Original Article

Comparison of Mirabegron and Solifenacin for the Management of Urge Incontinence in Menopausal Age Group

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Abstract

Objective: To compare efficacy and tolerability of Mirabegron and Solifinacin in urge incontinence in menopausal women.

Methodology: This RCT was conducted in the Maternal and Child Health (MCH) Center, Unit II, Pakistan Institute of Medical Sciences (PIMS), SZABMU (Shaheed Zulfiqar Ali Bhutto Medical University), Islamabad in two years from December 2020 to January 2022. A total of 63 patients each were randomized to receive Mirabegron (Group-A) or Solifinacin (Group B). Primary outcome was efficacy which was assessed by micturations per 24 hours, urge episodes, urges in incontinence and nocturia. The final outcome was measured on 3-month-follow-up.

Results: The mean age was 48.0 ± 5.2 years in Mirabegron and 50.7 ± 6.1 years in Solifinacin group. In Solifinacin group 4 (6.3%) patients still experienced urine leak compared to none (0.0%) in Mirabegron group (p-value, 0.04). The rate of night urination and micturition also found greater in the Solifinacin group. The number of protective garments used per day was significantly greater in the Solifinacin group (p-value, 0.001). After 3 months of therapy, more patients from Solifinacin group experienced drowsiness as sedation, and constipation than those in Mirabegron group (p- value, <0.001). Few cases were experiencing confusion/delirium, palpitations in Solifinacin group (p-value, 0.04) as noted on 3-month follow-up.

Conclusion: Mirabegron is better than Solifinacin in the management of urge incontinence in older women. Mirabegron was also found more tolerable.

Key words: Efficacy, Mirabegron, Solifinacin, overactive bladder.

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Introduction

Urinary incontinence, is stipulated as unintentional loss of urine by International-Continence Society that sets off a hygienic or social hindrance for an individual[1]. The symptoms of OAB and urge incontinence can manifest at any age group, but are predominantly common amongst the elderly. OAB can be assumed of as a symptom as described by the individuals, and on examination a sign that is observed. In adult female population, it's highly predominant indicator syndrome that significantly affects HR-QOL (health related quality of life).[2] OAB has an established impact on the physical, psychological QOL as well as socioeconomic aspects of life.[3] OAB describes an abrupt urge to urinate that's difficult to defer resulting in dripping of urine. Worldwide, around 400 million individuals suffer with signs of urgency and incidence (dry-OAB) and a fraction will have accompanying urine incontinence (wet-OAB)[4]. OAB is one of the most significant urinary problems. It shouldn't be assumed of as an ailment, because no exact etiology exists; causes are probably multifactorial in nature in most individual. The precise etiologies of OAB are miscellaneous and in numerous cases, partly understood.[5, 6]

Even in same individual, urinary incontinence might have various etiologies, with fluctuating extent of contribution, to the complete disorder. Structural as well

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as functional conditions involving the muscles of bladder, ureters, urethra & adjacent CT (connective tissue) can also contribute.[7,8] Non-pharmacological therapies improve control over bladder by adapting changes in lifestyle and behavior. By merging these approaches with pharmacotherapy or pharmacotherapy alone, prevention of adverse results may be obtained[7].

The most generally used pharmacologic drugs are the muscarinic receptors antagonists such as solifinacin for elderly individuals. Important consideration includes tolerability, lack of drug interactions and the accessibility of a range of prescriptions to tailor treatment to each individual patients. Many patients don't seek any kind of treatment just because of embarrassment and terror of surgery, as the misconception that the disease is intolerable or is typical and inevitable result of aging.[9]

