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ORIGINAL ARTICLE

Efficacy of Combination Therapy with Alpha-1 Blocker and 5-Phosphodiesterase Inhibitor in Patients with Benign Prostatic Hyperplasia Associated Lower Urinary Tract Symptoms (Luts)

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ABSTRACT

Objective: To evaluate the effectiveness of Alpha-1 Blocker in combination with Phosphodiesterase-5 Inhibitor versus Alpha-1 Blocker alone for the management of lower urinary tract symptoms in patients with Benign Prostatic Hyperplasia.

Material and Methods: A quasi-experimental study was undertaken at the Urology Department, Liaquat National Hospital, Karachi between May 2018 to November 2019. About sixty patients with benign prostatic hyperplasia and correlated lower urinary tract symptoms were included. The participants were distributed into two groups (Group A was prescribed combined therapy while Group B was prescribed monotherapy). The therapy was considered as successful if there was an improvement in the International Prostate symptom scoring of more than 3 points from the baseline to 12 weeks. Statistical analysis was performed using Excel sheet and SPSS v. 26.

Results: In group 1 (combined therapy), 22 (73.3%) (22/30) of the patients reported a significant reduction in International Prostate symptom scores after taking Tamsulosin with Sildenafil as compared to Group 2, where only 13 (43.3%) patients who were treated with Tamsulosin only reported improvement in the International Prostatic symptom scoring at 12 weeks of treatment.

Conclusion: The current study indicates that Tamsulosin in combination with Sildenafil is more effective in relieving the lower tract urinary symptoms in patients with benign prostate hyperplasia as compared to monotherapy.

Keywords: Benign prostatic hyperplasia, bladder outflow obstruction, alpha-blocker, lower urinary tract symptoms, tamsulosin, phosphodiesterase-5 inhibitor, sildenafil

INTRODUCTION

Benign prostatic hyperplasia (BPH) is the overgrowth of prostatic gland and stromal cells, resulting in the hyperplasia of the gland subsequently causing lower urinary tract symptoms (LUTS) and retention of urine owing to the obstruction. [1] It is a common phenomenon in elderly men. As per an estimation, four fifths of the men above 80 years show histopathological indication of the disease. Of these, almost 80% experience lower urinary tract symptoms. [2] According to estimates, about one-fourth of these patients would require intervention to relieve the symptoms associated with BPH. [3] In Pakistan, about half of the men aged above 65 years are at risk of developing LUTS secondary to BPH. [4]

There is no definitive time to treat the patients with BPH. The decision to treat patients is dependent upon the weight of the prostate, symptom duration, access to adequate surgical equipment, experienced surgeon, and the wish of the patient. [5] LUTS secondary to BPH present as symptoms of storage and voiding, resulting from the bladder outflow obstruction (BOO). The symptoms are usually treated with alpha blockers as the first line treatment. [6] Tamsulosin, a selective alpha-1 adrenoceptor blocker is associated with acute and long lasting relief. [7] Phosphodiesterase-5 inhibitors which are commonly used to treat penile dysfunction act by increasing cyclic guanosine monophosphate (cGMP), this potentiates Nitric oxide-mediated smooth muscle relaxation, resulting in penile erection and relaxation of bladder neck and prostate.

Recent evidence suggests that PDE-5 inhibitors not only affects erectile dysfunction but also improves LUTS. [8-10] Therefore based on the literature review it has been suggested that the adjunctive intake of an alpha-1 inhibitor and a PDE-5 inhibitor for the management of BPH associated LUTS may provide a better outcome as compared to monotherapy with alpha 1 blocker.

Our current study sought to assess the efficacy of combined therapy (Tamsulosin and Sildenafil) versus monotherapy (Tamsulosin) in our population so that if it is found to be efficacious then policy could be made to advocate and standardize this mode of treatment.

METHODS AND MATERIALS

A quasi-experimental study was performed at the Urology Department, Liaquat National Hospital, Karachi between May 2018 to November 2019. Ethical approval was obtained from the ethical committee of LNH prior to the study. A non-probability convenience sampling technique was used to conduct participants in the study. Sample size was calculated via OPEN EPI, by keeping the frequency of

group 1 (p1) as 80.9% and group 2 (55.5%), a confidence interval of 95%. A sample size of 60 (30 in each group) was obtained.

All men ≥ 40 years of age, suspected of having Benign prostatic hyperplasia on clinical findings of enlarged prostate on Digital Rectal Examination (DRE), confirmed on ultrasound findings of ≥ 20 gm prostate with Lower urinary tract symptoms for equal to or greater than six months with a score of 8 or higher were eligible to enroll in the study. Patients with clinically substantial bladder outlet obstruction, serum PSA levels > 4 ng/ml with risk of prostate cancer, with a history of prostatic surgery or radiotherapy, or acute urinary retention in need of a catheter, or active urinary tract infection or history of prostatitis were excluded from the study. Patients who had a history of prior use of alpha reductase inhibitor, alpha blocker or PDE5 inhibitor were also not included.

