Mirabegrone versus Solifenacine in Treatment of Overactive Bladder in Female Patients in Zagazig University Hospitals

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ABSTRACT

Background: Overactive bladder (OAB) syndrome, consisting of urgency, with or without urgency incontinence, often with frequency (voiding more than eight times in a 24- h period) and nocturia (need to wake up one or more times per night for urination), is a highly prevalent disorder with a significant impact on quality of life (QoL).
Objective: To evaluate the safety and efficacy of mirabegron 50 mg in comparison to solifenacin 5 mg in the treatment of female patients suffering from overactive bladder symptoms.
Patients and Methods: This prospective randomized study was conducted in Zagazig University Hospitals during the period From November 2018 to April 2019. Thirty consecutive female patients aged from 18 to 65 years old were included in this study. **Results:** Mirabegrone significantly was associated with hypertension only in one case, and Solifenacine significantly was associated with blurred vision, constipation and dry mouth. Comparison between mirabegron and solifenacin group according to day and night frequency, urge and urge incontinence pretreatment showed that there was no significant difference between both groups. Comparison between mirabegron and solifenacin groups according to day and night frequency, urge and urge incontinence after taking mirabegrone or solifenacin showed that mirabegron group was significantly lower as regards day and night frequency also in urgency and urgency incontinence post treatment.
Conclusions: Solifenacin and mirabegron were effective in improving over active bladder symptoms. Mirabegron showed greater tolerability with fewer patients discontinuing therapy because of side effects. mirabegron can be considered as the drug with the better balance between efficacy and tolerability in the treatment of OAB.
Keywords: Mirabegrone versus Solifenacine, Overactive bladder (OAB), Urgency incontinence.

INTRODUCTION

Overactive bladder (OAB) syndrome is a symptom complex defined as urinary urgency, usually accompanied by increased daytime frequency and nocturia, with or without urgency incontinence, in the absence of urinary tract infection or other obvious pathology [(1)]. Urgency incontinence is present in approximately one-third of OAB cases**.** Compared to other OAB symptoms, it has the greatest impact on quality of life (QoL), with higher rates of depression, psychological and emotional distress, and social isolation [(2)]**.** Urgency Incontinence is associated with significantly higher health care resource utilization and lower productivity; consequently, incontinence has a major socioeconomic impact [(3)]. OAB with 16.9% of women and 16.0% of men affected and prevalence among patients of both sexes increasing with age. The prevalence of OAB wet was 6.1%, while 10.4% of responders exhibited OAB dry. The prevalences of OAB wet and OAB dry were similar in women (9.3% and 7.6%). However, in men the prevalence of OAB dry was considerably higher than that of OAB wet (13.4% and 2.6%, respectively) [(4)].

Antimuscarinics are still the mainstay of oral pharmacological treatment for OAB, relaxing the detrusor muscle and reducing sensory symptoms during the storage phase of the micturition cycle by inhibiting muscarinic receptor subtypes, M2 and M3. Both subtypes are expressed in multiple tissues, increasing the risk of bothersome, anticholinergic adverse events (AEs) such as dry mouth, which along with lack of efficacy, is the most frequently cited reason for discontinuation of antimuscarinic treatment [(5)].

The β3-adrenoceptor agonist, mirabegron, which acts via a different mechanism of action to antimuscarinic, could potentially improve the efficacy and tolerability balance over current standard of care in the management of OAB. Mirabegron (25–100 mg) consistently demonstrated superiority over placebo with respect to reductions in incontinence episodes and micturition frequency, with a similar incidence of (AEs) as placebo [(6)]**.**

In current clinical practice, patients were often initiated on antimuscarinics however; symptom improvement was often insufficient, leading to dissatisfaction, particularly if incontinence persists. Increasing the antimuscarinic dose often exacerbates anticholinergic adverse events (AEs) that can lead to treatment discontinuation [(7)]. If oral therapy fails, intravesical on abotulinumtoxin A can be used to treat OAB symptoms [(8)], but it is associated with urinary tract infections, fluctuating response, and may require intermittent self-catheterization [(9)]. Other invasive alternatives include percutaneous tibial nerve stimulation and sacral nerve stimulation, but their penetrance in clinical practice is limited [(10)].

This work aimed to evaluate the safety and efficacy of mirabegron 50 mg in comparison with solifenacin 5 mg in the treatment of female patients suffering from overactive bladder symptoms.