Antimuscranics are considered drug of choice for urge incontinence and have been revealed to decrease inconvenient symptoms of frequency, urgency along with incontinence. Still, their routine use is frequently restricted by restricted efficacy and excruciating adverse events including dryness of the mouth, vision blurriness and constipation. Discontinuation is seen in 50% of patients within 3 months[10]. Based on available evidence and practice guidelines-health care professionals should therefore learn to identify, evaluate and manage OAB[11]. Alternate approaches in the management of urge incontinence revolves around Beta-adrenoceptors, which have a recognized role in facilitating relaxation of smooth muscles of bladder. B3 receptors are responsible for endorsing relaxation and storage of urine and constrain the activity of bladder afferents nerves[12]. By integrating patient imitated dose alteration into the protocol, the primary care GP can efficiently manage adverse event accompanying with urge incontinence without any compromising on effectiveness. Current dose alteration data with mirabegron suggest that individuals are willing to endure certain side-effects of these drugs in exchange of relief from these symptom. A new B3 receptor, Mirabegron, adrenergic medication has currently been introduced & has shown source help above mentioned drug is the first of an innovative class of drugs accredited for the management of OAB and has revealed to be well endured and effective in dealing of urge incontinence. It has lower side-effects which is the main cause of discontinuation of OAB medications[13]. Mirabegron represents a valid option for both antimuscranic naïve and or where they are refractory. Combination therapy is also effective for both anti-cholinergic resistant neurogenic bladders; proved by video dynamic evaluation[1].

A comprehensive cure is highly rare and the management of urge incontinence is a thought-provoking mission. The significance of diagnosis and appropriate treatment options cannot be overemphasized. Keeping in view the variable findings regarding relief and side effects of antimuscranics, a less complication prone drug can achieve high compliance and successful treatment.[10,12.13] Thus, this study aimed to find out a treatment with high efficacy and few adverse effects which will contribute to the general health in urge incontinence patients. To address the issue of discontinuation of drugs and mitigation of sufferings of patients due to drug related side effects, we planned to check the role of Mirabegron versus Solifinacin. The specific aim was to compare efficacy and tolerability of Mirabegron and Solifinacin in urge incontinence in menopausal women presenting at MCH Center, Pakistan Institute of Medical Sciences (PIMS), Islamabad.

Methodology

This prospective randomized control study was conducted in Obstetrics and Gynecology unit-II at PIMS, Islamabad. A total of 126 women were enrolled in a period of two years from 03-12-2020 to 01-01-2022. Ethical clearance was taken vide letter no. (No. F.1-1/2015/ERB/SZABMU/466) and a written informed consent was administered.

Using simple random technique the patients were enrolled equally into group A i.e. Solifinacin (n=63) and group B i.e. Mirabegron (n=63). Randomization list was developed using lottery method. Sample size was calculated by WHO sample size calculator using significance level of 5%, power of test 90%, test value of population (mean value of number of micturition in solifinacin=8.5) and anticipated population proportion (mean value of micturition in mirabegron group=8.4).[14] The sample size was 126 patients which was divided into 63 cases each.

Patients 45 years and above or menopausal patients with urge incontinence were included. The patients having CVS, neurological deficits, renal and diabetic conditions were excluded. Those suffering incontinences following pelvic surgeries (e.g. carcinoma, CA ovary, uterus and those with history of UTIs and aggravated symptom were also excluded.

All study specific details of eligible women were documented via questionnaire. Following, detailed history and examination preliminary tests (URINE R/E, URINE C/S) were done. Urinary urgency was assessed at baseline and then on follow-up of patients on OPD basis. The final follow- up was after 12 weeks of intervention. Simultaneously, the dropouts due to adverse effects were recorded as per protocol by contacting telephonically so no lost to follow-up.

