

Solifenacin and Mirabegron Monotherapies Versus Combination Therapy in Overactive Bladder: A Prospective Observational Study

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Overactive bladder (OAB) is a common medical condition, especially in the elderly population, that affects the quality of life. The primary treatment of OAB is a combination of behavioural measures and widely used anti-muscarinic drug therapy like solifenacin, which brings about significant side effects, thereby affecting the quality of life adversely. Mirabegron, a recently approved drug for treatment of OAB is a β_3 - adrenergic agonist, which relaxes the detrusor muscle. With this background, the current study was done to compare the efficacy and safety of solifenacin, mirabegron and combination of low doses of solifenacin and mirabegron on various parameters of OAB. A total no. of 70 patients with OAB symptoms coming to urology OPD were included in this study and they were divided into 3 groups - Group 1: 24 patients receiving solifenacin 10mg/day, Group 2: 23 patients receiving solifenacin 5mg/day plus mirabegron 25mg/day, Group 3: 23 patients receiving mirabegron 50 mg/day. Patients were assessed for change in mean numbers of micturition, urgency, incontinence per 24 hour and quality of life using Patient Perception of Bladder Control (PPBC) Questionnaire. They were followed up after 4 weeks and 12 weeks and change in the above parameters from baseline were noted. Patients receiving combination therapy achieved a significant reduction in urgency, frequency, nocturia and urge incontinence and decrease in side effects when compared with solifenacin and mirabegron alone. Combination therapy with solifenacin and mirabegron significantly improved quality of life and reduced side effects like dry mouth, blurred vision, constipation in OAB patients in comparison to solifenacin and mirabegron monotherapy.

Keywords: Overactive Bladder; Mirabegron; Solifenacin; Quality of life.

Overactive bladder (OAB) is defined as a symptom complex characterised by urinary frequency (≥ 8 micturitions/24 hours) and urgency, with or without urge incontinence and nocturia in the absence of local pathological or metabolic factors that would account for these symptoms.¹ OAB can significantly interfere with daily routines and

health related quality of life (HRQoL), including social, physical and psychological well-being, productivity and sexual health and can cause stress and depression.²

Antimuscarinic (AM) drugs are well-established oral pharmacological treatment for OAB, which relaxes the detrusor muscle and by

inhibiting muscarinic receptor subtypes, M2 and M3 reduces sensory symptoms during the storage phase of the micturition cycle. 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.³

Recent advances in the understanding of OAB have identified three α -adrenoceptor subtypes (α_1 , α_2 , α_3) in the detrusor muscle and urothelium, α_3 being the predominant α -receptor subtype in human urinary bladder.⁴⁻⁸

Mirabegron is the first α_3 adrenoceptor agonist that has been shown to relax the detrusor muscle during the bladder storage phase and increase bladder capacity.⁹

As these agents have different mechanisms of action, combining a α_3 -adrenoceptor agonist with an AM agent may improve efficacy in OAB treatment; combinations with reduced doses may deliver an improved tolerability profile compared with monotherapy, without compromising efficacy.¹⁰

The PPBC (Patient Perception of Bladder Control) Questionnaire, recommended by the EMEA (European Medicine Evaluation Association) is a valid and responsive global measure.¹¹⁻¹²

However, there is paucity of data that demonstrate the effectiveness and superiority of combination therapy over monotherapy.

Aims and Objectives

To evaluate the efficacy and safety of solifenacin and mirabegron monotherapies compared with low dose combination therapy.

METHODS

This prospective, observational & questionnaire-based study was conducted in

the Department of Urology and Department of Pharmacology of V.S.S. Institute of Medical Science & Research, Burla, for a period of 6 months (April-September 2019), after obtaining approval from IEC (Institutional Ethics Committee).

A total number of 70 patients aged ≥ 18 years with OAB symptoms, coming to urology OPD were included in the study after taking written informed consent. They were divided into 3 groups: Group 1: 24 patients receiving solifenacin 10mg/day.

Group 2: 23 patients receiving solifenacin 5mg/day plus mirabegron 25mg/day

Group 3: 23 patients receiving mirabegron 50 mg/day.

They were followed up after 4 weeks and 12 weeks and change in the parameters from baseline were noted. During the follow up period 6 patients from group 1 and 4 patients from group 3 were lost to follow up.

Patients were assessed for change in mean numbers of micturition, urgency, incontinence, nocturia per 24 hour and quality of life using PPBC questionnaire.

