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ORIGINAL ARTICLE

Comparative Study of Mirabegron and Tolterodine for the Treatment of Overactive Bladder in Women

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ABSTRACT

Background: Overactive bladder is a disease of multifactorial etiology resulting from various potential pathophysiological mechanisms. Tolterodine and Mirabegron are established treatment therapy for patients with overactive bladder owing to its efficacy and safety. Tolterodine, muscarinic receptor antagonist, acts on both M2 and M3 receptors and Mirabgron is a β_3-adrenoceptor agonist.

Objective: To compare the efficacy and safety of Mirabegron versus Tolterodine for the treatment of overactive bladder in women.

Study Design: Randomized clinical trial study

Place and Duration of Study: Department of Urology, Jinnah Hospital Lahore from 10th April 2022 to 9th April 2023.

Methodology: One hundred and sixty female patients were enrolled. They were divided in two groups; each group comprised equal number of patients. Group A patients were given Mirabegron 50mg once daily for 12 weeks and group B were given Tolterodine 2mg twice daily for 12 weeks. The overactive bladder symptom score (OABSS) was calculated by using prescribed questionnaire for each patient before start of therapy and at each follow up visits at 2nd, 4th, 8th and 12th week of treatment. Side effects like dry mouth, constipation, headache, dizziness and blurred vision were also noted.

Results: The mean ages were 38.67±13.30 years in Mirabegron group, while in Tolterodine group, 38.45±11.43 years. The mean body mass index was 26.33±6.79 kg/m^2 in Mirabegron group and in Tolterodine group, body mass index was 30.13±6.62 kg/m^2. The pre-treatment mean over active bladder symptoms score was 13.70±1.06 in Mirabegron group while in Tolterodine group, OABSS was 13.60±1.14. After the treatment, mean OABSS was 5.41±1.13 in Mirabegron group and in Tolterodine group, OABSS was 6.98±0.92. Regarding after treatment, 22 (27.5%) patients had constipation in Mirabegron group and 37 (46.2%) patients had constipation in Tolterodine group. After treatment, in Mirabegron group, 24 (30%) patients were presented with dry mouth and in Tolterodine group, 38(47.5%) patients had dry mouth. Regarding after treatment, 21(26.2%) patients were presented with complaint of dizzines in Mirabegron group and 37(46.2%) patients in Tolterodine group. After treatment, 19(23.8%) patients had headache in Mirabegron group and 33(41.2%) patients had headache in Tolterodine group. According to after treatment, in Mirabegron group, there were 21(26.2%) patients with complaint of blurred vision and 37 (46.2%) patients presented with blurred vision. The efficacy in Mirabegron group was 93.8% and in Tolterodine group, 46.2%.

Conclusion: Mirabegron is more effective than tolterodine for the treatment of overactive bladder among women in terms of reducing over active bladder symptoms score after treatment.

Keywords: Mirabegron, Tolterodine, Overactive bladder

INTRODUCTION

Overactive bladder (OAB) is a disorder with a complex etiology that may be caused by different pathophysiological processes.[1] A definition of OAB provided by the International Continence Society states that it is urine urgency, frequently associated with frequency and nocturia, with or without urge urinary incontinence, in the absence of a urinary tract infection or other evident pathology.[2]

In the absence of a urinary tract infection, metabolic disorders (affecting urination), or urinary stress incontinence induced by effort or overexertion, OAB is considered as pathology of bladder dysfunction.[3] Treatment like behavioral therapy, such as caffeine reduction, fluid consumption modification, weight loss, bladder training, and pelvic muscle training are helpful for management of OAB, other treatment options are anti-muscarinic or β_3-adrenoceptor agonist medications. Anti-muscarinic drugs are the mainstay of OAB treatment when behavioral therapy and dietary adjustments fails.[4]

Muscarinic receptor antagonist, Tolterodine works on both M2 and M3 subtypes of receptors. OAB symptoms in women may also be alleviated by using this drug. In addition, treatment of OAB with Tolterodine was found to have positive effect on sexual function of patients with OAB.[5] For individuals with OAB, Mirabegron has been demonstrated in phase III studies to be an effective and tolerable therapeutic alternative option to anti-muscarinic medication.[6] Mirabegron was shown to have comparable rates of side effects as a placebo in phase III studies, but a lower frequency of dry mouth compared with Tolterodine.[7]

Overactive bladder is more frequent in women than men and affects a large percentage of the world's population. Thus, the current study is planned to compare efficacy and safety of Mirabegron and Tolterodine in female patients with OAB.