The dose of Mirabegron was kept at 25 mg and Solifinacin at 5 mg. However, if the participant failed to respond and comply to lower dose in 1st two months the dosage was increased to 50 mg for Mirabegron and 10 mg for Solifinacin and noted accordingly. Bladder Diary was used by each patient for record on daily basis. They were taught and counseled about their entry of intake output record on daily basis. Patients were followed one monthly for 3 months subsequently monitored on a specified outcome proforma attached hereby as Annexure A. Data was entered and analyzed using the SPSS version 21. Descriptive statistics was calculated for both the qualitative as well as quantitative variables. For the qualitative variables (example micturitions /24 hrs, urgency episodes /24 hrs. and nocturia) frequency and percentage were calculated. Mean and standard deviation was calculated for age, parity, weight and height. Chi-square test was applied to compare efficacy and tolerability between both groups A and B. A p-value of ≤ 0.05 was considered statistically significant.

Results

In this study a total of 126 women were allocated to receive either mirabegron (n=63) or solifinacin (n=63). The average age of patients in Mirabegron group was 48.0 ± 5.2 years whereas in Solifinacin group it was 50.7 ± 6.1 years. There were some changes noted in the educational background of the patients, in the Mirabegron group approximately majority of the cases 29 (46.0%) had middle education and around one-fifth 12 (19.0%) had intermediate level education, whereas in the 2nd group majority 29 (46.0%) had secondary level education followed by intermediate 8 (12.7%) education and this difference in education level of patients in the two groups was found statistically significant (p-value, <0.001). The mean height of patients in Mirabegron group was 153.0 ± 8.2 cm whereas in Solifinacin group it was 155.8 ± 6.1 cm and this difference was not statistically significant. When history of mode of delivery was assessed, in Mirabegron group there were 16 (25.3%) patients who had a c-section whereas in Solifinacin group 8 (12.7%) patients had history of c-section and this difference was though apparent, however, statistically it was not proven (p-value, 0.07). There were 35 (55.6%) women with menopause status in Mirabegron group compared to 42 (66.6%) in Solifinacin group, this difference in the two proportions was also not statistically significant (p-value, 0.23). (Table I)

Table I: Demographic characteristics of patients in two groups.

	Mirabegron (n=63)	Solifinacin (n=63)	p-value
Age (years)			
Mean ± SD	48.0 ± 5.2	50.7 ± 6.1	0.11
Education			
Quran	4 (6.3%)	4 (6.3%)	<0.001
Middle	29 (46.0%)	8 (12.7%)	
Secondary	6 (9.5%)	29 (46.0%)	
Intermediate	12 (19.0%)	8 (12.7%)	
Graduate	5 (7.9%)	4 (6.3%)	
Illiterate	7 (11.2%)	10 (15.8%)	
Height (cm)			
Mean ± SD	153.0 ± 8.2	155.8 ± 6.1	0.49
Weight (kg)			
Mean ± SD	75.3 ± 9.4	74.5 ± 7.3	0.34
Parity			
Mean ± SD	4.3 ± 1.4	4.3 ± 1.3	0.90
History of mode of delivery			
C-section	16 (25.3%)	8 (12.7%)	0.07
SVD	47 (74.7%)	55 (87.3%)	
Menopause			
Yes	35 (55.6%)	42 (66.6%)	0.23
No	28 (44.4%)	21 (33.3%)	
Occupation			
House wife	43 (68.2%)	45 (71.4%)	0.56
Working women	20 (32.8%)	18 (28.6%)	

The comparison of the outcomes of the studies was done. In majority of the study subject's urinary leakage before reaching toilet was once a day or several time a day was examined. Urinary leakage was same in both of the groups, but on first, second and third follow-ups in Mirabegron group significantly less patients had leakage once a day (p-value, 0.003) compared to Solifinacin group. a greater number of patients in Solifinacin group mentioned a few drops than Mirabegron (p-value, 0.02). The number of protection pads used by women per day was compared among study groups, at baseline the frequency was similar, however, on later follow-ups Solifinacin group patients were using greater pants (4-6 and 8-10) per day for protection than those patients in the Mirabegron group

(p-value, 0.02). Overall there were significant variations noted on different follow-ups among the two groups. (Table II).