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PATIENTS AND METHODS

From November 2018 to April 2019, thirty consecutive patients (all were female) aged from 18 to 65 years old with over active bladder syndrome were enrolled in this prospective, randomized (closed envelop) study.

Patients were divided randomly into 2 groups of 15 patients each using one to one randomization method: **In group A,** the patients received mirabegron 50 mg once a day for 12 weeks. **In group B,** the patients received solifenacin succinate 5 mg once a day for 12 weeks.

Inclusion criteria: Gender: female, age of 18 years to 65 years, patient with symptoms of OAB for ≥ 3 months associated with at least 2 incontinence episodes and patients who were prescribed previous medication will enter a 2-4 weeks to wash out previous medication.

Exclusion criteria: Progressive neurological disease such as parkinsonism, post voiding residual urine more than 150 cc, uncontrolled narrow angle glaucoma and hypertensive patient.

Ethical approval and written informed consent:

An approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Physical Examination.

Local Examination.

Examination of external genitalia:

Pelvic examination in female is performed with the patient in lithotomy position during relaxation and during cough and Valsalva and should include inspection (labia and introitus, urethral meatus, stress examination for pelvic organ prolapse (pop)

Investigations:

- **Urine analysis, urine culture for** UTI & hematuria.
- Blood urea & serum creatinine.
- **Pelvi-abdominal Ultra sound: to** detect bladder capacity pre and post voiding, stone or bladder anomalies.
- Post void residual volume (PVR: ml).

In each of the two arms patients evaluated first by OABSS and abd u/s (post voiding residual urine) , then prescribe the drug for 12 weeks then after 12 weeks we repeat OABSS and (PVR).

Statistical analysis

Analysis of the collected data was performed using IBM© SPSS© Statistics version 23 (IBM© Corp, Armonk, NY, USA). Qualitative data were introduced as number and percentages whereas quantitative data were presented as mean ± standard deviations and ranges. The comparative studies between 2 quantitative data groups were examined by t-test or ANOVA and Chi-square test was used for qualitative data. Fisher's exact test was used to compare differences between categorical data, which are presented as number and percentage. Correlations among numerical variables were examined using the Pearson correlation. Correlation between two quantitative variables in one group was done using linear Correlation coefficient. Diagnostic accuracy of continuous variables was examined using Receiver operator characteristic curve (ROC) analysis. P-value ≤ 0.05 was considered significant.

RESULTS

Table (1): PVR distribution at different times pre- and post-treatment between studied groups

	Mirabegrone	Solifenacine	t	P
PVR pre treatment	**51.73 ± 16.8**	**51.26±20.1**	**-0.777**	**0.444**
PVR 1m	**51.93 ± 13.7**	**51.8 ± 15.9**	**-1.177**	**0.249**
PVR 2m	**53.2 ± 11.7**	**53.1 ± 16.2**	**-0.496**	**0.532**
PVR 3m	**55.53 ± 11.1**	**55.45 ± 16.3**	**-0.556**	**0.421**

There was no significant difference between groups regarding PVR pre and post treatment. Both groups significantly increased from pre-treatment to 3 months post-treatment.

Table (2): OABS score distribution at different times pre and post treatment between studied groups

	Mirabegrone	Solifenacine	t	P
OABS score pre treatment	**10.93 ± 3.01**	**9.66 ± 3.26**	**1.104**	**0.279**
OABS score 1m	**9.2 ± 2.65**	**9.53 ± 2.64**	**-0.345**	**0.733**
OABS score 2m	**7.6 ± 2.58**	**9.06 ± 2.01**	**-1.732**	**0.094**
OABS score 3m	**6.86 ± 2.31**	**7.66 ± 1.58**	**-2.188**	**0.036***

There was no significant difference between both groups regarding OABS score at pre-treatment, 1-month or 2 months but mirabegrone was significantly lower at 3 month and was distributed as 6.86 ± 2.31 and 7.66 ± 1.58 respectively. Both groups significantly decreased from pre-treatment to 3 months post treatment.

Table (3): Complication distribution between studied groups

			Group		X^2	P
			Mirabegrone	Solifenacine		
Complications	No	N	14	11	1.68	0.19
		%	93.3%	73.3%		
	Blurred vision	N	0	1	4.8	0.021*
		%	0.0%	6.7%		
	Constipation	N	0	1	4.8	0.021*
		%	0.0%	6.7%		
	Dry mouth	N	0	2	11.46	0.0007**
		%	0.0%	13.4%		
	Hypertension	N	1	0	4.8	0.021*
			6.7%	0.0%		
Total		N	15	15		
		%	100.0%	100.0%		

Mirabegrone significantly was associated with hypertension only in one case. Patients' blood pressure was 170/80, controlled. **Solifenacine** significantly associated with blurred vision, constipation and dry mouth.

