the end of follow-up), placebo-controlled (placebo prepared by the Pharmaceutics Department in a tablet formulation similar to the original drug but without any active ingredients), comparative study between tamsulosin 0.4 mg once daily (OD) at day time plus sildenafil 25 mg OD at night and tamsulosin 0.4 mg OD at day time plus placebo at night in the treatment of patients with LUTS/BPH. Patients who fulfilled the entry criteria at selection were randomised into the two groups. Patients were randomly assigned blinded medication (placebo or sildenafil, plus tamsulosin) using a computer generated pseudorandom code in a 1:1 ratio by the study centre with a fixed block size of four.

Main outcome measures

The primary endpoint was clinical efficacy assessments for LUTS/BPH, which were evaluated by the IPSS and QoL score. The secondary endpoints were maximum urinary flow rate (Q_{max}); erectile function evalu-

ated using the five-item version of the International Index of Erectile Function questionnaire (IIEF-5); safety profiles, which were assessed by physical examination (heart rate and blood pressure), and monitoring clinical adverse events i.e. tolerability. The results of the IPSS + QoL score, Q_{max} and IIEF-5 were used to evaluate related symptoms before treatment and at 3 and 6 months after treatment in both groups.

Statistical analysis

The sample size was calculated based on an observed difference of 3.2 points on average in the IPSS between the two treatment groups [7]. Considering the expected attrition rate to be 10%, therefore, a total sample size of 150 (75 patients in each group) was calculated to provide a power of 90% and a two-sided type I error of 0.05 (95% CI), with 1:1 allocation ratio between groups. G*Power V3.1.9 was used in the calculation [8] (University of Düsseldorf, Germany). Data are expressed as the mean (SD). The percentage change in the IPSS and IIEF-5 score was calculated by determining the mean IPSS and IIEF-5 score (before, and at 3 and 6 months after treatment) then: mean before treatment – mean at 3/6 months after treatment/mean before treatment × 100. Statistical analyses were carried out using the chi-square test, analysis of covariance, and independent and paired *t*-tests. All analyses were two-tailed, with a significance level of 5%. Analyses were performed using the Statistical Package for the Social Sciences (SPSS®) 20.0 software package (SPSS Inc., Chicago, IL, USA).

Results

Study population

A Consolidated Standards of Reporting Trials (CONSORT) flow chart is shown in Fig. 1. In all, 150 patients were randomised to receive tamsulosin + sildenafil (75 men) referred to as Group A or tamsulosin + placebo (75) referred to as Group B. Among the 150 men enrolled, 142 (94.7%) completed the 3-month follow-up evaluation (Group A: 70/75; Group B: 72/75), and 131 patients (87.3%) finished the 6-month follow-up evaluation (Group A: 63/75; Group B: 68/75). All the