Furthermore, the tolerability of the drugs was compared among the two groups. Slight to moderate symptoms of drowsiness as sedation were experienced by significantly more patients in the Solifinacin group (<0.001), however, severe symptoms were found in fewer patients in the Mirabegron group as well (0.04). In the same way moderate to severe change in bowel movements as constipation were experience by more patients in the Solifinacin group after intervention than Mirabegron group (<0.001). Blurring of vision and eye-sight problems were found slight to moderately more in Solifinacin group (0.02), however, few cases in Mirabegron also experience these symptoms severely (p-value, 0.04) Dry mouth was experienced slight to moderately by significantly more patients in the Solifinacin group than those in the Mirabegron group (p-value, 0.02). When asked about encountering any confusion/delirium after medication usage, the majority of the patients in both group mentioned they didn't experienced it, however, few patients in both groups mentioned its encounter (p-value, 0.91). Slight palpitations (high pulse and heart rates) were experienced by more patients in Solifinacin group (14.2% vs 0.0%) (p-value, 0.03), however, moderate level palpitations were also experience by more patients in the Mirabegron group (6.3% vs 0.0%) (p-value, 0.04). There were significant variations noted in the tolerability between the two drugs on various follow-up visits. (Table III)

Discussion

Over active bladder (OAB) and/or urge incontinence are common presentations in older women after menopausal status. The condition has many psychological, medical and social effects for this group of women. A new class of drugs approved for OAB is Mirabegron, a β3 receptor agonist. The management of this chronic condition is often limited by lack of patient adherence to medications due to low tolerance.[1,2]

Table II: Comparison of efficacy of interventions in the two groups.

	Mirabegron (n=63)		Solifinacin (n=63)		p-value
	Baseline	Final Follow-up	Baseline	Final Follow-up	
How often does urine leak before you can get to the toilet?					
Never/not now	0 (0.0%)	30 (47.6%)	0 (0.0%)	26 (41.2%)	0.04
Once or less per week	0 (0.0%)	5 (7.9%)	4 (6.3%)	4 (6.3%)	0.01
More than once a week	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (6.3%)	0.72
Once a day	4 (6.3%)	28 (44.4%)	0 (0.0%)	29 (46.0%)	0.003
Several times a day	59 (93.6%)	0 (0.0%)	59 (93.6%)	0 (0.0%)	0.02
Every time	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
How much urine usually leaks before you can get to the toilet?					
A few drops or none	12 (19.0%)	55 (87.3%)	4 (6.3%)	51 (81.0%)	0.02
Enough to make underpants/pads wet	9 (14.3%)	8 (12.6%)	18 (28.6%)	12 (19.0%)	0.01
Enough to wet outer clothes	38 (60.3%)	0 (0.0%)	41 (65.1%)	0 (0.0%)	0.78
Urine runs down legs onto floor	4 (6.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.02
What type of protection do you use for your urine leakage?					
None	35 (55.5%)	55 (87.3%)	18 (28.5%)	51 (81.0%)	0.59
Underpants liners or mini-pads	0 (0.0%)	8 (12.6%)	25 (39.6%)	12 (19.0%)	0.001
Maxi-pads	8 (12.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.04
Incontinence pads	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.03
Diapers	20 (31.7%)	0 (0.0%)	20 (31.7%)	0 (0.0%)	0.02
No of protection garments used for urine leakage per day?					
2 or less	43 (68.2%)	63 (100.0%)	23 (29.1%)	55 (87.3%)	0.04
4-6	12 (19.0%)	0 (0.0%)	16 (25.3%)	8 (12.6%)	0.02
8-10	8 (12.6%)	0 (0.0%)	24 (31.7%)	0 (0.0%)	0.01
How often do you urinate at night?					
Do not urinate at night	12 (19.0%)	55 (87.3%)	54 (85.7%)	50 (79.3%)	0.34
1-2 times per night	0 (0.0%)	0 (0.0%)	9 (14.2%)	0 (0.0%)	0.008
3-4 times per night	51 (80.9%)	8 (12.6%)	0 (0.0%)	13 (20.6%)	0.11
What is the number of micturations per 24 hours?					
1-2	13 (20.6%)	38 (60.3%)	5 (7.9%)	20 (31.7%)	0.007
3-4	11 (17.4%)	16 (25.3%)	1 (1.5%)	35 (39.6%)	0.02
5-6	13 (20.6%)	9 (6.3%)	8 (12.6%)	8 (12.6%)	0.04
6-8	26 (41.3%)	0 (0.0%)	49 (77.8%)	0 (0.0%)	<0.001