Table (4): OABS score items of frequency and urgency distribution at pre-treatment between studied groups

			Group		Total	X^2	P
			Mirabegrone	Solifenacine			
Frequency day pre- treatment	≤7	N	3	4	7	1.29	0.52
		%	20.0%	26.7%	23.3%		
	8-14	N	5	7	12		
		%	33.3%	46.7%	40.0%		
	≥15	N	7	4	11		
		%	46.7%	26.7%	36.7%		
Frequency Night pre-treatment	Zero	N	3	5	8	0.79	0.85
		%	20.0%	33.3%	26.7%		
	One	N	6	5	11		
		%	40.0%	33.3%	36.7%		
	Two	N	3	3	6		
		%	20.0%	20.0%	20.0%		
	Three	N	3	2	5		
		%	20.0%	13.3%	16.7%		
Urgency pre-treatment	< 1 /week	N	6	6	12	0.93	0.81
		%	40.0%	40.0%	40.0%		
	≥ 1 / week	N	4	6	10		
		%	26.7%	40.0%	33.3%		
	Once /day	N	3	2	5		
		%	20.0%	13.3%	16.7%		
	≥ 2 /day	N	2	1	3		
		%	13.3%	6.7%	10.0%		
Urgency incontinence Pre-treatment	None	N	5	5	10	2.01	0.73
		%	33.3%	33.3%	33.3%		
	< 1 /week	N	2	5	7		
		%	13.3%	33.3%	23.3%		
	≥ 1 / week	N	3	2	5		
		%	20.0%	13.3%	16.7%		
	Once /day	N	2	1	3		
		%	13.3%	6.7%	10.0%		
	≥ 2 /day	N	3	2	5		
		%	20.0%	13.3%	16.7%		
Total		N	15	15	30		
		%	100.0%	100.0%	100.0%		

Comparison between mirabegron and solifenacin groups according to day and night frequency, urge and urge incontinence pre-treatment, there was no significant difference between the 2 groups

Table (5): OABS score items of frequency and urgency distribution at post treatment between studied groups

			Group		Total	X^2	P
			Mirabegrone	Solifenacine			
Frequency day post treatment	**≤7**	N	12	6	18	5.0	0.025*
		%	80.0%	40.0%	60.0%		
	8-14	N	3	9	12		
		%	20.0%	60.0%	40.0%		
	≥15	N	0	0	0		
		%	0.0%	0.0%	0.0%		
Frequency night post treatment	**Zero**	N	12	5	17	6.66	0.036*
		%	80.0%	33.3%	56.7%		
	One	N	2	7	9		
		%	13.3%	46.7%	30.0%		
	Two	N	1	3	4		
		%	6.7%	20.0%	13.3%		
	Three	N	0	0	0		
		%	0.0%	0.0%	0.0%		
Urgency post treatment	**< 1 /week**	N	10	6	16	3.93	0.26
		%	66.7%	40.0%	53.3%		
	≥ 1 / week	N	3	7	10		
		%	20.0%	46.7%	33.3%		
	Once /day	N	1	2	3		
		%	6.7%	13.3%	10.0%		
	≥ 2 /day	N	1	0	1		
		%	6.7%	0.0%	3.3%		
Urgency incontinence post treatment	**None**	N	11	5	16	6.79	0.045*
		%	73.3%	33.3%	53.3%		
	< 1 /week	N	3	7	10		
		%	20.0%	46.7%	33.3%		
	≥ 1 / week	N	1	1	2		
		%	6.7%	6.7%	6.7%		
	Once /day	N	0	2	2		
		%	0.0%	13.3%	6.7%		
	≥ 2 /day	N	0	0	0		
		%	0.0%	0.0%	0.0%		
Total		N	15	15	30		
		%	100.0%	100.0%	100.0%		

Comparison between mirabegron and solifenacin groups according to day and night frequency, urge and urge incontinence after taking mirabegrone or solifenacin. Mirabegron group was significantly lower regarding day and night frequency also in urgency and urgency incontinence post-treatment.

