ROLE OF MONOTHERAPY ALPHA BLOCKERS VERSUS COMBINATION ALPHA BLOCKERS AND ANTICHOLINERGICS IN THE MANAGEMENT OF LOWER URINARY TRACT SYMPTOMS/BENIGN PROSTATIC HYPERPLASIA

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ABSTRACT

Objective: To compare the mean international prostate symptom score between monotherapy (alpha blockers) versus combination therapy (alpha blockers plus cholinergic antagonist) in the management of lower urinary tract symptoms due to benign prostatic hyperplasia.

Study Design: Quasi experimental study.

Place and Duration of Study: Armed Forces Institute of Urology Rawalpindi, from Sep 2018 to Feb 2019.

Methodology: One hundred and sixty male patients, who presented with lower urinary tract symptoms secondary to benign prostatic hyperplasia with prostate size up to 70 grams were enrolled. Patients in group I received Tamsulosin 0.4 mg OD + placebo while those in group II received Tamsulosin 0.4 mg OD + Solifenacin 5mg OD for 4 weeks. Baseline and Post 04weeks' treatment international prostate symptom score was recorded and analyzed.

Results: Mean age of presentation in group I was 57.44 ± 8.74 years while in group II, it was 56.43 ± 8.98 (p=0.47). Baseline characteristics were similar in both groups. Baseline international prostate symptom score was 19.11 ± 7.93 in group I and 20.01 ± 8.18 in group II respectively (p=0.49). In group I, mean international prostate symptom score at 4 weeks was 16.71 ± 7.86 and in group II, it was 12.48 ± 8.04 (p-value <0.001), implying that international prostate symptom score was significantly lower in group II in comparison with group I at 4 weeks.

Conclusion: Statistical significant difference of combination therapy of α-blocker and antimuscarinic compared with α-blocker monotherapy was observed in the present study.

Keywords: Cholinergic antagonists, Lower urinary tract symptoms, Prostatic hyperplasia, Solifenacin, Tamsulosin.

INTRODUCTION

Benign prostatic hyperplasia (BPH), one of the most common urinary disorders affecting elderly, is a recognized major cause of lower urinary tract symptoms (LUTS) having considerable negative impact on patients' health-related quality of life (QoL) (especially sleep, emotional wellbeing and routine daily activities)[1]. BPH currently affects 60% of men over 60 years of age and 90% of men in their 8th decade and approximately, in 2018, 1 billion new BPH cases were diagnosed worldwide[2]. The epidemiology of LUTS in today's ageing population, which is expected to grow exponentially over the next few decades due to increasing life expectancy, will pose major financial threat to already over-whelmed healthcare systems across the globe. The pathogenesis of BPH, primarily a non-malignant disease of the stroma and epithelial tissues, remains incompletely understood hovering around multiple factors, essential being advancing age and androgen-dependent prostate being exposed to sex hormones[3].

BPH-LUTS constellation encompasses voiding symptoms (intermittency, slow stream and hesitancy), storage symptoms (urgency, frequency, nocturia) and/or post-micturition symptoms (post-micturition dribbling, incomplete bladder emptying). Knutson *et al* found that 50% of patients with BPH had overactive bladder (OAB), which may be the principal or major contributory cause of LUTS[4]. Storage symptoms of OAB espe-

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cially nocturia, the most troublesome/bothersome LUTS, is highly prevalent coexisting in up to 42% of men aged ≥75 years leading to higher rate of depression and sleep disturbances. Because of the similarities and the overlap in symptoms of BPH and OAB, it can be difficult to separate the two conditions clinically[5].

Conventional options available in urological armamentaria to manage BPH-LUTS are watchful waiting, lifestyle modification, pharmacological therapy and surgery. Medical intervention, a highly efficacious modality, revolves around α-blockers, antimuscarinics and 5α-reductase inhibitors (5-ARIs), used alone or in combination. However, α-blocker monotherapy, the most frequently prescribed medication for majority of men with moderate-to-severe LUTS associated with BPH; didn't have any impact on nocturia[6]. The storage component is commonly undertreated and antimuscarinics are infrequently prescribed (<25% reported to receive an anti-muscarinic) due to a widely held, yet unverified, fear of post-void residual (PVR) increase, or, worse, acute urinary retention (AUR)[7].