Table III: Comparison of tolerability of interventions in the two groups.

	Mirabegron (n=63)		Solifinacin (n=63)		p-value
	Baseline	Final Follow-up	Baseline	Final Follow-up	
Do you experience drowsiness in the form of sedation by using medicines?					
Not at all	51 (80.9%)	59 (93.6%)	37 (58.7%)	39 (62.0%)	<0.001
Slightly	4 (6.3%)	4 (6.3%)	12 (19.0%)	0 (0.0%)	0.04
Moderately	4 (6.3%)	0 (0.0%)	8 (12.7%)	24 (38.0%)	<0.001
Greatly	4 (6.3%)	0 (0.0%)	6 (9.5%)	0 (0.0%)	0.04
Have you felt any change in your bowel habits like constipation by using medications?					
Not at all	48 (76.1%)	36 (57.1%)	34 (54.0%)	20 (31.7%)	<0.001
Slightly	9 (14.3%)	14 (22.2%)	17 (27.0%)	4 (6.3%)	0.16
Moderately	0 (0.0%)	13 (20.6%)	12 (19.0%)	21 (33.3%)	<0.001
Greatly	6 (9.5%)	0 (0.0%)	0 (0.0%)	18 (28.5%)	<0.001
Do you suffer from eye-sight problems like blurring of vision?					
Not at all	48 (76.1%)	59 (93.6%)	40 (63.4%)	59 (93.6%)	<0.001
Slightly	7 (11.1%)	4 (6.3%)	14 (22.2%)	4 (6.3%)	0.02
Moderately	4 (6.3%)	0 (0.0%)	4 (6.3%)	0 (0.0%)	0.99
Greatly	4 (6.3%)	0 (0.0%)	5 (7.9%)	0 (0.0%)	0.04
Have you encountered any symptoms of dry mouth by using medicines?					
Not at all	13 (20.6%)	55 (20.6%)	30 (47.6%)	43 (68.3%)	<0.001
Slightly	0 (0.0%)	4 (6.3%)	9 (13.3%)	12 (19.0%)	0.04
Moderately	36 (57.1%)	4 (6.3%)	15 (61.9%)	8 (12.7%)	0.02
Greatly	14 (22.2%)	0 (0.0%)	9 (61.9%)	0 (0.0%)	0.81
Do you experience confusion /delirium by using medicines?					
Not at all	59 (93.6%)	63 (100.0%)	58 (92.0%)	55 (26.9%)	0.09
Slightly	4 (6.3%)	0 (0.0%)	5 (7.9%)	4 (0.0%)	0.91
Moderately	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0.04
Greatly	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (6.3%)	0.04
Have you encountered any Palpitations (increase in Pulse, Heart Rate) by using medicines?					
Not at all	48 (76.1%)	59 (93.6%)	62 (98.4%)	54 (85.7%)	0.05
Slightly	15 (23.8%)	0 (0.0%)	1 (1.6%)	9 (14.2%)	0.03
Moderately	0 (0.0%)	4 (6.3%)	0 (0.0%)	0 (0.0%)	0.04
Greatly	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-

In this study, the mean age of patients was slightly greater in the Solifinacin group (45.3 vs 43.0 years) compared to Mirabegron group. Previous evidence also suggest that the prevalence of OAB is greater in older patients over 75 years of age.[15] In most of the counties where Mirabegron is licensed for use the age bracket for use is patients over 30 years of age.[14] Another study by Batista et al reported mean age of 57 years in their female study population treated for overactive bladder.[16] Urge incontinence is an older age condition and this study confirms it further.