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MATERIAL AND METHODS

This randomized clinical trial, a comparative study was conducted at Department of Urology, Jinnah Hospital Lahore from 10th April 2022 to 9th April 2023. A total of 160 cases were enrolled; 80 in each group was calculated with power of study at 80% and significance level at 5% and percentage of efficacy i.e. 38% with Mirabegron and 20% with Tolterodine.[8] In group A, patients were given 50mg Mirabegron once daily for 12 weeks and group B patients were given 2mg Tolterodine twice daily for 12 weeks. All female patients with age 20-60 years and OAB symptoms including urinary frequency, urgency or urge incontinence for 3 months or more were included. All pregnant and lactating females, utero-vaginal prolapsed, indwelling catheters or practicing intermittent self- catheterization, untreated urinary tract infection, chronic inflammation, urethral stenosis, bladder stones, previous pelvic radiation therapy, malignant diseases of pelvic organs, hypersenstivity of drugs, narrow angle glaucoma, uncontrolled diabetes, immunocomrpmised, neurogenic bladder, hepatic and renal impairment were excluded. A thorough history regarding marital status, number of children, numbers of vaginal deliveries,

severity and duration of voiding symptoms were taken. Clinical examination was performed to rule out palpable bladder or vaginal prolapse. Urine examination and ultrasound was performed to rule out UTI and presence of any significant post void residual urine. UTI was treated with appropriate antibiotic therapy according to culture and sensitivity before inclusion. The OABSS was calculated by prescribed questionnaire for each patient before start of therapy and at each follow up visits. After initiation of treatment, patients were then followed at 2nd, 4th, 8th and 12th week. If there is increase in OABSS owing to worsening of symptoms or no reduction in score despite one month of medication, such cases were declared as 'Non-responder/Treatment Failure'. Side effects like dry mouth, constipation, headache, dizziness and blurred vision were also noted. All the data was entered and analyzed by using SPSS-25. Shapiro-Wilk test was applied to determine the normality of data. In order to examine the persistence, effectiveness, and side effects in both groups, independent samples t-tests and chi-square analyses were used to compare the mean OABSS in both groups.A p-value of less than 0.05 was deemed statistically important.

RESULTS

The mean ages were 38.67±13.30 years in Mirabegron group, while in Tolterodine group, 38.45±11.43 years and statistically no significant (P=0.909) difference was found. The mean body mass index were 26.33±6.79 kg/m^2 in Mirabegron group and in Tolterodine group, body mass index was 30.13±6.62 kg/m^2. The difference was statistically significant (P<0.001) [Table1].

The pre-treatment mean over active bladder symptoms score was 13.70±1.06 in Mirabegron group while in Tolterodine group was 13.60±1.14. Statistically it was found no significant (p=0.567) difference. After the treatment, mean over active bladder symptoms score was 5.41±1.13 in Mirabegron group and in Tolterodine group, was 6.98±0.92. Statistically there was significant (p<0.001) difference (Table 2).

According to pre-treatment, there were 2 (2.5%) patients had constipation in Mirabegron group and 4 (5%) patients had constipation in Tolterodine group. Statistically it was found no significant (p=0.482) difference. Regarding after treatment, 22 (27.5%) patients had constipation in Mirabegron group and 37 (46.2%) patients had constipation in Tolterodine group. Statistically it was found significant (p=0.014) difference. No case of dry mouth was reported before treatment. After treatment, in Mirabegron group, 24 (30%) patients were presented with dry mouth and in Tolterodine group, 38 (47.5%) patients had dry mouth. Statistically there was significant (p=0.014) difference. According to pre-treatment, there was no patient with complaint of dizzines was registered. Regarding after treatment, 21(26.2%) patients were presented with complaint of dizzines in Mirabegron group and 37(46.2%) patients in Tolterodine group. Statistically there was significant (p=0.009) difference. Before treatment, no patient was presented with headache. After treatment, 19(23.8%) patients had headache in Mirabegron group and 33(41.2%) patients had headache in Tolterodine group. Statistically there was significant (p=0.018) difference. At pre-treatment, no case was registered related to blurred vision. According to after treatment, in Mirabegron group, there were 21(26.2%) patients with complaint of blurred vision and 37 (46.2%) patients in Tolterodine group presented with blurred vision. Statistically there was significant (p=0.009) difference (Table 3).

The efficacy in Mirabegron group was 93.8% and in Tolterodine group, 46.2%. This difference was statistically significant (P<0.001) [Table 4].

Table 1: Descriptive statistics of the patients between two groups

Variable	Mirabegron Group	Tolterodine Group	P value
Age (years)	38.67±13.30	38.45±11.43	0.909
Body mass index (kg/m^2)	26.33±6.79	30.13±6.62	<0.001

Table 2: Comparison of over active bladder symptom score (OABSS) before and after treatment between two groups

OABSS	Mirabegron Group	Tolterodine Group	P value
Pre-Treatment	13.70±1.06	13.60±1.14	0.567
After Treatment	5.41±1.13	6.98±0.92	<0.001

Table 3: Comparison of side effects before and after treatment in both groups

Side Effects	Mirabegron Group	Tolterodine Group	P value
Constipation			
Pre-Treatment	2 (2.5%)	4 (5%)	0.483
After Treatment	22 (27.5%)	37 (46.2%)	0.014
Dry Mouth			
Pre-Treatment	-	-	-
After Treatment	24 (30%)	38 (47.5%)	0.014
Dizziness			
Pre-Treatment	-	-	-
After Treatment	21 (26.2%)	37 (46.2%)	0.009
Headache			
Pre-Treatment	-	-	-
After Treatment	19 (23.8%)	33 (41.2%)	0.018
Blurred Vision			
Pre-Treatment	-	-	-
After Treatment	21 (26.2%)	37 (46.2%)	0.009