Tamsulosin, a selective inhibitor of a1A/1D-adrenoceptors expressed amongst smooth muscles of ureter, trigone, prostate and bladder neck, relaxes these smooth muscles leading to reduced bladder outlet resistance and voiding pressure thus effectively decreasing incidence of dysuria, frequency, and pain compared to placebo[8]. Solifenacin inhibits acetylcholine binding on all five subtypes of G-protein-coupled cholinergic reporters, M2/3 being most frequently found detrusor smooth muscle, interstitial and nerve cells of bladder, effectively reducing spontaneous myocyte activity leading to decreased frequency as well as intensity of bladder contractions. The international prostate symptom score (IPSS) is a self-administered, reproducible and validated psychometric tool allowing objective quantification of disease severity once diagnosed and determine response to therapy[9].

In recent years, several randomized, double-blinded trials have demonstrated that combination therapy is more effective and safe particularly tackling most bothersome nocturia when compared with monotherapy[10,11]. Safety profile studies of anticholinergics in patients at risk for AUR have clearly shown that the incidence of urinary retention is very rare[12]. There was limited data of well deigned local study leading to weak endorsement of use of potentially-effective anticholinergics in clinical practice. Therefore, we aimed to further analyze clinical significance of combination of tamsulosin and solifenacin in reducing LUTS associated with BPH in our target population.

METHODOLOGY

Current study was conducted at Armed Forces Institute of Urology, Rawalpindi over six months from September 2018 to February 2019. The study protocol was approved by the hospital ethical review Committee (Certificate no Uro-01/ERC-104585/TRG/19). Non probability consecutive sampling technique utilized at outpatient department to enroll 160 patients (WHO calculator, confidence interval 95%, power of test 80%, mean IPSS population I 7.4 & II 9.713) after satisfying inclusion criteria (age 40-70 years, LUTS secondary to bladder outlet obstruction with prostate size up to 70 grams, maximum urinary flow rate of ≤15 ml/sec, nocturia (≥1 void per night) & moderate to severe IPSS score. Patients having neurogenic bladder, uncontrolled hypertension, elevated prostate specific antigen, anticholinergics or α-blockers use in past, urethral stricture, PVR >150ml, congestive cardiac failure or history of prostate surgery were excluded. Randomization into two groups (80 each) was done by computer generated random number table and written informed consent obtained. Both investigators and patients were blinded to the randomization scheme andmedications. Sequentially numbered containers having Tamsulosin + placebo or solifenacin + Tamsulosin were administered by duty nurse knowing allocation sequence and patient grouping.

Patients in group I (alpha blocker group) received Tab. Tamsulosin (0.4 mg) OD and

placebo while patients in group II (Combination group) received Tab. Solifenacin (5mg) OD plus Tab. Tamsulosin (0.4 mg) OD for 4 weeks. IPSS was recorded at day one and after 4 weeks of treatment on a pre-designed proforma by investigators involved in the study.

Statistical analysis was done using SPSS version 24. Descriptive statistics were used to calculate means ± standard deviation for quantitative variables. Frequencies with percentage were calculated for qualitative variables. Effect modifiers like age, size of prostate, flow rate, nocturia were controlled by stratification and t-test applied post stratification. A *p*-value ≤0.05 was considered significant.

RESULTS

A total of one hundred and sixty male were enrolled and randomly allocated. Baseline characteristics were similar in both groups. Both groups were comparable in terms of BMI, Comorbid, prostate size, urine flow rate and nocturia. Mean age of presentation in group I was 57.44 ± 8.74 and 56.43 ± 8.98 years in group II respectively (*p*=0.47) (table-I).

Table-I: Demographic variables of the patients (n=160).

Demographic variable	Group I (n=80) (Tamsulosin)	Group II(n=80) (Solifenacin + Tamsulosin)	*p*-value
Age (years) (Mean ± SD)	57.44 ± 8.74	56.43 ± 8.98	0.47
Age Groups			
40-55 Years	27 (33.75%)	33 (41.25%)	0.327
56-70 Years	53 (66.25%)	47 (58.75%)	
Body Mass Index (BMI)	31.54 ± 3.92	32.38 ± 3.63	0.163
Comorbidities			
Hypertension	48 (60%)	45 (56.2%)	0.63
Diabetes	19 (23.8%)	23 (28.8%)	0.47
Coronary artery disease	24 (30%)	29 (36.3%)	0.40
COPD	08 (10%)	07 (8.8%)	0.79
Charlson Comorbidity Index			
Mild CCI 1-2	27 (33.8%)	23 (28.8%)	
Moderate CCI 3-4	48 (60%)	50 (62.5%)	0.71
Severe CCI >5	05 (6.2%)	07 (8.7%)	
Prostate Size (Gram) (Mean ± SD)	48.29 ± 10.14	49.29 ± 10.96	0.55
Stratified Prostate Size			
≤50 GRAMS	59 (73.75%)	53 (66.25%)	0.30
≥51-70 GRAMS	21 (26.25%)	27 (33.75%)	
Urinary flow rate (ml) (Mean ± SD)	11.36 ± 2.94	10.68 ± 2.70	0.13
Stratified Flow Rate			
13-15 ml/sec	39 (48.8%)	27 (33.8%)	.054
<13 ml/sec	41 (51.3%)	53 (66.3%)	
Nocturia (Voids/Night) (Mean ± SD)	3.84 ± 1.55	3.95 ± 1.48	0.64
Stratified Nocturia			
2-3 VOIDS/NIGHT	38 (47.5%)	32 (40.0%)	0.34
>3 VOIDS/NIGHT	42 (52.5%)	48 (60.0%)	
Counselling of the Patients			
Yes	63 (78.8%)	64 (80%)	0.85
No	17 (21.2%)	16 (20%)	
Urine Vol (ml) (Mean ± SD)	326.06 ± 36.01	336.24 ± 37.37	0.81
Post-Void Residual Volume (ml) (Mean ± SD)	62.70 ± 18.24	62.20 ± 18.82	0.86