DISCUSSION

There was no significant difference between groups as regards PVR pre- and post-treatment distribution. Both groups significantly increased from pre-treatment to 3 months post-treatment for: **mirabegrone group** (PVR pre 51.73 ± 16.8), (PVR 1 m 51.93 ± 13.7), (PVR 2 m 53.2 ± 11.7) and (PVR 3 m 55.53 ± 11). **Solifenacine group** (PVR pre 51.26 ± 20.1), (PVR 1 m 51.8 ± 15.9), (PVR 2 m 53.1 ± 16.2) and (PVR 3 m 55.45 ± 16.3).

There was no significant difference between both groups as regards pre-OABS score distribution at pre, 1 month or 2 months but mirabegrone was significantly lower than solifenacine at 3 month and was distributed as 6.86 ± 2.31 and 7.66 ± 1.58 respectively. Both groups significantly decreased from pre-treatment to 3 months follow up.

In the present study, mirabegrone was significantly associated with hypertension only in one case (6.7%) and solifenacine significantly associated with blurred vision in one case (6.7%), constipation in one case (6.7%) and dry mouth in two cases (13.4%).

Periodic monitoring of blood pressure is recommended as it can increase blood pressure especially in hypertensive patients. Although it is not recommended for use in severe uncontrolled hypertensive patients but randomized placebo-controlled studies (data submitted for its approval) showed dose-dependent increase in supine blood pressure in healthy volunteers. Approximately mean maximum systolic/diastolic blood pressure increase was 3.5/1.5 mmHg over the placebo in healthy volunteers as compared to the 1 mmHg increase over placebo in OAB patients [(11)].

In a study by **Schiavi *et al.*** [(12)] and at the follow-up visits, 20 cases (11.7%) and 18 cases (10.5%) taking solifenacin reported constipation and dry mouth, respectively, while these numbers were only 4 cases (2.3%) and 5 cases (2.9%) in patients taking mirabegron, respectively. Many studies have been performed to evaluate the efficacy of solifenacin and mirabegron versus placebo, but only one recent study including male and female patients compared these two treatments and demonstrated similar clinical improvements with a lower incidence of dry mouth with mirabegron [(13)].

In the current study, comparison between mirabegron and solifenacin groups concerning day and night frequency, urge and urge incontinence pretreatment showed that there was no significant difference between groups. Comparison between both groups after taking mirabegrone or solifenacin showed that mirabegron group was significantly lower as regards day and night frequency also in urgency and urgency incontinence post treatment.

In the current study and after 12 weeks of treatment with mirabegrone, the frequency per day (< 7 times per day) increased from 20% (3 cases) to 80% (12 cases), the frequency per day (8-14 times per day) decreased from 33.3% (5 cases) to 20% (3 cases), the frequency per day (> 15 times per day) decreased from 46.7% (7 cases) to zero% (no cases).

In the current study and after 12 weeks of treatment with solifenacin, the frequency per day (< 7 times per day) increased from 26.7% (4 cases) to 40% (6 cases), the frequency per day (8-14 times per day) increased from 46.7% (7 cases) to 60% (9 cases), the frequency per day (> 15times per day) decreased from 26.7% (4 cases) to zero% (no cases).

In the current study the frequency at night in the mirabegrone group after 12 weeks of treatment, the number of patients experienced no frequency at night increased from 20% (3 cases) to 80% (12 cases), the number of patients experienced one episode of frequency at night decreased from 40% (6 cases) to 13.3% (2 cases), The number of patients experienced two episodes of frequency at night decreased from 20% (3 cases) to 6.7% (1 case) and the number of patients experienced three episodes of frequency at night decreased from 20% (3 cases) to zero% (no cases). In the current study, the frequency at night in the solifenacin group after 12 weeks of treatment, the number of patients experienced no frequency at night showed no change {33.3% (5 cases) before treatment and 33.3% (5 cases after treatment). the number of patients experienced one episode of frequency at night increased from 33.3% (5 cases) to 46.7% (7 cases). The number of patients experienced two episodes of frequency at night showed no change {20% (3 cases) before treatment and 20% (3 cases) after treatment} and the number of patients experienced three episodes of frequency at night decreased from 13.3% (2 cases) to zero% (no cases).

