Original Article

Therapeutic effectiveness and adverse drug reactions of mirabegron versus solifenacin in the treatment of overactive bladder syndrome

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Abstract

Introduction: Overactive bladder (OAB) syndrome is a chronic disease characterized by urinary urgency with or without urge incontinence, frequency, and nocturia and antimuscarinic drugs such as solifenacin have been the mainstay of treatment. Mirabegron a beta 3 adrenoreceptor agonist has recently gained importance in the management of OAB. The rationale of the study is that mirabegron improves the storage function without affecting voiding which increases the therapeutic effectiveness. The objective was to determine the therapeutic effectiveness of mirabegron versus solifenacin.

Methods: A prospective observational study was conducted on 298 patients with OAB syndrome attending the urology outpatient department of government medical college after obtaining institutional review board clearance. Patients of both genders, belonging to the 18–65 years of age group, attending the urology outpatient department were selected for the study. Patients were evaluated using the OAB-validated 8-question awareness tool (OAB-V8 score) before and after receiving drugs by direct questionnaire method after receiving informed consent. Patients were prescribed either solifenacin 5 mg or mirabegron 25 mg once daily by the urologist. Follow-up was done after 4 and 12 weeks. Adverse drug reactions of the drugs were assessed using the Central Drug Standard Control Organization suspected adverse reaction (ADR) form, and ADRs were notified to the nearest ADR monitoring center.

Results: The mirabegron group showed maximum improvement in the mean OAB-V8 score values from baseline at 4 weeks (12.82 ± 5.86, $P < 0.001$) and 12 weeks (5.74 ± 3.31, $P < 0.001$) when compared to solifenacin. OAB-V8 scores of the solifenacin group also showed significant improvement from the baseline at 4 weeks (15.30 ± 5.54, $P < 0.001$) and 12 weeks (8.05 ± 4.59, $P < 0.001$). Heart rate, systolic, and diastolic blood pressures did not show significant changes during the follow-up in both the study groups. Thirteen patients developed ADRs such as dry mouth (four patients) and constipation (nine patients) in the solifenacin group. No ADRs were noted in the mirabegron group.

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Conclusion: Mirabegron showed maximum improvement in the OAB-V8 scores in patients with OAB syndrome, although the solifenacin group also showed improvement. Adverse effects were less in the mirabegron group when compared to the solifenacin group.

Keywords: Antimuscarinic agent, beta 3 adrenoreceptor agonist, mirabegron, overactive bladder validated 8-question awareness tool score, overactive bladder syndrome, solifenacin

INTRODUCTION

Overactive bladder (OAB) syndrome is defined by the International Continence Society as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection, or any other obvious pathologies.[1] OAB affects both genders and all ages, but the prevalence tends to increase with age. OAB affects daily activities and nocturnal bladder control, which can affect sleep.[1] Despite this negative burden on society, its underlying pathophysiology is not yet fully understood, which complicates the development of targeted therapeutic interventions. OAB symptoms are commonly attributed to involuntary bladder muscle contractions known as detrusor overactivity (DO). Hence, the link between OAB symptoms and DO represents the simplistic way to understand the multifactorial pathophysiological mechanisms.[2] Current treatment includes behavioral therapy, pharmacological treatment, minimally invasive procedures, and surgeries.[3] Antimuscarinic drugs such as solifenacin succinate are still the mainstay of treatment as they relax the detrusor muscle and reduce the sensory symptoms during the storage phase of the micturition cycle by inhibiting the muscarinic receptor subtypes M2 and M3.[4] Anticholinergic side effects such as dry mouth and constipation are the major reason for its discontinuation.[4] β3 adrenoreceptors are also predominantly present over the detrusor muscle and urothelium.[5] Beta adrenoreceptor agonists like mirabegron act by relaxing the detrusor muscle during the storage phase of the micturition cycle without affecting other voiding parameters such as maximum urinary flow rate (Q_{max}), detrusor pressure at Q_{max}, and residual volume of urine.[5] Major adverse effects of mirabegron include hypertension, nausea, headache, increased pulse rate >10 beats/min regardless of dose/food, nasopharyngitis, and urinary tract infection.[6] A mixed-treatment comparison study showed that mirabegron had better patient compliance than other antimuscarinic drugs because it exhibited fewer adverse effects.[6] The objective was to determine the therapeutic effectiveness of mirabegron versus solifenacin in the treatment of OAB syndrome using the OAB-validated 8-question awareness tool (OAB-V8). The OAB-V8 is a brief, self-administered patient-reported outcome questionnaire with good predictive validity designed to make patients aware of their urinary symptoms and to screen for the presence of OAB.[7,8]