Inclusion criteria

Male or female patient ≥ 18 years of age with symptoms of OAB

Exclusion criteria

1. Pregnant / lactating Female
2. Neurogenic bladder.
3. Patient with significant stress/urgency incontinence
4. An indwelling catheter.
5. Patient with diabetic neuropathy.
6. Uncontrolled hypertension.
7. Evidence of a symptomatic UTI, interstitial cystitis, bladder stones, malignant disease of the pelvic organs.
8. Uncontrolled narrow angle glaucoma, urinary or gastric retention.
9. Severe renal impairment or End Stage Renal disease.

Table 1. Age Distribution of Patients with OAB

Age	No./ Percentage of cases
< 25 year	02 (3.33%)
25 – 50 year	15 (25%)
> 50 year	43 (71.67%)
Mean age (Mean \pm SD)	51.3 \pm 12.7

Table 2. Sex Distribution of Patients with OAB

Gender	No./ Percentage of cases
Males	18 (30%)
Females	42 (70%)

Statistical analysis

Statistics have been done using Graph pad prism version 6.0 using ANOVA and non-parametric scales. p-value < 0.05 was taken as statistically significant.

Overall, 70 patients complaining of bladder difficulties had been recruited at the beginning, of which 10 patients were lost to follow

Table 3. Duration of Symptom and Baseline Data of OAB Patients

Baseline Data	Mean ± SD
Duration of symptoms (in months)	38.01± 9.91
Number of micturitions/24hr	9.58± 1.68
Urgency episodes/24hr	3.25± 2.24
Incontinence episodes/24hr	2.11± 1.78
Nocturia/24hr	2.25± 1.12

up. Out of 60 patients, majority of patients belong to age group > 50 years as shown in Table 1.

Out of 60 cases, 18 (30%) were males and 42(70%) were females as presented in Table 2.

The mean duration of symptoms was 38.01± 9.91 months. The baseline micturition data in terms of mean number of micturitions, urgency, incontinence episodes and nocturia has been presented in Table 3.

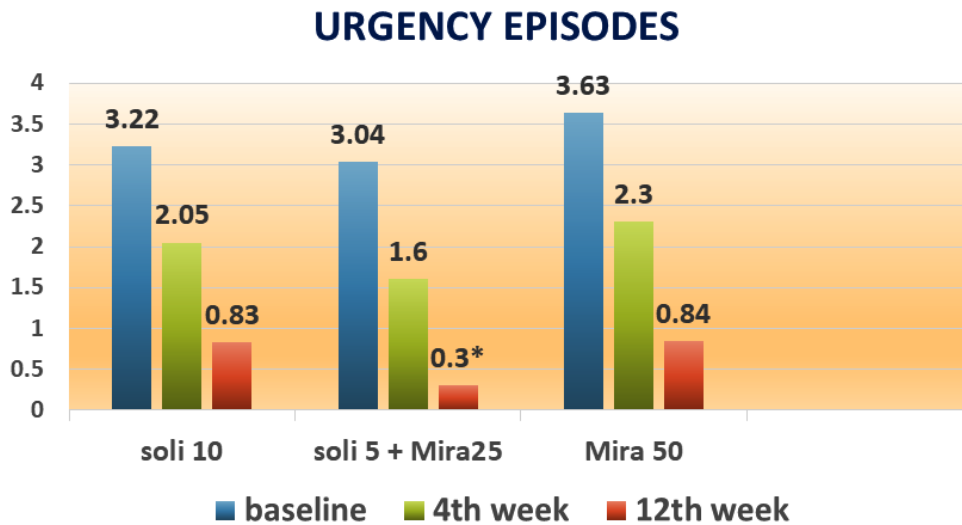
Compared with monotherapies, the combination therapy resulted in a significant improvement in reducing the mean number of micturitions/ 24hr from baseline to End of Treatment (EoT).

Out of all the three groups the frequency of urgency episodes was significantly reduced (3.04-0.3) in patients taking combination therapy as compared to the solifenacin and mirabegron monotherapy.

Table 4. Mean Change in Frequency of Micturition/24hr among Different Drug Groups

	SOLI 10 n = 18	SOLI5+MIRA25 n = 23	MIRA 50 n = 19
Baseline	9.778±0.249	9.793±0.289	9.211±0.554
4 th week (1 st Visit)	8.056±0.235	7.478±0.250	7.316±0.367
12 th week (2 nd Visit)	6.167±0.020	4.696±0.146***	5.474±0.159

Data expressed as mean ± SEM and analysed by ANOVA *P<0.05, (**) P<0.01, (***) P<0.001



Data expressed as mean ± SEM and analysed by ANOVA *P<0.05, (**) P<0.01, (***) P<0.001

Fig. 1. Changes from baseline to EoT in mean no. of urgency episodes/24hr in different groups

In all the treatment groups a trend towards a decrease in mean number of incontinence episodes/24hr was observed from baseline to EoT but the reduction was not statistically significant.