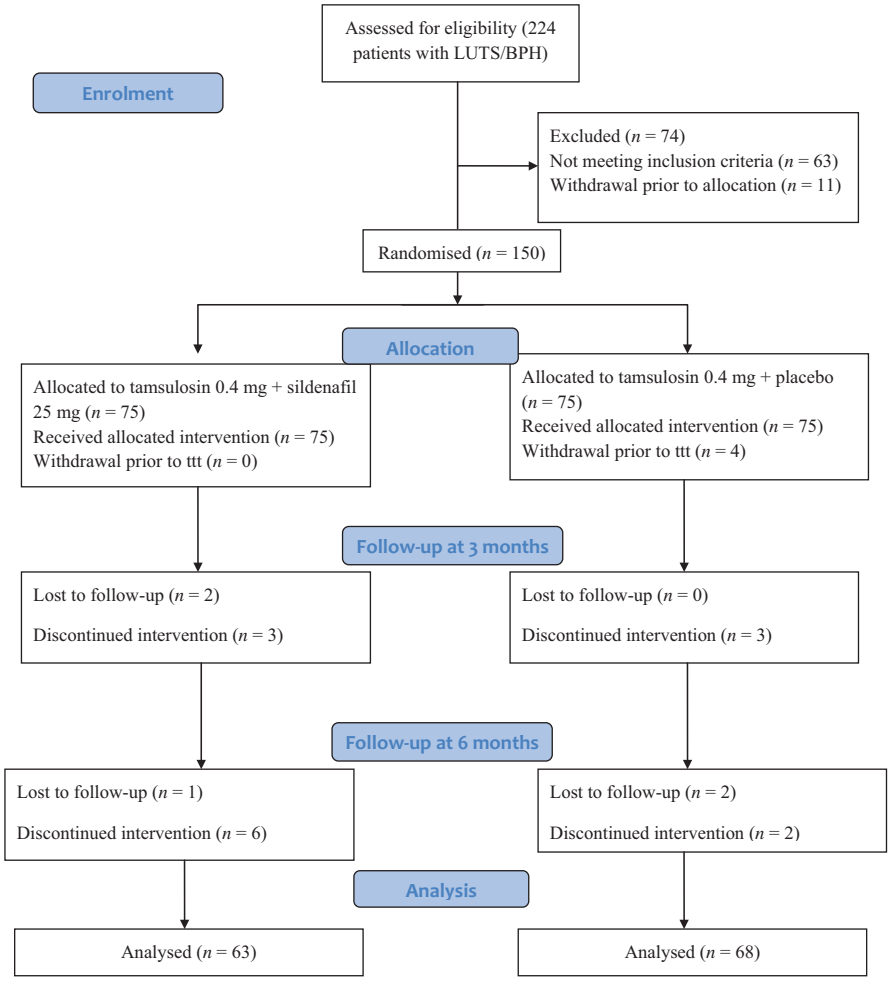


Fig. 1 CONSORT diagram of patient disposition. ttt, time to treat.

Table 1 Patients' baseline characteristics.

Variable	Group A	Group B	*P*
Mean (SD)			
Age, years	65.8 (4.5)	66.3 (4.5)	0.497
IPSS	20.8 (5.3)	21.9 (4.8)	0.185
Q_{max}, mL/s	11 (3)	10.3 (2.8)	0.142
PVR, mL	47.8 (26.9)	50.2 (26.8)	0.585
IIEF-5 score	14.1 (4.1)	13.7 (4.4)	0.566
BMI, kg/m^2	23.2 (3.6)	24.1 (3.4)	0.118

patients' baseline characteristics including: age, BMI, IPSS, Q_{max}, post-void residual urine volume (PVR), and IIEF-5 were not significantly different between the groups and are given in Table 1.

Efficacy on IPSS, QoL and Q_{max}

IPSS changes (Fig. 2)

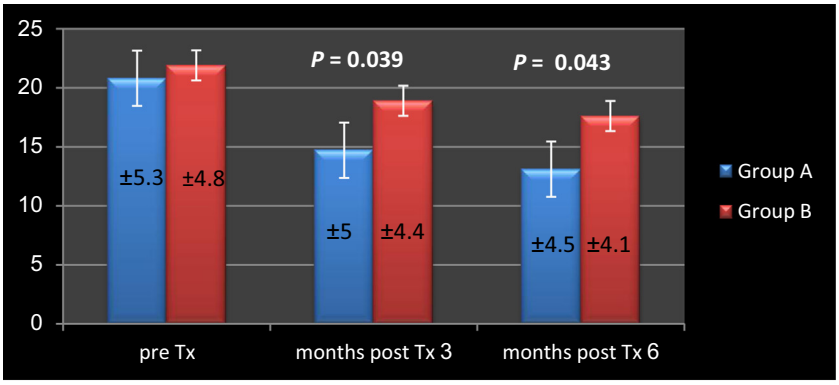
At the 3-month follow-up, the mean (SD) IPSS was 14.7 (5) in Group A and 18.9 (4.4) in Group B. Thus, the IPSSs were significantly improved ($P < 0.001$) in both groups, but this improvement was more marked in Group A (−29.3%) than in Group B (−13.7%).