METHODS

A prospective observational study was conducted in the Department of Urology of a Government Medical College in Central Kerala from December 1, 2019, to June 1, 2021 (18 months) in patients with OAB syndrome, who received solifenacin or mirabegron. After getting approval from the institutional review board (IRB number: 112/2019), patients of any gender, belonging to the 18–65 years of age group, who gave informed consent, and attended the outpatient department were selected for the study. Patients with hypersensitivity and other contraindications for the use of mirabegron and solifenacin, known cases of cardiac/hepatic/renal disease, hypertension (blood pressure [BP] ≥140/90 mmHg),[9] patients receiving medications such as tricyclic antidepressants, typical antipsychotics, and atypical antipsychotics were excluded from the study. Demographic data were recorded as per the information provided by the patients themselves. Patients were evaluated using the OAB-V8 score before and after receiving drugs by direct questionnaire method. Patients were prescribed solifenacin

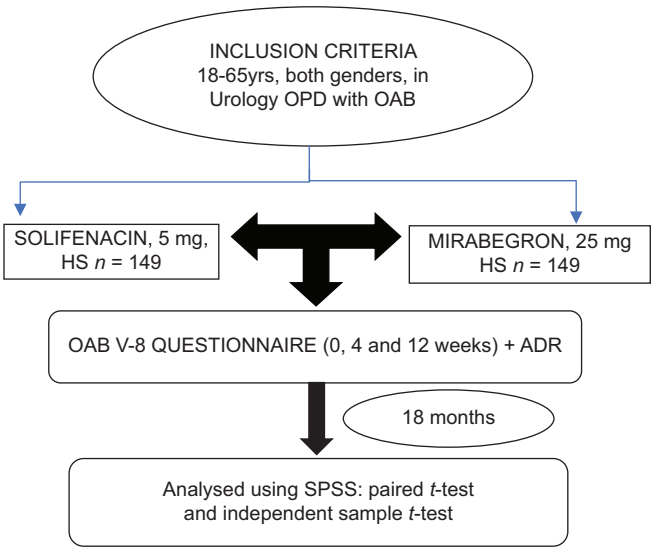

Figure 1: Flowchart of methodology, OPD = Outpatient department, OAB = Overactive bladder, OAB-V8 = OAB validated 8-question awareness tool, ADR = Adverse reaction

5 mg and mirabegron 25 mg once daily and were followed up after 4 and 12 weeks. Adverse drug reactions of the drugs were assessed using the Central Drug Standard Control Organization adverse reaction (ADR) form and were notified to the adverse drug reaction monitoring center.

Data were entered into an Excel spreadsheet and analyzed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corporation (trial version). Values of OAB-V8 score, systolic pressure, diastolic BP, and heart rate were tested for normality and were found to be normally distributed. Quantitative variables were expressed as mean and standard deviation. Follow-up visits between the baseline and each visit were analyzed using a paired *t*-test and a comparison between the two groups was done using an independent sample *t*-test and statistical significance was fixed at $P < 0.05$ [Figure 1].

RESULTS

The total number of participants was 298 with 149 in each group. The mean age of participants was 52.70 ± 11.68 years and 51.56 ± 12.39 in the solifenacin and mirabegron groups, respectively. About 66.44% of the solifenacin group and 65.77% of the mirabegron group belonged to 50–65 years. Both groups were comparable at baseline as suggested by $P > 0.05$ on doing an independent sample *t*-test. When comparing the duration of lower urinary tract symptoms (LUTS) among both the groups, 47.65% of the solifenacin group and 40.9% of the mirabegron had LUTS for 4–6 months. On doing a Chi-square, the duration of LUTS was comparable with $P = 0.31$. Similarly, heart rate and systolic and diastolic BP were comparable in both groups, as shown in Table 1. On determining the Pearson's correlation of age as well as gender with OAB outcome at 12 weeks, we could not find any correlation ($r = -0.033$ [gender], $r = 0.06$ [age]).

Table 1: Baseline characteristics

	Solifenacin	Mirabegron	*P*
Age (years)	52.70±11.68	51.56±12.39	0.41
OAB-V8	28.07±5.89	28.89±6.50	0.26
HR	69.64±4.28	70.12±4.05	0.32
SBP (mmHg)	128.94±9.78	126.98±8.91	0.07
DBP (mmHg)	80.03±3.85	79.28±3.81	0.09

OAB-V8=Overactive bladder validated 8-question awareness tool, BP=Blood pressure, HR=Heart rate, SBP=Systolic BP, DBP=Diastolic BP

When comparing the OAB-V8 score of solifenacin at baseline and 4 weeks, as shown in Table 2, a mean difference of 12.77 ± 5.14 was found which was statistically significant with a $t = 30.29$ and $P < 0.001$. At 12 weeks, the mean ± standard deviation [SD] of the OAB-V8 score declined to 8.05 ± 4.59 when compared with the baseline ($t = 39.860$, $P < 0.001$).