In the present study, Mirabegron was found significantly more effective in the management of urge incontinence than Solifinacin. The endpoints of frequency of urinary leak and frequency of micturations per 24 hours has been found significantly less after 3 months intervention in Mirabegron group. Many previous studies have also witnessed mirabegron to be more effective. A meta-analysis by Kelleher C and colleagues reported that relief of key OAB symptoms shaped by mirabegron 50 mg is significantly better than placebo, and similar to a variety of common antimuscarinics, with the advantage of significantly fewer bothersome anticholinergic side effects such as dry mouth. They also concluded that combination therapy with 5 mg solifenacin plus 25 or 50 mg mirabegron provides an effectiveness benefit compared with mirabegron 50 mg, with the expected side effects of individual antimuscarinics.[17] The study by Chappel et al 2013 witnessed mirabegron significantly reduced the number of micrurations per 24 hours.[18] Gratzke C and colleagues compared monotherapies of Mirabegron and Solifinacin with its combination treatment and found combination to be more effective, however, in the individual comparison of the two drugs Mirabegron was found superior in significantly reducing the urinary leakage and micturition episodes per 24 hours.[19] Many other similar trials have also witnessed Mirabegron's superiority. Yamaguchi et al from Japan reported that Mirabegron is significantly effective than placebo in the management of patients with OAB.[20]

These evidences suggest that Mirabegron offer some potential benefits over solifenacin for treating incontinence in women with OAB. The benefits are in terms of better efficacy of Mirabeegron. Solifenacin, being an antimuscarinic medication, at times can relax the bladder too much, leading to difficulty urinating, especially in older women while Mirabegron, as a beta-3 agonist, has a lower risk of causing urinary retention. There are instances of significant side effects after antimuscarinic therapy, its effects cause dry mouth, constipation and blurred vision[21]. On the other hand, Mirabegron due to its different mechanism of action has lower risk of these side effects[22]. The advantages of Mirabegron witnessed in this study, need to be further validated in different settings and communities. Though the cost of Mirabegron is greater than Solifenacin but the better effectiveness and compliance make it a superior choice. And this way in the longer run through better effects, Mirabegron reduces burden over the individuals and healthcare system.

Many other similar studies by Herschorn et al. 2013; and Nitti et al. 2013 have also witnessed a similar effect of Mirabegron and Solifenacin[23,24]. Evidence suggests that Solifenacin and Merabegron reduce and control the urinary symptoms like frequency, urgency and incontinence in an over active bladder. This leads to improved quality of life of the older age women[16,25]. Though similar effect has been witnessed by some investigators, the safety profile of both therapies differ significantly. The practitioners should prescribe both drugs, keeping in view individual condition and demands of patients. Overall, comparative evidence suggests that Mirabegron has significant advantages over its competitors. It has better efficacy and tolerability as witnessed and validated by the current study as well.

The present study has many advantages; firstly, urinary incontinence is a very embarrassing condition for affected women and this study compared two interventions to address the issue of women with incontinence. Secondly, a reasonable sample of subjects was achieved and compared in the two study arms. The limitations are related to the COVID-19 period where patient presentation became limited and study was extended further for a year.

Conclusion

Based on the current study findings it is concluded that Mirabegron is better than Solifinacin in the treatment of urge incontinence in older women. The efficacy of Mirabegron in reducing the frequency of urine leakage and micturation per 24 hours was better than Solifinacin. Furthermore, Mirabegron was found more tolerable. Thus it is suggested that in the local health facility Mirabegron can be safely and effectively utilized in women with chronic condition of urge incontinence.

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