At the 6-month follow-up, the mean (SD) IPSS was 13.1 (4.5) in Group A and 17.6 (4.1) in Group B. Thus, the IPSSs were still significantly improved ($P < 0.001$) in both groups, but this improvement was again more marked in Group A (−37%) than in Group B (−19.6%).

So, this means that the IPSSs were significantly improved in Group A compared to Group B ($P = 0.039$ and 0.043 at the 3- and 6-month follow-up, respectively). The 6-month scores were not significantly improved compared with the 3-month scores in either of the groups ($P = 0.056$ and 0.073 for Groups A and B, respectively).

QoL score changes

The QoL score before treatment showed no significant difference between the two treatments. In Group A, the 3- and 6-month follow-up scores were greatly reduced compared to the score before treatment (both $P < 0.001$). In Group B there was also a significant difference in the 3- and 6-month follow-up scores compared with the score before treatment (both $P < 0.05$). The patients' QoL was improved, with QoL scores being significantly decreased in Group A more so than in Group B at both the 3- and 6-month follow-ups.



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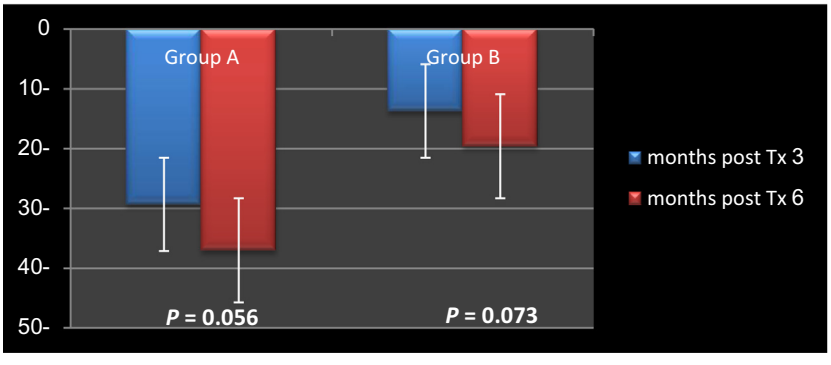

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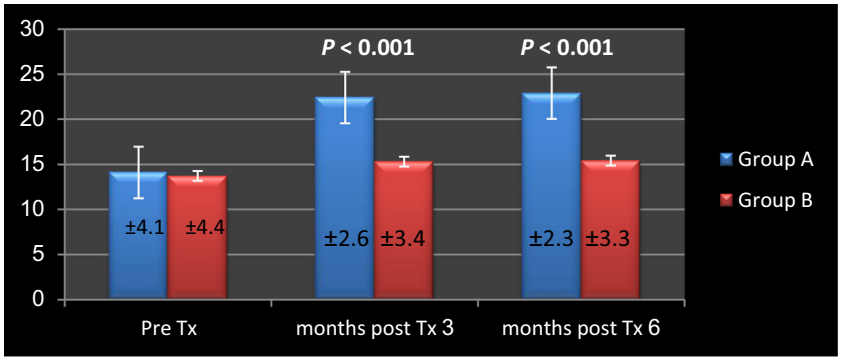
Fig. 2 Changes in the mean total IPSS (A) and percentage changes in mean IPSS (B) before and after treatment in the two groups. Tx, treatment.



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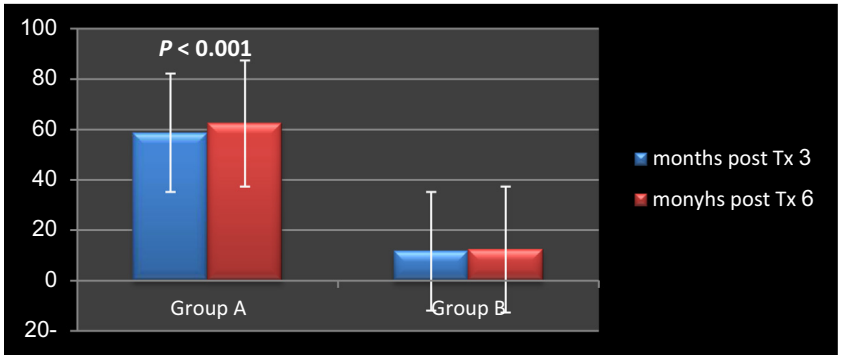

B

Fig. 3 Changes in the mean total IIEF-5scores (A) and percentage changes in mean IIEF-5 scores (B) before and after treatment in the two groups. Tx, treatment.