When comparing the OAB-V8 score of the mirabegron group at baseline and 4 weeks, it showed a mean difference of 16.07 ± 4.78 which was found to be statistically significant with $P < 0.001$. At 12 weeks, the mean ± SD of the OAB-V8 score declined to 5.74 ± 3.31 when compared with the baseline. It was found to be statistically significant with a mean difference of 23.154 ± 5.549, $t = 22.950$, and $P < 0.001$, as shown in Table 2.

On comparing the OAB-V8 (4 weeks) score among both the drug groups, the mean and standard deviation in solifenacin and mirabegron were 15.30 ± 5.54 and 12.82 ± 5.86, respectively. The difference was found to be statistically significant with $P < 0.001$. Similarly, as shown in Table 3, the OAB-V8 (12) score mean difference was statistically significant with $P < 0.001$. However, we could not find statistically significant differences in heart rate, systolic and diastolic BP over the span of 4 and 12 weeks in the solifenacin and mirabegron groups, as demonstrated in Table 3.

There were no serious ADRs in any of the study groups warranting discontinuation of study medication. Thirteen patients developed ADRs during the study which included dry mouth (four patients) and constipation (nine patients) in the solifenacin group. No adverse drug reactions were noted with the mirabegron group. Since the ADRs were mild and did not disturb the routine activities of the patients, neither the drug was stopped nor the dose of the drug was changed.

DISCUSSION

OAB syndrome is a chronic disease that has the potential to greatly impair the quality of life.[10] Guidelines recommend bladder training and lifestyle advice as first-line treatments

Table 2: Comparison of overactive bladder validated 8 scores from baseline in follow-up visits at 4 weeks and 12 weeks for solifenacin and mirabegron

OAB-V8 score	Mean±SD		Mean difference±SD/(95% CI)		*P*	
	Solifenacin group	Mirabegron group	Solifenacin group	Mirabegron group	Solifenacin group	Mirabegron group
Baseline	28.07±5.89	28.89±6.51	12.772±5.147	16.074±4.78	<0.001	<0.001
4 weeks	15.30±5.54	12.82±5.86	11.939–13.605	15.30–16.84		
Baseline	28.07±5.89	28.89±6.51	20.020±6.131	23.15±5.54	<0.001	<0.001
12 weeks	8.05±4.59	5.74±3.31	19.028–21.013	22.25–24.05		

OAB-V8=Overactive bladder validated 8-question awareness tool, SD=Standard deviation, CI=Confidence interval

Table 3: Overactive bladder-validated 8 scores, heart rate, systolic and diastolic blood pressure at 4 weeks and 12 weeks for solifenacin and mirabegron

	Solifenacin	Mirabegron	Mean difference	95% CI of the difference	*P*	*t*
OAB-V8 (4 weeks)	15.30±5.54	12.82±5.86	2.48	1.18–3.78	<0.001	3.75
OAB-V8 (12 weeks)	8.05±4.59	5.74±3.31	2.31	1.40–3.22	<0.001	4.99
HR (4 weeks)	69.54±4.33	70.13±3.89	0.59	−1.53–0.34	0.217	−1.23
HR (12 weeks)	69.58±4.25	70.17±3.92	−0.59	−1.52–0.34	0.214	−1.25
SBP (4 weeks)	128.97±9.82	127.09±8.89	1.87	−0.25–4.01	0.085	1.73
SBP (12 weeks)	128.79±9.81	127.06±8.75	1.73	−0.38–3.85	0.109	1.61
DBP (4 weeks)	79.77±3.48	79.38±3.50	0.38	−0.41–1.18	0.337	0.96
DBP (12 weeks)	79.68±3.37	79.40±3.51	0.28	−0.50–1.06	0.480	0.71

OAB-V8=Overactive bladder validated 8-question awareness tool, HR=Heart rate, SBP=Systolic blood pressure, DBP=Diastolic blood pressure, CI=Confidence interval

for OAB, followed by primary pharmacotherapy using antimuscarinic agents (i.e., darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium), or β3-adrenoreceptor agonist (mirabegron) for OAB.[11,12]