In the current study, urgency in the mirabegrone group after 12 weeks of treatment, the number of patients experienced urgency <1/week increased from 40% (6 cases) to 66.7% (10 cases). The number of patients experienced urgency ≥ 1 / week decreased from 26.7% (4 cases) to 20% (3 cases). The number of patients experienced urgency once /day decreased from 20% (3cases) to 6.7% (1 case) and the number of patients experienced urgency ≥ 2/day decreased from 13.3% (2 cases) to 6.7% (1 case). In the current study, urgency in the solifenacin group after 12 weeks of treatment, the number of patients experienced urgency < 1 /week shows no change {40% (6 cases) before treatment and 40% (6 cases) after treatment}, the number of patients experienced urgency ≥ 1 / week increased from 40% (6 cases) to 46.7% (7 cases), the number of patients experienced urgency once /day shows no change { 13.3% (2 cases) before treatment and 13.3% (2 cases) after treatment} and the number of patients experienced urgency ≥ 2 /day decreased from 6.7% (1 case) to zero% (no cases).

In the current study urgency incontinence in the mirabegrone group after 12 weeks of treatment, the number of patients experienced no urgency incontinence increased from 13.3% (5 cases) to 73.3% (11 cases). The number of patients experienced urgency < 1 /week increased from 13.3% (2 cases) to 20% (3 cases). The number of patients experienced urgency incontinence ≥

1 / week decreased from 20% (3 cases) to 6.7% (1 case). The number of patients experienced urgency incontinence once /day decreased from 13.3% (2 cases) to zero % (no cases) and the number of patients experienced urgency incontinence ≥ 2 /day decreased from 20% (3 cases) to zero% (no cases). In the current study, urgency incontinence in the solifenacin group after 12 weeks of treatment, the number of patients experienced no urgency incontinence showed no change {13.3% (5 cases) before treatment and 13.3% (5 cases) after treatment}. The number of patients experienced urgency < 1 /week increased from 33.3% (5 cases) to 46.7% (7 cases). The number of patients experienced urgency incontinence ≥ 1/ week decreased from 13.3% (2 cases) to 6.7% (1 case). The number of patients experienced urgency incontinence once /day increased from 6.7% (1 cases) to 13.3% (2 cases). The number of patients experienced urgency incontinence ≥ 2/day decreased from 13.3% (2 cases) to zero% (no cases). In a study by **Schiavi *et al.*** [(12)]**,** and at the end of 12 weeks of treatment, a reduction in the mean number in 24 h of voids (9.78 ± 2.52 vs 6.23 ± 1.54. Urgent micturition episodes /24 h (5.32 ± 1.54 vs 1.32 ± 1.21, nocturia episodes (2.94 ± 0.85 vs 1.09 ± 1.21, and urinary incontinence episodes/ 24 h (0.75 ± 0.86 vs 0.28 ± 0.56, was observed in the solifenacin group. In the mirabegron group, they observed a reduction in the mean number of voids in 24 h (9.21 ± 1.87 vs 5.97 ± 1.67, urgent micturition episodes /24 h (5.11±1.89 vs 1.45 ± 1.11, nocturia episodes (3.13 ± 0.87 vs 0.94 ± 1.13, and urinary incontinence episodes/ 24 h (0.82 ± 1.07 vs 0.30 ± 0.64, but no significant differences were observed between the two groups.

Currently, mirabegron is considered at the same level as solifenacin for the treatment of OAB patients regarding safety and efficacy but the high cost to solifenacin increases the discontinuation rate, although not having the same side effects [(14)]. Therefore, before proceeding with other treatments, such as hormonal or non-hormonal therapy in postmenopausal patients [(12)], or second-level therapies, such as sacral nerve neuromodulation or intravesical botulinum toxin, mirabegron can be considered as the drug with the better balance between efficacy and tolerability in the treatment of OAB**.** In addition, our results showed that mirabegron might be considered first-line pharmacologic therapy in OAB treatment [(15)]. **Hampel *et al.*** [(16)] performed a study aimed to evaluate the efficacy and safety of solifenacin in patients with overactive bladder (OAB). They concluded that solifenacin provided good reduction in all OAB symptoms and was well tolerated in this population of patients aged > 60 years. There was no change in cognitive function in these elderly patients taking solifenacin for 12 weeks and there was no apparent worsening of function in a subgroup of patients with documented dementia at study entry [(16)].

CONCLUSION

Both solifenacin and mirabegron were effective in improving over active bladder symptoms. Mirabegron showed greater tolerability with fewer patients discontinuing therapy because of side effects. Mirabegron can be considered as the drug with the better balance between efficacy and tolerability in the treatment of OAB.

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