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COMBINATION OF MIRABEGRON AND SOLIFENACIN VERSUS MIRABEGRON ALONE FOR MANAGEMENT OF OVERACTIVE BLADDER IN WOMEN

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ABSTRACT

Introduction: Until now, the problem of treatment for OAB still remains challenging. Thus, the introduction of totally new drug mirabegron, which is a b3-adrenoreceptor agonist, has turned out to be much in demand among specialists engaged in OAB. In clinical practice, most OAB patients are initiated on an antimuscarinic, which is escalated to a higher dose or switched to an alternative antimuscarinic or the b3-adrenoceptor agonist, mirabegron. **Objectives:** To compare the efficacy of combination of mirabegron and solifenacin with mirabegron alone for overactive bladder in women. **Materials & Methods:** A total of 480 women having overactive bladder, 20 to 50 years of age were included. Patients with UTI, pregnancy, bladder stone, pelvic malignancy, spinal injury, multiple sclerosis, parkinson disease, diabetic neuropathy were excluded. Patients in group A took mirabegron 25mg + solifenacin 5 mg once daily for 12 weeks and in group B, patients took mirabegron 25 mg once daily for 12 weeks. Urinary incontinence was assessed at baseline and after 12 weeks of treatment on the base of history. OABS score at baseline and after 12 weeks of treatment. Patients were followed for 12 weeks by taking patient's contact number. Efficacy was assessed as per operational definition after 12 weeks of treatment. **Results:** Mean OABS score at baseline and after 12 weeks in group A was 10.33 ± 3.12 and 4.43 ± 1.32 and in group B was 10.13 ± 2.98 and 6.87 ± 2.76 respectively. Efficacy of Group A (combination of mirabegron and solifenacin) was seen in 143 (59.58%) patients while in Group B (mirabegron alone) was seen in 117 (48.75%) patients with p-value of 0.017. **Conclusion:** This study concluded that combination of mirabegron and solifenacin is better than the mirabegron alone for management of overactive bladder in women.

KEYWORDS: overactive bladder, mirabegron, solifenacin.

INTRODUCTION

Overactive bladder (OAB) syndrome is diagnosed if patients experience urinary urgency, with or without urgency urinary incontinence, usually with nocturia and frequency, which is not due to an obvious pathogenic cause.[1] These symptoms are due to over activity of detrusor muscle as demonstrated by urodynamic tests but urethro-vesical dysfunctions can also cause similar clinical features.[2] Several studies have demonstrated that OAB symptoms increase with age.[3] In a large population-based study, 3.4% of men and 8.7% women aged 40-44 years reported symptoms of OAB, which increased to 41.9% of men and 31.3% of women aged ≥75 years. Older individuals also frequently report symptoms of nocturia, with >80% of individuals aged 80-90 years having at least one void per night.[4]

In adults, prevalence ranges from 7 to 27% in men and 9–43% in women. Risk factors for OAB include smoking, obesity, arthritis, depression, heart disease, and irritable bowel syndrome. Additional risk factors specific for men include race (higher in non-White men), increasing age, and a history of prostate disease; additional risk factors for women include neurological conditions (e.g., multiple sclerosis), diabetes, pregnancy, urinary tract infection, uterine prolapse, hysterectomy, and menopause.[5]

Current treatments for OAB include behavioral therapy, pharmacological treatment, minimally invasive procedures, and other surgical option.[6] First-line treatment of OAB is antimuscarinic agents (e.g., solifenacin), which relax the detrusor muscle and modulate bladder function in the storage phase. Nevertheless, antimuscarinic drugs have short-term persistence due to inadequate efficacy or adverse events (AEs), including dry mouth, constipation, and blurred vision.[7]

The other class of oral pharmacotherapy approved for the treatment of OAB is β3-adrenergic receptor agonists.[8] Mirabegron is a relatively new drug, an oral ß3 adrenoreceptor agonist which facilitates urine storage by relaxing detrusor muscle. This different mechanism of action provides mirabegron comparable efficacy to anti-muscarinics, also less side effects than them such as dry mouth, constipation, blurred vision or cognitive impairment. Acceptable safety and tolerability of mirabegron leads to less discontinuation by patients in long-term treatment.[9]