Table 4: Comparison of efficacy between study groups

Efficacy	Mirabegron Group	Tolterodine Group	P value
Yes	75 (93.8%)	37 (46.2%)	<0.001
No	5 (6.2%)	43 (53.8%)	

DISCUSSION

Overactive bladder is a chronic medical condition which has a tremendous impact on the quality of life in a significant amount of population and affects performance of daily activities such as work, travelling, physical exercise, sleep and sexual function. Treatment of overactive bladder include lifestyle modifications, medications, nerve stimulation and in some cases surgery. Tolterodine and Mirabegron are established medical therapy for patients with overactive bladder. There was a marked significant of difference between Mirabegron and Tolterodine in terms of OABSS and side effects like constipation, dry mouth, dizziness, headache and blurred vision. In this study on pre-treatment in Mirabegron group, the mean OABSS of the patients was 13.70±1.06 and in Tolterodine group, the mean OABSS of the patients was 13.60±1.14 (p=0.567). After treatment in Mirabegron group, the mean OABSS of the patients was 5.41±1.13 and in Tolterodine Group, the mean OABSS of the patients was 6.98±0.92 (p<0.001). There was a significant reduction in mean OABSS in Mirabegron group than Tolterodine. These results are compared with other studies, the SCORPIO trial compared Mirabegron to placebo and Tolterodine in people with OAB in Europe and Asia. Khullar and colleagues[9], a total of 1978 adults with OAB comparing placebo, Mirabegron 50 mg, Mirabegron 100 mg, and Tolterodine ER 4 mg. The Mirabegron groups had statistically significant reduction in overactive bladder symptom score. Similarly, in the ARIES trial, Nitti and colleagues randomized 1329 adults in North America to receive placebo, Mirabegron 50 mg, or Mirabegron 100 mg.[10] Over the 12th weeks follow-up period there was a significantly greater improvement in incontinence, in Mirabegron groups compared to the placebo group. As often seen in OAB trials, there was a significant placebo effect including severity of urgency, nocturia and OABSS also improved, with more in the Mirabegron groups than the placebo arm.

A systematic review and meta-analysis performed in 2017 by Sebastianelli et al[11] found that Mirabegron is an effective treatment for patients with overactive bladder, decreasing incontinence, OABSS, urgency, and frequency; improving voiding volume while having a slight side effect.

Hsiao et al[12] showed the urodynamic and bladder diary parameters of Mirabegron and Tolterodine changed in a comparable way. Mirabegron, on the other hand, may reduce the OABSS.

Constipation was reported before treatment, 2(2.5%) patients in Mirabegron group and 4(5%) patients in Tolterodine group (p=0.483). At the end of treatment, 22(27.5%) patients in the Mirabegron group and 37(46.2%) patients in the Tolterodine group had constipation (p=0.014). In this study, patients were more likely to develop constipation with Tolterodine than Mirabegron.

To compare these results of constipation with other studies, serious treatment emergent adverse event (TEAE) rates were likewise similar for the three groups, at 5.2% for Mirabegron 50 mg, 6.2% for Mirabegron 100 mg, and 5.4% for Tolterodine. TEAEs of all levels of severity were reported in 59.7%, 61.3% and 62.6%, respectively, and were most commonly hypertension, gastrointestinal disturbance (predominantly constipation), and headache, which occurred equally across the three groups. They conclude that Mirabegron demonstrated an acceptable safety and tolerability profile with improvements in OAB symptoms at the first measurable time of 1 month, with sustained improvement throughout 12 months.[13]

Adverse event like dry mouth was not reported pre-treatment but after treatment, patients in Mirabegron group had a dry mouth rate of 30%, but patients in Tolterodine group had a dry mouth rate of 47.5% (p=0.014). There was a significant difference to develop dry mouth with Tolterodine than Mirabegron. To compare adverse event of dry mouth with other studies, Chapple et al[14] confirmed the safety, tolerability and effectiveness of Mirabegron, Solifenacin, and Tolterodine. Anticholinergic causes greater dry mouth in the Anti-muscarinic group than in the Mirabegron group.

We identified statistically significant differences in side effects like dizziness, headache, and blurred vision across study groups that these adverse events are more common in Tolterodine group than Mirabegron (Table 3).

According to this study, efficacy was achieved in 112 (70%) patients. In Mirabegron, efficacy was achieved in 75(93.8%) patients and in Tolterodine group, efficacy was achieved in 37(46.2%) patients. This difference was statistically significant (p<0.001 (Table 4). These results are compared with other studies that Mirabegron has shown superiority over placebo in Phase III(a) clinical trials in patients with OAB.[15-18]

CONCLUSION

Mirabegron is more effective than Tolterodine for the treatment of overactive bladder among women in terms of reducing OABSS after treatment. The safety profile of Mirabegron also surpasses the Tolterodine as having decrease of side effects and compliance of treatment has been found among patients under treatment.

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