The above graph showed statistically significant improvement in mean no of nocturia episodes/24hr in the patients taking combination therapy.

Patients with major PPBC improvement from baseline to EoT belonged to the combination therapy when compared to the other two monotherapies.

The frequency of antimuscarinic side effects (dry mouth, constipation, urinary retention) had lower incidence in combination therapy compared with solifenacin group. Mirabegron group had more incidence of headache compared to other two groups.

DISCUSSION

OAB is a common and bothersome symptom complex, which significantly affects patient’s quality of life.¹³

The PPBC (Patient Perception of Bladder Control) is a valid and responsive global measure of bladder condition that performs well among patients with OAB. The PPBC was also highly responsive to improvements in micturition frequency, urgency episodes, incontinent episodes, nocturia and patient-reported HRQL.¹¹

In this study the mean age was found to be 51.3 years, which corroborates with the study conducted by Abrams et al which showed mean age to be 54.6 years.¹⁴ This signifies that OAB is more common in older age group. In the present study, majority of study cases were females, mean

Table 5. Change from baseline to EoT in mean no of incontinence episodes/24 hr in all three groups

	SOLI 10 n = 18	SOLI5+MIRA25 n = 23	MIRA 50 n =19
Baseline	1.889±0.386	2.087±0.343	2.368±0.496
4 th week (1 st Visit)	1.222±0.274	0.652±0.161	1.316±0.359
12 th week (2 nd Visit)	0.500±0.166	0.173±0.080	0.368±0.156

Data expressed as mean ± SEM and analysed by ANOVA *P<0.05, (**) P<0.01, (***) P<0.001

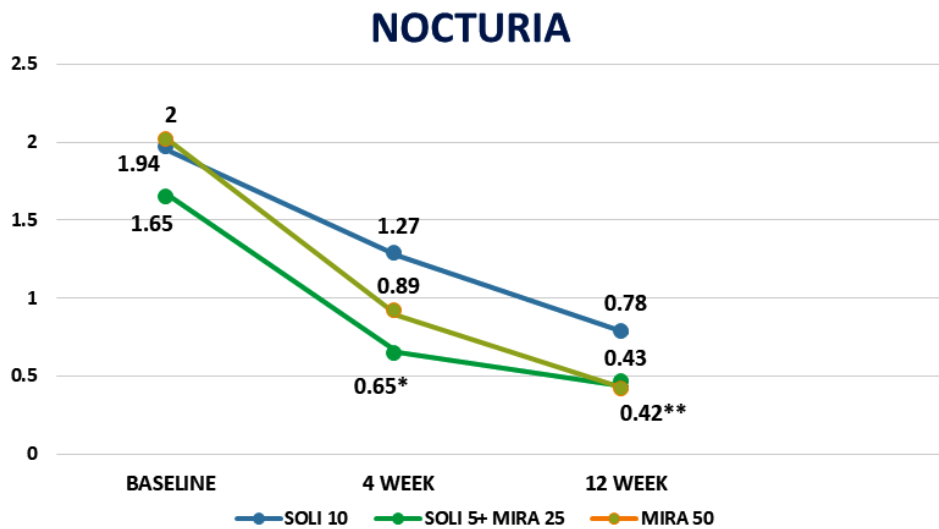


Fig. 2. Mean Change in no of nocturia episodes/24 hr from baseline to EoT

Data expressed as mean ± SEM and analysed by ANOVA *P<0.05, (**) P<0.01, (***) P<0.001

percentage being 71.42 which is similar to a study done by Khuller *et al* where female prevalence was 72%.¹⁵ This reveals that females are more prone for developing OAB related symptoms.