As mirabegron has a different mechanism of action from antimuscarinic agents, combining mirabegron with an antimuscarinic agent such as solifenacin may improve tolerability while maintaining efficacy compared with an escalating dose of antimuscarinic monotherapy. The concept of combining two oral pharmacotherapies with different modes of action is intended to improve OAB symptoms and persistence with treatment without adding to antimuscarinic side effects. This approach may potentially alleviate the need for antimuscarinic medication dose escalation or more invasive procedures. The efficacy of combining mirabegron and solifenacin was 65.2% and of mirabegron alone it was 54% after 12 weeks.[10]

Overactive bladder symptoms are associated with a negative impact on health-related quality of life. OAB symptoms may lead to depression and anxiety, and sleep disturbances, which can adversely affect a patient's daily, social and professional functioning among females. Treatment of OAB is still a challenge for urologists. There is no local data available on the comparison of these two modalities in females. So, the results of my study will be helpful in highlighting the better management plan for the treatment of overactive bladder among females in future.

MATERIALS AND METHODS

After taking permission from ethical review committee, this randomized controlled trial was done from January 2022 to December 2022. Total 480 women having overactive bladder (with at least 01 episode of urinary urgency/week with or without urinary incontinence and nocturia at least 01 episode/night. Its severity was assessed using overactive bladder symptom score (OABS score). The OABS score is a symptom assessment questionnaire designed to quantify OAB symptoms into a single score. The questionnaire consists of 4 questions on OAB symptoms. The total score ranges from 0 to 15 points, with higher scores indicating higher symptom severity), 20 to 50 years of age presented with lower urinary tract symptoms to Urology Department of Shahida Islam Teaching Hospital in Lodhran and Bahawal Victoria Hospital, Bahawalpur were selected. Patients with UTI, pregnancy, bladder stone, pelvic malignancy, spinal injury, multiple sclerosis, parkinson disease, diabetic neuropathy were excluded.

All the patients were randomly divided into two groups by using computer generated random number table. Patients in group A took mirabegron 25mg + solifenacin 5 mg once daily for 12 weeks and in group B, patients took mirabegron 25 mg once daily for 12 weeks. Urinary incontinence was assessed at baseline and after 12 weeks of treatment on the base of history. OABS score at baseline and after 12 weeks of treatment. Patients were followed for 12 weeks by taking patient's contact number. Efficacy was assessed as per operational definition after 12 weeks of treatment. All the information was collected on performa by myself.

All the data was entered and analyzed on SPSS Version 25. Mean ± Standard deviation were calculated for age, duration of disease, BMI, number of urinary incontinence at baseline and after 12 weeks, OABS score at baseline and after 12 weeks. Frequency and percentages were calculated for improvement in urinary incontinence, improvement in OABS score and efficacy. Chi-square test was used to compare efficacy between two groups.

RESULTS

Age range in this study was from 20-50 years with mean age of 36.85 ± 6.61 years. The mean age of patients in group A was 36.49 ± 7.87 years and in group B was 35.93 ± 6.19 years. Majority of the patients 257 (53.54%) were between 36 to 50 years of age.

Mean BMI was 28.30 ± 2.20 kg/m2. Mean duration of disease was 12.47 ± 2.57 months. Mean number of urinary incontinence at baseline and after 12 weeks in group A was 2.44 ± 1.32/week and 1.23 ± 0.89/week and in group B was 2.65 ± 1.54 and 2.01 ± 1.04/week respectively. Mean OABS score at baseline and after 12 weeks in group A was 10.33 ± 3.12 and 4.43 ± 1.32 and in group B was 10.13 ± 2.98 and 6.87 ± 2.76 respectively.

Efficacy of Group A (combination of mirabegron and solifenacin) was seen in 143 (59.58%) patients while in Group B (mirabegron alone) was seen in 117 (48.75%) patients with p-value of 0.017.