In group I mean baseline IPSS was 19.11 ± 7.93 while in group II it was 20.01 ± 8.18,

statistically insignificant (*p*=0.49). Mean IPSS at 4 weeks in group II (alpha blockers and anticholinergics) was significantly lower in comparison with group I (alpha blockers) [16.71± 7.86 vs 12.48 ± 8.04, *p*-value 0.001] (table-II). Similar trend was noted when data was stratified with respect to age, prostate size, baseline IPSS, urine flow rate and nocturia. Mean IPSS at 4 weeks in group II was significantly lower (*p*-value <0.05) (table-III).

Table-II: International Prostate Symptom Score in both groups baseline, baseline stratified and at 4 weeks post treatment.

Variable	Group I (n=80) (Tamsulosin)	Group II (n=80) (Solifenacin + Tamsulosin)	*p*-value
Baseline International Prostate Symptom Score (Mean ± SD)	19.11 ± 7.93	20.01 ± 8.18	0.49
Stratified Baseline International Prostate Symptom Score			
Moderate International Prostate Symptom Score 8-19	14.11 ± 3.21	14.02 ± 3.15	0.89
Severe International Prostate Symptom Score 25-35	29.50 ± 3.22	29.45 ± 3.14	0.95
International Prostate Symptom Score at 4 weeks (Mean ± SD)	16.71 ± 7.86	12.48 ± 8.04	0.001

Table-III: Data stratification of mean international prostate symptom score at 04 weeks with respect to age, prostate size, baseline international prostate symptom score, Urine flow rate and nocturia in both groups.

Variable	International Prostate Symptom Score at 04 weeks post treatment		*p*-value
	Group I (n=80) (Tamsulosin) (Mean ± SD)	Group II (n=80) (Solifenacin + Tamsulosin) (Mean ± SD)	
Age Groups			
40-55 Years	11.93 ± 3.26	6.70 ± 3.30	0.001
56-70 Years	19.15 ± 8.40	16.53 ± 7.91	0.11
Stratified Prostate Size			
≤50 gram	12.88 ± 4.86	7.64 ± 4.49	0.001
≥51-70 gram	27.48 ± 3.23	21.69 ± 3.86	0.001
Baseline International Prostate Symptom Score			
international prostate symptom score 8-19	11.80 ± 3.37	6.71 ± 3.16	0.001
international prostate symptom score 25-35	26.92 ± 3.22	21.58 ± 3.78	0.001
Urine Flow Rate			
13-15 ml/sec	12.00 ± 3.31	6.04 ± 3.17	0.001
<13 ml/sec	21.20 ± 8.33	15.75 ± 7.79	0.002
Nocturia			
2-3 Voids/Night	11.89 ± 3.29	6.50 ± 3.15	0.001
>3 Voids/Night	21.07 ± 8.26	16.46 ± 7.84	0.008

DISCUSSION

LUTS are associated with BPH in >90% of cases characterized by a cluster of chronic urinary symptoms, most bothersome being nocturia coexisting in up to 42% of men aged ≥75 years leading to higher rate of depression and sleep disturbances[14]. The disease entity necessitates appropriate attention due to ever increasing socioeconomic implications in wake of increasing life expectancy of men[11-15].

Although pharmacological treatment of BPH is a success story in urological clinical practice, it mainly focused on obstructive component. The storage component is commonly undertreated and antimuscarinics are infrequently prescribed (<25% reported to receive an antimuscarinic) due

to a widely held, yet unverified, fear of post-void residual (PVR) increase, or, worse, acute urinary retention (AUR)[16].