Q_{max} changes

At the 3-month follow-up, the mean (SD) Q_{max} was 14.3 (2.9) mL/s in Group A and 12.4 (2.4) mL/s in Group B. At the 6-month follow-up, the mean (SD) Q_{max} was 14.9 (3) mL/s in Group A and 12.9 (2.4) mL/sin Group B. The Q_{max} was significantly improved ($P < 0.001$) at the 3- and 6-month follow-ups in both groups, but this improvement was more marked in Group A (30% and 35.5% at the 3- and 6-month follow-up, respectively) than in Group B (20.4% and 25.2% at the 3- and 6-month follow-up, respectively). There was no significant difference between both groups for Q_{max} score improvements ($P = 0.261$ and $P = 0.274$ at the 3- and 6-month follow-up, respectively). The 6-month scores were not significantly better than the 3-month scores in either group ($P = 0.243$ and $P = 0.220$ for Groups A and B, respectively).

Efficacy on erectile function

IIEF-5 score changes (Fig. 3)

At the 3-month follow-up, the mean (SD) IIEF-5 score was 22.4 (2.6) in Group A and 15.3 (3.4) in Group B. At the 6-month follow-up, the mean (SD) IIEF-5 score was 22.9 (2.3) in Group A and 15.4 (3.3) in Group B. The IIEF-5 score was highly significantly improved ($P < 0.001$ at both the 3- and 6-month OD follow-ups) in Group A, whilst it was also significantly improved in Group B ($P = 0.017$ and $P = 0.012$ at the 3- and 6-month follow-ups, respectively). This improvement was more marked in Group A (58.7% and 62.4% at the 3- and 6-month follow-up, respectively) than in Group B (11.7% and 12.4% at the 3- and 6-month follow-ups, respectively). The IIEF-5 scores were highly significantly improved in Group A vs Group B ($P < 0.001$ at both the 3- and 6-month follow-ups).

Safety

Of the 150 patients that took the study drugs for up to 6 months, 19 (12.7%) discontinued treatment because they were lost to follow-up (five men) or had adverse events (14). Nine patients in Group A had 11 adverse events (flushing, four; headache, two; dyspepsia, one; dizziness, two; gastric upset, two), and five patients in Group B had dizziness. There were no serious adverse events reported during the study and there was also no evidence of either significant hypotension or syncope during the 6-month treatment period.

Discussion

In ageing males, BPH and ED are common diseases. There is a high probability of BPH occurring concurrently with ED [9,10]. PDE5-Is are first-line medications for ED, and α_1-adrenergic receptor blockers are highly effective in the management of LUTS/BPH. Close observation of both pathological conditions and medication-based treatments have been the first-line therapy for LUTS/BPH [11]. The pathophysiology of male LUTS is highly complex, multifactorial and still not completely understood [12]. The relationship between male LUTS/BPH and ED is supported by many theories: (i) autonomic hyperactivity and metabolic syndrome hypothesis, (ii) impaired nitric oxide/-cyclic guanine monophosphate (NO/cGMP) signalling pathway in the prostate and penis, (iii) increased rho-kinase activation/endothelin pathway, (iv) pelvic atherosclerosis and ischaemia [13,14]. Notably, PDE5-Is have received much attention in the treatment of LUTS/BPH. This could be due to: (i) selective distribution of PDE5 that is mostly expressed and biologically active in the muscular compartment with the following rank order of activity: bladder neck > prostatic urethra > prostate [15], (ii) PDE5-Is increase NO levels in smooth muscle mediating its relaxation in the corpus cavernosum and bladder, thus facilitating penile erection plus bladder neck and prostate relaxation [16], (iii) PDE5-Is ameliorate the dynamic component (bladder dysfunction and urethral contractions) of male LUTS as they induce inhibition of the rho A/rho-kinase contractile mechanism in the bladder [17], (iv) PDE5-Is can restore morphological and functional changes in the bladder and prostate induced by chronic pelvic ischaemia, as PDE5 is highly expressed in the pelvic vasculature [18,19]. These findings suggest that the concurrent administration of an α_1-adrenergic receptor blocker and a PDE-5I to patients with LUTS/BPH with or without ED may potentiate, or improve to some extent, the beneficial effects of each drug administered alone.