The lower urinary tract symptoms (LUTS) were defined as daytime frequency (>8 micturition/day), urgency (the sudden, almost uncontrollable need to urinate), urge incontinence (urinary incontinence preceded by a sudden, uncontrollable impulse to void), nocturia (>2 micturition at night time), hesitancy (difficulty or delay in beginning the flow of urine), poor or intermittent flow, straining (need to push or strain to begin urination) and sense of incomplete voiding. Significant Improvement in IPSS was defined as reduction in International Prostate symptom scoring of more than three points from one week to 12 weeks of treatment would be labeled as significant improvement in IPSS.

Patients were evaluated on the basis of IPSS and Digital rectal exam (DRE) assessment by the senior resident with postgraduate training of more than 3 years. The prostate size evaluation was done on ultrasonography. A total of sixty individuals who fulfilled the eligibility prerequisites were inducted. All participants were distributed into two treatment groups: Group A patients were given a combination of alpha-1 blocker (Tamsulosin 0.4 mg HS) and PDE-5 inhibitor (Sildenafil 25 mg OD), while in the control Group B, 30 patients were given alpha-1 blocker (Tamsulosin 0.4 mg HS) alone. Informed verbal and written consents were obtained from all participants.

Following baseline investigations were done for e.g., Blood Urea and Creatinine level, Urine D/R and C/S, Serum PSA level, UFM and Ultrasound Bladder + Prostate + post void. Baseline IPSS was recorded by a senior resident in OPD before starting the study.

All patients were reassessed at the end of 12 weeks by recording IPSS. During this period, patients were advised to follow in OPD in case of any adverse effects. Final outcome was measured by the presence of significant improvement in IPSS (i.e. decrease in symptom scoring of > 3 points from the baseline).

All data was recorded in a predesigned pro forma. All information about the patient's age, duration of symptoms, prostate size, clinical group, initial and final IPSS and final outcome on the basis of improvement in IPSS were recorded. SPSS (statistical package for social sciences) version 26 and Microsoft Excel was used to run the statistical analysis on the data. For continuous parameters, mean and standard deviation were determined. Frequency and percentage were determined for qualitative variables i.e., significant improvement in IPSS after treatment. Chi-square test and independent t tests were applied to find significant alterations between the two groups. A p-value of less than 0.05 was considered as statistically significant.

RESULTS

The average age ± SD of the participants was noted to be 60.5 ± 6.75 years (43-74 years). The mean duration of symptoms was 12.18 ± 6.08 months. Most of the patients, 34 (56.7%), had LUTS for 6-9 months duration, while only 5 patients (8.3%) had LUTS for 13-15 months of duration. See table 1 for group wise comparison.

Table 1: Characteristics of Study Participants (n=60)

	Group A	Group B	p-value
Age (years)	60.90 ± 6.97	60.17 ± 6.62	0.472
Body weight (kg)	64.2 ± 7.8	65.3 ± 8.6	0.370
Mean size prostate (g)	56.36 ±13.30	55.03 ±17.54	0.567
Mean duration of Symptoms	11.28 ± 3.08	12.46 ± 4.12	0.541
Qmax (ml/s)	14.4 ± 4.1	13.6 ± 2.8	0.128
RU (ml)	14.0 ± 12.9	17.1 ± 14.6	0.134

The mean size of the prostate was 55 ±18.07 grams. The distribution of patients according to the size of the prostate is given in figure 1. The overall baseline IPSS was 18.97 ±3.54. The mean difference in IPSS before and after treatment between the groups is shown in table 2.

Table 2: Change in International Prostate Symptom Score from Baseline to 12th week of Treatment

	Group A	Group B	p-value
Final IPSS	14.70 ± 3.38	15.97 ± 4.94	<0.0001
Baseline IPSS	18.90 ± 3.25	19.03 ± 3.87	

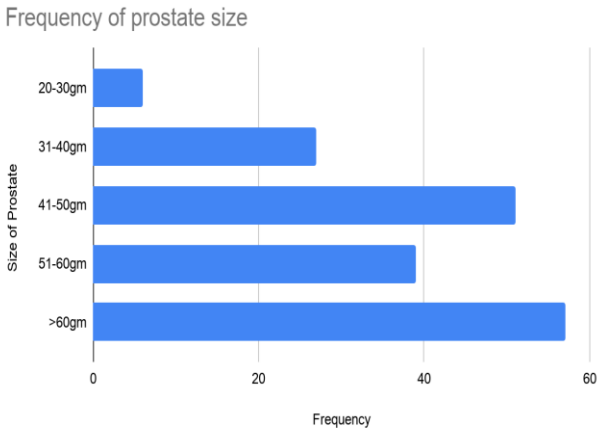

Figure 1: Distribution of patients according to the Prostate Size

The final average international prostate symptom score was 14.7 ± 3.38 in group A and 15.9 ± 4.93 in group B. The change in IPSS from baseline to 12th week of treatment was significantly improved among the group (p<0.0001). See table 2.