Combination therapy to treat BPH presenting with both storage and voiding symptoms is focus of high volume of rapidly evolving research and several studies have favored its efficacy as well as safety[17,18]. Wu *et al*[16] concluded in their study that combination therapy was not only more effective but also cost effective in long term as compared to monotherapy. Similarly in their meta-analysis, Dimitropoulos *et al*[17] reported superiority of combination over tamsulosin alone in terms of improvement in IPSS. With this rationale EUA recommended use of anticholinergics in addition if insufficient relief of storage symptoms obtained with alpha blocker monotherapy[19]. Additional studies were warranted to validate and substantiate these findings particularly in local settings due to absence of well-organized study to date.

In our study, a total of one hundred and sixty patients were enrolled. Patients in group I received alpha blockers while group II received alpha blockers and anticholinergics in combination and baseline as well as post 4 weeks therapy IPSS recorded. Our results revealed similar baseline characteristics in both groups. Mean IPSS at 04 weeks in group II was significantly lower in comparison with group I [16.71 ± 7.86 vs 12.48 ± 8.04 with *p*-value 0.001].

Our data showed concordance with already published data on the subject albeit with different study population. Wang *et al*[20] randomized 166 patients having BPH with OAB to receive tamsulosin or its combination with solifenacin respectively to evaluate efficacyas well as safety. Not only IPSS & QoL were found significantly improved in combination therapy group but also objective indexes such as PVR, Qmax, daytime urination frequency, night urination frequency and urge urinary incontinence suggesting it as obviously safe, superior and effective treatment.

Filson *et al*[21] performed a meta-analysis of seven pooled placebo controlled randomized trials to compare combination therapy with tamsulosin monotherapy to identify efficacy and safety of combination approach among men BPH-LUTS. Their analysis found significantly greater improvement in IPSS storage sub scores and voiding frequency in patients using combination therapy. Authors recommended combination therapy as being more effective and safe with a minimal risk of increased PVR, decreased maximal urinary flow rate or AUR.

Kaplan *et al*[22] recruited 398 men ≥ 45 years of age in double-blind, placebo controlled trial to assess safety, tolerability and efficacy of Solifenacin + tamsulosin combination in men having OAB bladder symptoms after alpha blocker monotherapy. Their analysis revealed that patients on combination modality showed greater reductions in frequency but of statistical insignificance (p=0.135) and statistically significant reductions in urgency (p<0.001).

Lee *et al*[23] in their 12-week, randomized, double-blind, placebo-controlled trial randomly allocated 176 patients to receive either tamsulosin 0.4mg or its combination with 5mg solifenacin once daily for 12 weeks. Changes in baseline IPSS, frequency volume bladder diary charts, patient perception of bladder condition (PPBC), uroflowmetry, PVR and voiding/storage IPSS subscores were analyzed. Their results conferred to our study findings revealing significant reductions in IPSS storage sub score, urgency episodes, micturition frequency and improvement in the QoL in combination group.

Kim *et al*[24] aimed to determine the benefits and safety of combination treatment through a systematic review and meta-analysis. Sample comprised 3,548 subjects (2,195 experimental subjects and 1,353 controls) from sixteen RCTs. Based upon mean change in baseline IPSS [-0.03 (95% CI: -0.14-0.08)], authors concluded that combination therapy with alpha blocker and anticholinergics is more effective in relieving LUTS due to BPH.

Hao *et al*[25] analyzed 4084 patients (2106 (51.57%) patients in co-therapy while 1978

(48.43%) in monotherapy) in their meta-analysis systematically to assess clinical efficiency and safety of co-therapy. Patients receiving tamsulosin & solifenacin combination disclosed significant improvements in Storage IPSS subscore, micturition/urgency episodes per 24 hours. They concluded that antimuscarinics are must add drug regimen for patients with LUTS-BPH, particularly those dominated by storage symptoms. These results together with obtained in this study strongly support use of combination therapy in management of BPH-LUTS with significantly better efficacy in reducing both voiding and storage component.

LIMITATION OF STUDY

The results of present study should be interpreted with care as efficacy was measured after 4 weeks only. Moreover, the study was carried out in a single center with smaller target population. There was no comparison of side effects as well as cost of the treatment. Large multicenter RCTs are required to further clarify the role of combination therapy. Various aspects of drug therapy like cost analysis, patient satisfaction and side effect profile, need to be studied to make this combination modality part of effective BPH care program.

CONCLUSION

Statistical significant difference of combination therapy of α-blocker and antimuscarinic compared with α-blocker monotherapy was observed in the present study in terms of robust reduction in symptoms/ improvement in mean IPSS at 4 weeks in BPH patients.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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