The mean duration of symptoms in this study was 38.01 months which was comparable to a study done by Paul Abrams *et al*, which showed mean value to be 48.5 months.¹⁴

In the current study combination therapy has significantly reduced the mean no. of micturitions /24hr from 9.79 at baseline to 4.69 at 12 weeks (Table 1). A study done by Krauwinkle *et al*, showed that the mean number of micturition was decreased from 10.73 to 8.24.¹⁶

In the present study the mean reduction in urgency episodes/day was from 3.09 to 0.30 in

the combination group, which was statistically significant and better than the findings in a study by Yamaguchi *et al* (2.86 to 1.82).¹⁷

In this study the mean reductions in incontinence episodes shown by the combination group was comparable to the other two monotherapies. No statistically significant difference was seen among different drug groups in reduction of incontinence episodes. This finding corroborates with the study done by Christian Gratzke *et al*.¹⁸

In the current study, the mean reduction in number of nocturia episodes was comparable in two groups that is in combination group (1.6 to 0.4) and mirabegron monotherapy (2 to 0.42) Figure 2. There was statistically significant reduction

Table 6. Mean change in PPBC SCORE from baseline to EoT

	SOLI 10 n = 18	SOLI5+MIRA25 n = 23	MIRA 50 n = 19
baseline	4.444±0.145	4.391±0.163	4.737±0.200
4 th week (1 st Visit)	3.500±0.121	3.217±0.156	2.947±0.178
12 th week (2 nd Visit)	2.222±0.152	1.609±0.104**	1.789±0.144

Data expressed as mean ± SEM and analysed by ANOVA *P<0.05, (**) P<0.01, (***) P<0.001

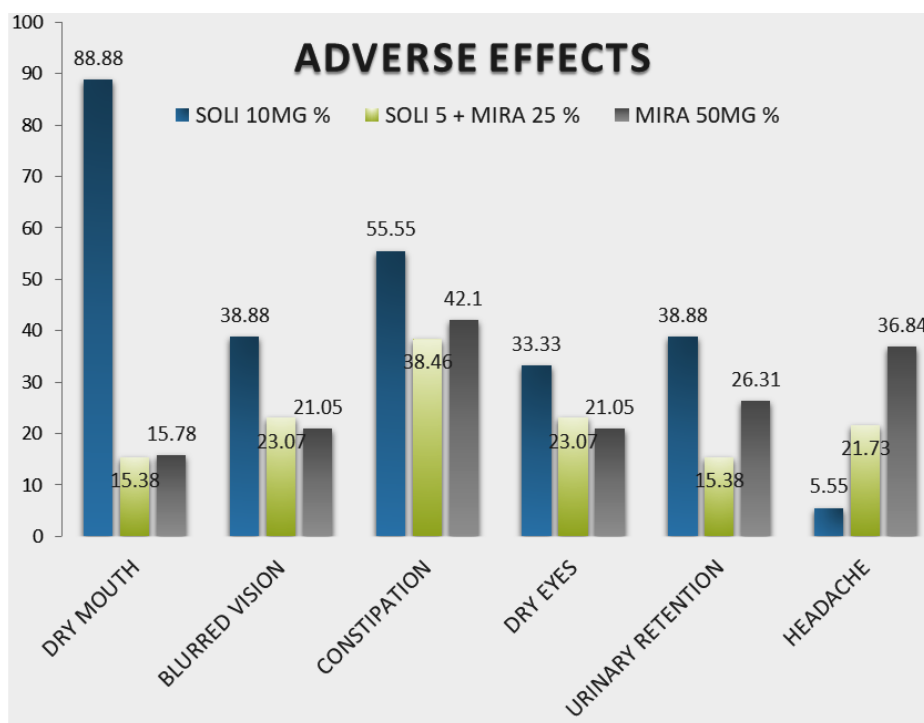


Fig. 3. Adverse Effect Profile of Different Drug Groups

in mean number of nocturia episodes per 24hr in combination group. This finding was in agreement to study done by Yamaguchi *et al.*¹⁷

The mean reduction in PPBC score in the current study improved significantly with combination therapy (4.3 to 1.3) compared to solifenacin group (4.4 to 2.2) and mirabegron group (4.7 to 1.7).

As shown in Figure 3, higher incidence of adverse effects like dry mouth, blurred vision, constipation and urinary retention was seen in solifenacin group as compared to mirabegron and combination group. Incidence of headache was found to be higher in mirabegron group as compared to the other two groups. Occurrence of the above-mentioned adverse effects were comparable to a study done by Jose E. Batista *et al.*¹⁹

Limitation of the study

Small sample size, short follow up duration and the fact that a single item questionnaire cannot provide the depth or breadth of information that can be obtained from multi-item measures.

CONCLUSION

Analysis of combination therapy of solifenacin and mirabegron demonstrated significant improvements over monotherapies (solifenacin 10 mg & mirabegron 50 mg) in frequency of micturition, urgency and nocturia episodes without increasing bothersome adverse effects associated with antimuscarinic therapy. The combination of mirabegron and an antimuscarinic agent may provide an attractive therapeutic approach to maximise efficacy and minimise the side effect burden.

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Conflict of Interest

There is no conflict of interest.

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