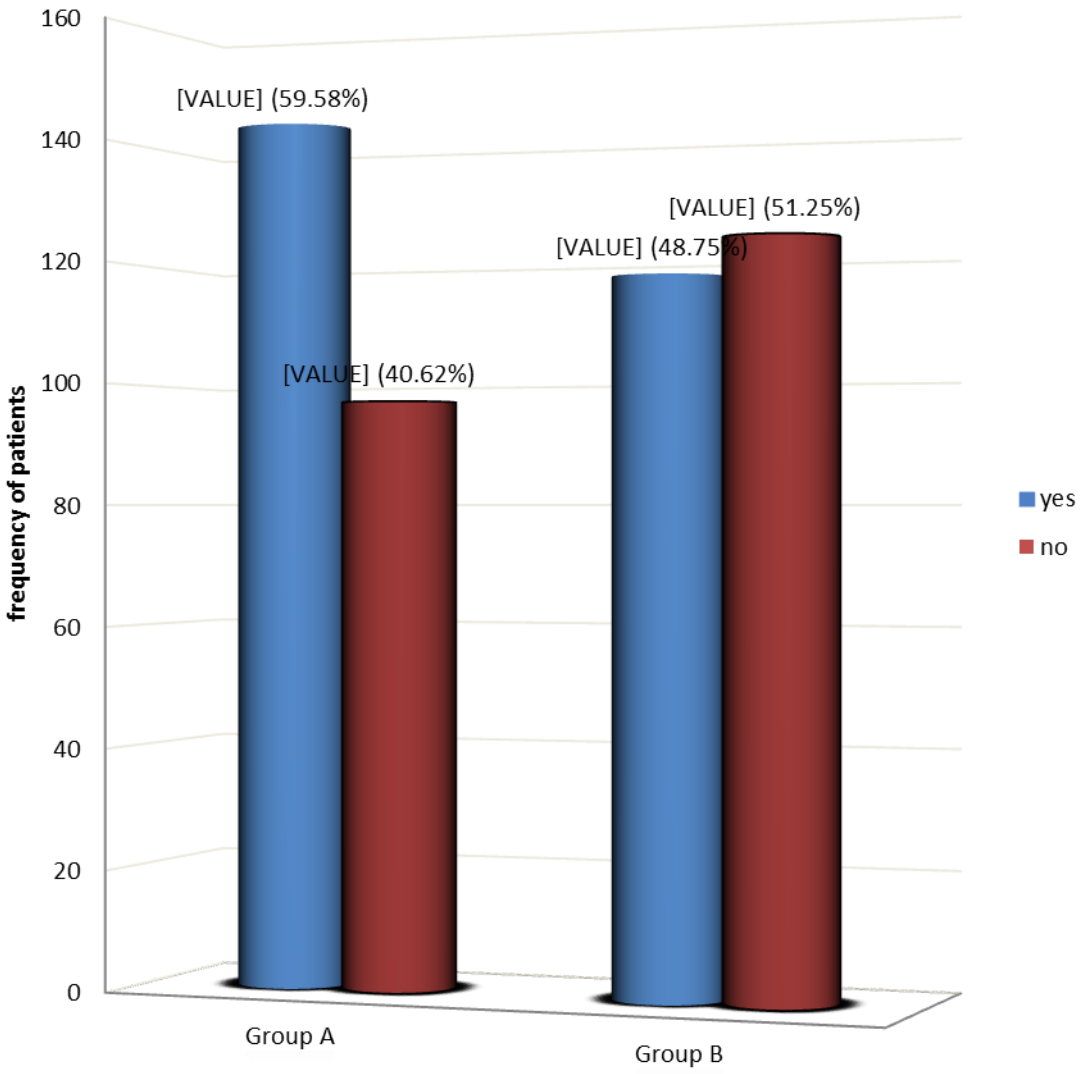

Figure I: Comparison of the efficacy of combination of mirabegron and solifenacin with mirabegron alone for overactive bladder in women.