The mean age of the solifenacin and mirabegron groups was 52.70 ± 11.68 and 51.56 ± 12.39 years, respectively, which corroborates with the study done by Mahapatra *et al*.[13] The baseline characteristics in both the groups were comparable for OAB-V8 score, systolic and diastolic BP, and heart rate and it is in line with other studies done. No significant change in the systolic or diastolic BP and heart rate was observed throughout the study as it was in other study groups.[14,15]

Both the drugs showed a statistically significant reduction in OAB-V8 scores at 4 weeks and 12 weeks compared to baseline. The mean OAB-V8 score values were decreased in each follow-up visit for both the drugs, and the maximum improvement was seen with mirabegron. Studies done elsewhere have shown better perception of bladder control in patients with the mirabegron group as well as its combination with solifenacin when compared to solifenacin alone.[13] Even though both the drugs produced comparable relief of symptoms when compared to the placebo, the mirabegron group had fewer side effects.[14] SCORPIO, ARIES, and CAPRICORN were randomized controlled trials that compared mirabegron (at varying doses) with a placebo and tolterodine tartrate Modified release (MR) 4 mg (as an active control in SCORPIO only). The results indicated statistically significant improvements from baseline to week 12 in the mean number of micturition in 24 h in the mirabegron groups.[15]

Chapple *et al*., in a Phase 2 study, showed a significant reduction in the mean number of voids per 24 h, and an increase in the mean volume voided per void in patients taking 5 mg, 10 mg, and 20 mg of solifenacin as compared to placebo.[16] A randomized, multicenter Phase 3 study (SYNERGY II) demonstrated statistically superior efficacy in reducing the number of incontinence episodes and micturition for mirabegron and solifenacin as a combination than their monotherapy.[17] In this study, monotherapy with mirabegron showed more improvement in the OAB-V8 score than solifenacin. Combination therapy was not evaluated.

Schiavi MC *et al*. found clinically relevant improvements in OAB symptoms and quality of life in both groups.[18] Studies done by Kay *et al*. showed that darifenacin and tolterodine do not cross the blood–brain barrier to any significant degree and affect cognitive function.[19] Cognitive impairment has not been reported with solifenacin to date which is in line with this study. The occurrence of ADRs was comparable to a study done by Batista *et al*.[3] Mirabegron was found to be superior to solifenacin with respect to treatment-related adverse events in Sjogren's syndrome patients having OAB syndrome.[20] Kinjo *et al*. found that discontinuation due to side effects was significantly more frequent in the solifenacin group compared to the mirabegron group (27.3% vs. 7.9%, $P < 0.05$). In contrast, discontinuation due to lack of efficacy was significantly more frequent in the mirabegron group than in the solifenacin group (36.8% vs. 5.6%, $P < 0.05$).[21] A study done by Ozkidik *et al*. highlights that mirabegron is safe, effective, and tolerable in the long-term treatment of OAB symptoms in females after surgery for stress urinary incontinence.[22] Constipation and dry mouth were seen in the solifenacin group. No adverse drug reactions were noted in the mirabegron group as compared to solifenacin in this study. However, none dropped out from the study as both the drugs were effective as well as tolerable and the ADRs encountered in the solifenacin group were mild.

The strengths of the study include the prospective design with a follow-up of 12 weeks using a validated OAB V-8 score in a tertiary care center with a huge patient load. The available literature showed an equivalent efficacy of mirabegron with solifenacin, whereas we could demonstrate a better effectiveness profile without confounding due to

age or gender. Hence, mirabegron may be considered the first choice drug for treating OAB syndrome for those who can afford it. However, it was a single-center study without long-term follow-up and we evaluated only monotherapy. Future multicentric studies need to be planned with a larger sample size, long-term follow-up to assess compliance, pharmacoeconomic evaluations, and the effectiveness of combinations of mirabegron with various other anticholinergics.

CONCLUSION

The values of the OAB-V8 score among the solifenacin and mirabegron group were found to be progressively decreasing from the baseline and showing improvement in the subsequent follow-up visits at 4 weeks and 12 weeks. Maximum improvement was seen with mirabegron. Four and nine patients in the solifenacin group developed dry mouth and constipation, respectively, during this study which was reported to the adverse drug reaction monitoring center. No adverse drug reactions were noted in the mirabegron group. Neither the drug was discontinued nor the dose was changed in the solifenacin group as the adverse drug reactions were not bothersome. In this study, mirabegron is superior to solifenacin with respect to therapeutic effectiveness and treatment-related adverse events.

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Conflicts of interest
There are no conflicts of interest.

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