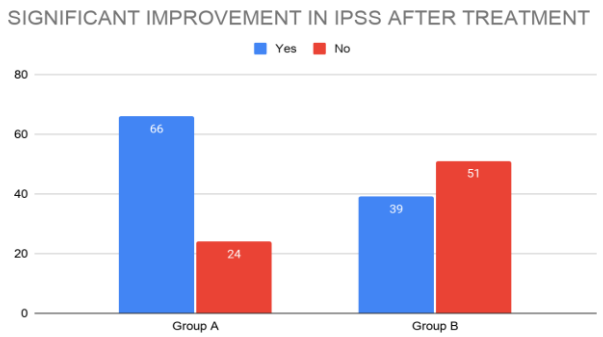

Figure 2: Efficacy of Combined therapy (Tamsulosin and Sildenafil) versus Monotherapy (Tamsulosin) as depicted by improvement in international prostate symptom score (IPSS)

In Group A (Tamsulosin + Sildenafil) 22 patients 73.3% had significant improvement while in Group B (Tamsulosin) only 13 patients 43.3% had significant improvement (p=0.035) See figure 2. Improvement in the IPSS did not significantly differ post stratification of age, duration of symptoms, and prostate size among the groups.

DISCUSSION

The current study indicates that the combination therapy with alpha 1 blocker and PDE 5 inhibitors is more efficacious in relieving the LUTS associated with BPH as compared to monotherapy with alpha 1 inhibitor. Our study is in accordance with the previous literature. Bechara et al. in his study demonstrated the efficacy of tamsulosin as monotherapy versus tamsulosin as an adjunct to tadalafil for the treatment of LUTS in patients with BPH. It was concluded that IPSS and IPSS-QOL were significantly improved in patients who were administered the combined therapy ($P < 0.001$). [11]

Similarly, in a randomized controlled trial, Liguori et al., reported the efficacy and safety of a combined therapy with tadalafil and alfuzosin in patients with erectile dysfunction and LUTS. It was found that the combined therapy had the greatest improvement in erectile function and LUTS (37.6%) as compared to monotherapy with alfuzosin alone (15%) or tadalafil alone (36.3%). Similarly, significant improvement in IPSS was observed in combination group (41.6%) as compared to Alfuzosin (27.2%) or Tadalafil (8.4%).[12]

Our study has shown an efficacy of 73.3% in patients who were administered both drugs in combination versus 43.3% in patients who were administered Tamsulosin only. The difference was statistically significant (p=0.035). Our study replicated the findings of the study revealed by Kaplan et al. who demonstrated that a combination of alfuzosin and sildenafil (24.1%) is more effective in improving the symptoms of LUTS and penile dysfunction as compared to monotherapy with either alfuzosin (15.6%) or sildenafil (11.8%) with no additional complication rate ($p<0.03$). [13] Similar conclusions were drawn by Porst et al., in his multicentre randomized controlled trial with 581 men with BPH associated with ED and LUTS. [14] Stief et al., evaluated the efficacy of oral vardenafil for the treatment of BPH associated with LUTS. He concluded that vardenafil administered twice daily significantly improved the IPSS as compared to the placebo group (p=0.0013). However, no drug combinations were assessed in the study. [15]

A double-blinded study was conducted at 21 centres by McVary et al., to assess the potential of Tadalafil in relieving the LUTS associated with BPH. Tadalafil significantly improved the mean IPSS at 6 weeks (5 mg tadalafil -2.8 vs placebo -1.2) and at 12 weeks (5/20 mg tadalafil -3.8 vs placebo -1.7). The authors reported increased erection, epigastric or back pain, headache, and other upper respiratory symptoms as most common adverse effects. [16] No notable side effects were reported in the current study.

In conclusion, our study demonstrates that in patients with LUTS secondary to BPH, a combination therapy of Tamsulosin (0.4 mg OD) plus Sildenafil (25 mg HS) significantly improves IPSS as compared to monotherapy with Tamsulosin (p=0.035). The results of our study are found to be consistent with those previously reported with other alpha-1 blockers along with 5 phosphodiesterase inhibitors in patients with BPH associated LUTS.

There are some limitations to this study. One of them is that it was conducted in only one centre and was not a multicentre study. Another limitation of my study was that only patients belonging to a single ethnic group were included so multi-ethnicity was not done.

CONCLUSION

The current study indicates that combination therapy with Tamsulosin 0.4 mg OD and Sildenafil 25 mg OD for 12 weeks was well tolerated and more effective than alpha-1 blocker monotherapy (Tamsulosin 0.4 mg OD) in improving BPH associated LUTS. Large-scale, randomized placebo-controlled trials with increased sample size are required to evaluate the long-term efficacy and safety profiles of the alpha 1 blocker and PDE-5 inhibitors in patients with BPH associated LUTS and erectile dysfunction.

Conflict of Interest: None declared

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