- **P-value = 0.017 which is statistically significant**

DISCUSSION

OAB syndrome is a symptom complex defined as urinary urgency, in the absence of UTI or other obvious pathology.[11,12] OAB symptoms are chronic and often bothersome, which can significantly impact quality of life (QoL), leading to pessimism, social isolation and depression.[13,14] Antimuscarinics are the mainstay of oral pharmacotherapy for OAB, but persistence with treatment is limited by insufficient effectiveness and associated adverse events.[15] Until now, the problem of treatment for OAB still remains challenging. Thus, the introduction of totally new drug mirabegron, which is a b3-adrenoreceptor agonist, has turned out to be much in demand among specialists engaged in OAB.[16] In clinical practice, most OAB patients are initiated on an antimuscarinic, which is escalated to a higher dose or switched to an alternative antimuscarinic or the b3-adrenoceptor agonist, mirabegron. Some studies demonstrated that combination of mirabegron and antimuscarinic may improve efficacy without compromising tolerability, thus promoting treatment persistence.[17-20] I have conducted this study to compare the efficacy of combination of mirabegron and solifenacin with mirabegron alone for overactive bladder in women Age range in this study was from 20-50 years with mean age of 36.85 ± 6.61 years. The mean age of patients in group A was 36.49 ± 7.87 years and in group B was 35.93 ± 6.19 years. Majority of the patients 257 (53.54%) were between 36 to 50 years of age. Higher mean age was observed by Batista et al.[21], Wagg et al.[22] and Khullar et al.[23] The higher mean age may be due to geographical variations, racial, ethnic differences, and genetic causes may have significant influence on overactive bladder in their study subjects.[21-23]

In my study, efficacy of Group A (combination of

mirabegron and solifenacin) was seen in 143 (59.58%) patients while in Group B (mirabegron alone) was seen in 117 (48.75%) patients with p-value of 0.017. In a study, the efficacy of combining mirabegron and solifenacin was 65.2% and of mirabegron alone it was 54% after 12 weeks.[10]

The Symphony trial, a multinational phase II double-blind RCT, compared 1306 people with OAB across 12 groups, 6 combination groups (solifenacin 2.5, 5 or 10 mg plus mirabegron 25 or 50 mg), 5 monotherapy groups (solifenacin 2.5, 5 or 10 mg, or mirabegron 25 or 50 mg), or placebo,[24] with a 2 week placebo run-in period. Compared to solifenacin 5 mg monotherapy, at 12 weeks follow up those treated with mirabegron 25 mg or 50 mg in combination with solifenacin 2.5 mg, 5 mg and 10 mg had significantly reduced numbers of micturitions per 24 h, with a trend for increasing effect with increasing doses of solifenacin and mirabegron. All treatment groups, including placebo, demonstrated a reduction in the number of urgency episodes from baseline, and none of the active treatment groups significantly reduced incontinence episodes compared with placebo.[24]

Following this, the SYNERGY study was a larger phase III trial comparing solifenacin 5 mg in combination with mirabegron 25 mg and 50 mg with solifenacin 5 mg, mirabegron 25 mg and mirabegron 50 mg as monotherapy and placebo.25 Conducted at 425 sites in 42 countries, a total of 3398 participants were randomized in a 2:2:1:1:1:1 ratio to the combination groups and monotherapy/placebo groups respectively. Participants completed 2 weeks of placebo run-in prior to 12 weeks of therapy. As with Symphony, all the treatment groups demonstrated a reduction in UI episodes per 24 h, with a greater reduction in the combination therapy groups than monotherapy or placebo, with reductions of −1.34 for placebo, −1.7 and −1.76 for mirabegron 25 mg and 50 mg respectively, −1.79 for solifenacin 5 mg, −2.04 for mirabegron 25 mg with solifenacin 5 mg, and −1.98 for mirabegron 50 mg with solifenacin 5 mg. However, although the combined solifenacin 5 mg/mirabegron 50 mg arm was superior to solifenacin 5 mg monotherapy for UI episodes (mean adjusted difference of −0.2 episodes/24 h, 95% CI −0.44−0.04, p = 0.033), superiority to mirabegron 50 mg was not demonstrated (mean adjusted difference −0.23 95% CI −0.47, 0.01, p = 0.052). Pre-specified subgroup analysis demonstrated a small but statistically significant improvement for reduction in micturition episodes per 24 h and incontinence episodes per 24 h for both combination groups (mirabegron 25 mg and 50 mg with solifenacin 5 mg) compared to mirabegron and solifenacin monotherapy, with all active treatment groups having greater improvements in UI episodes/24 h versus placebo, with effect sizes for the combined therapy groups (combined solifenacin and mirabegron 25 mg group: −0.70 episodes/24 h and solifenacin/mirabegron 50 mg group −0.65 episodes/24 h) that were higher than those obtained with monotherapy (range −0.37 episodes/24 h for mirabegron 25 mg to −0.45 episodes/24 h for solifenacin 5 mg). It is interesting to note that there was no additional benefit from the higher dose of mirabegron when comparing the two combination arms, and taken as a whole the data from this trial did not show a consistent and clinically significant benefit from combining mirabegron with solifenacin.[25]