In the Kaplan et al. [20] study, improvements in the IPSS were significant for all three treatments but were the greatest for the combined therapy. They reported that after treatment with alfuzosin monotherapy (10 mg OD), sildenafil monotherapy (25 mg OD) or a combination of the two drugs for 12 weeks in patients with previously untreated LUTS and ED, that Q_{max}, PVR and storage symptoms were significantly improved with alfuzosin alone and with the combined treatment. For IIEF scores, improvements were significant for sildenafil alone but greater with the combined treatment and was not significant for alfuzosin alone. Likewise, increases in the frequency of penetration and maintained erections were greater in the combined therapy group than in the alfuzosin or sildenafil alone groups [20]. These investigations showed that the combined use of a PDE5-I and α_1-adrenergic receptor blocker might be more effective than monotherapy with either agent [7].

Liu et al. [21] in their review and meta-analysis of five RCTs assessing the use of PDE5-Is alone vs placebo in men with LUTS/BPH concluded that PDE5-Is are effective and safe, and should be used as a first-line for treating men with coincidental LUTS/ED. Laydner et al. [22] reported a significant improvement in both urinary and erectile function, without a change in Q_{max}, in a systematic review without meta-analysis, including four trials on PDE5-Is alone in men with LUTS/BPH. Finally, Martinez-Salamanca et al. [23], analysed the role of combined therapy with PDE5-Is and α_1-adrenergic receptor blockers, reporting a significant improvement in urinary symptoms with no evidence of an effect on urodynamic parameters, in a non-systematic descriptive review [23].

In our present study, IPSSs were significantly improved in the two groups, but this improvement was more marked with combined therapy than for α_1-adrenergic receptor blocker alone, and the 6-month scores were insignificantly improved compared to the 3-month scores in the two groups. These results are consistent with those of Kaplan et al. [20] and Zhe et al. [7].

In the present study, Q_{max} was significantly improved at the 3- and 6-month follow-ups in both groups, but this improvement was more marked with combined therapy (Group A) than for α_1-adrenergic receptor blocker alone (Group B). Q_{max} was improved in both treatment groups and was not significantly different, and the 6-month scores were insignificantly improved compared to 3-month scores in both groups.

One of the most remarkable outcomes of the Gacciet al. [6] meta-analysis of 12 RCTs was that the combination of PDE5-Is and α_1-adrenergic receptor blockers could significantly improve Q_{max} as compared with α_1-adrenergic receptor blockers alone. Improvement of Q_{max} above 1 mL/s in combined therapy, as compared with α_1-adrenergic receptor alone, was reported by all authors in the previous study [6].

Limitations of the present study are the relatively small population size, short follow-up duration (6 months) and thus no long-term efficacy endpoints, and the dose of sildenafil citrate used (25 mg OD) is experimental. Thus further prospective studies with longer durations of follow-up are recommended.

Conclusion

Sildenafil citrate in combination with tamsulosin improved LUTS, erectile function, and patient QoL more than tamsulosin monotherapy with the merit of a comparable safety profile in patients with LUTS/BPH.

Financial disclosure

None.

Conflict of interest

None.

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