The BESIDE study specifically recruited adults with OAB who had not responded to 4 weeks of therapy with solifenacin.26 Following single-blind 5 mg solifenacin run-in, those participants who reported at least one episode of incontinence on a three-day diary were randomized to receive either solifenacin 5 mg, solifenacin 10 mg or solifenacin 5 mg with mirabegron 25 mg, increasing to 50 mg after 4 weeks. A total of 2174 people entered the second phase of the study, and were randomized in a 1:1:1 ratio and followed for 12 weeks. The primary outcome measure was reduction in incontinence episodes from baseline, and secondary end-points included number of urgency episodes, mean voided volume, and nocturia, and patient perception of bladder condition score. There was a greater reduction in incontinence episodes per 24 h for the combination group than the solifenacin 5 mg group (–1.80 versus –1.53 respectively), and the combination was non-inferior to solifenacin 10 mg for the majority of the reported end-points. The incidence of TEAEs was lowest in the solifenacin 5 mg group (33.1%) and highest with solifenacin 10 mg (39.4%), with the combination group falling between these two at 35.9%. Classical anticholinergic effects, constipation and dry mouth, were the commonest TEAEs reported, and these were unsurprisingly highest in the solifenacin 10 mg group and similar in the combination and solifenacin 5 mg groups. This suggests that, although the effect of adding mirabegron and increasing the solifenacin dose were similar, the bothersome anticholinergic side-effects of higher-dose solifenacin could be avoided by adding mirabegron.[26]

Given the well-reported issues concerning anticholinergic use in older adults,[27] a pre-specified subgroup analysis of the BESIDE study was reported, analysing the results in the over-65 and over-75 age groups.[28] Of the initial BESIDE group, 30.9% were aged 65 or over, and 8.9% were 75 or over. In the efficacy analysis there were no significant interactions between age group and treatment group for the ⩾65 group (p = 0.825) or ⩾75 group (p = 0.96), suggesting that age did not influence the efficacy of any of the three treatment arms. The older groups were more likely to have TEAEs, and in particular constipation was reported slightly more commonly in the ⩾75 group in all three treatment arms, and the incidence of cardiovascular effects was <2% across the board. Cognitive adverse events were not specifically reported in this study. Additionally, a responder analysis to the BESIDE trial

has also been reported,[29] exploring if the reported changes to objective symptoms were translated to significant improvements in patient-reported outcomes (PRO). The authors defined PRO responders as those who achieved a change from baseline to end of treatment that exceeded the predefined minimally important difference on the OAB Questionnaire[30] or the Patient Perception of Bladder Condition questionnaire.[31] There were differences in favour of the combination arm compared to both solifenacin groups in the proportion of responders who reported a 50% reduction in incontinence episodes and normalization of micturition frequency, and those receiving combination treatment had greater odds of achieving complete cure of incontinence [OR 1.47 (95% CI 1.17–1.84)] compared to solifenacin 5 mg monotherapy.[31]

CONCLUSION

This study concluded that the combination of mirabegron and solifenacin is better than the mirabegron alone for management of overactive bladder in women. So, we recommend that combination of mirabegron and solifenacin should be used routinely in every women with overactive bladder in order to achieve better results.

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