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Is Combination Therapy (Mirabegron + Solifenacin) better than Monotherapy (Solifenacin) in the Treatment of OAB?

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Abstract

OAB is a common and distressing chronic bladder condition presenting with symptoms of urinary frequency, urgency, and urge incontinence. Pharmacotherapy with antimuscarinic agents is one of the major treatment options for OAB. Mirabegron in combination with antimuscarinic drugs is being used for treatment-resistant OAB. Given that the two groups have different modes of action, it is logical to think that combination therapy would have advantages over monotherapy.

Purpose: To study the efficacy of combination therapy (Mirabegron + Solifenacin) versus monotherapy (Solifenacin) in the treatment of patients with primary OAB.

Materials and Methods: A Hospital-based prospective observational study was carried out on patients diagnosed with primary OAB. A total of 48 patients were included (24 in each arm).

Results: The median urgency episodes reduced from 6 at baseline to 1 at 12 weeks ($p<0.001$), median frequency episodes from 12.5 at baseline to 6 at 12 weeks ($p<0.001$), median nocturia episodes from 5.5 at baseline to 1 at 12 weeks for ($p<0.001$), median incontinence episodes from 4 at baseline to 0 at 12 weeks for the combination therapy ($p<0.001$).

Conclusions: Combination therapy demonstrated significant improvements over monotherapy in all primary outcome variables measured and may provide an attractive therapeutic approach to maximize efficacy and minimize the side effect burden.

Keywords: Primary OAB; Mirabegron; β 3adrenergic receptor agonist; Solifenacin.

Introduction

Overactive bladder (OAB) is a disorder comprising of symptoms such as urgency, incontinence, frequency, and nocturia.[1] OAB should be seen as a complex, multifactorial symptom syndrome resulting from multiple potential pathophysiological mechanisms. Customized and individualized medical care should be offered which paves the way for better clinical outcomes in OAB.[2] The estimated prevalence among the population 40 years of age is 15.6% and 17.6% for male and female gender respectively. Prevalence in the Indian population is reported to be 14%.[3-6]

OAB is associated with comorbidities and reduced quality of life. Despite its high prevalence, symptoms are significantly underreported due to embarrassment to patients and also because of a lack of awareness of caregivers.[7]

Multiple treatment options exist in the management of OAB. These include lifestyle modifications, bladder retraining, and pelvic floor exercises, pharmacotherapy, botulinum toxin injections, neuromodulation, surgery, and intravesical therapy with capsaicin and resiniferatoxin. Pharmacotherapy can either be used alone or in combination with other forms of therapies. Pharmacotherapy is one of the mainstays of treatment options for OAB.

Inhibition of bladder contractility (antimuscarinic agents and tricyclic antidepressants), improvement of local tissue health (estrogens), and reduction in urine production (desmopressin) are some of the objectives of pharmacotherapy. Oxybutynin, Tolterodine, Propiverine, Solifenacin, Darifenacin, Trospium Chloride, and Fesoterodine form the repertoire of the antimuscarinic class of drugs in current use.

These agents show a paucity of bladder selectivity causing adverse effects like constipation, dry mouth, blurred vision, drowsiness, gastroesophageal reflux, and urinary retention. The impact of these adverse effects is known to have a significant effect on compliance and long term management of OAB.[8] With the current treatment options available satisfactory results have been difficult to achieve. Thus there is a need to identify safer and feasible combination therapies for achieving symptom control and remission in OAB.

Methodology

A prospective observational study was undertaken from November 2017 to September 2019. The patients were included in the study after obtaining written informed consent. The study was approved by the Institution Ethics Committee.

Medical history, neurological examination, urine culture, renal function tests, ultrasonography, micturating cystourethrogram, urodynamic studies, and check cystoscopy was obtained as per the proforma. Baseline urgency, micturition, incontinence frequency, and episodes of nocturia were documented. Socio demographics details were documented as per the proforma.

A total of 48 patients diagnosed to have primary overactive bladder attending Urology Outpatient services were included in the study. The sample size was calculated based on a previous study conducted by Osamu Yamaguchi et al (MILAI study).[9] It was found that 38.2% of patients had a reduction in the frequency of micturition to <8 between 2 drug groups. In the present study expecting the difference of 38% in frequency, considering the power of 80% and alfa error of 5%, the sample size was calculated to be 24 in each arm.

Inclusion criteria

All the patients above 18 years of age of both sexes with symptoms of the overactive bladder more than 3 months.

- Micturition frequency: 8 or > 8 episodes per day.
- Urgency
- Incontinence episodes
- Nocturia episodes: 1 or > 1 micturitions during night sleep.

Exclusion criteria

Conditions causing symptoms similar to overactive bladder. UTI's, uncontrolled DM, neurological conditions like Parkinson's disease, spinal cord causes & causes of peripheral innervation like diabetic cystopathy were excluded in both sexes. In males BPH, stricture disease, meatal stenosis, phimosis & prostatitis were excluded. Functional and behavioral conditions were excluded. Side effects of medications causing symptoms similar to OAB were excluded.

Patients diagnosed with OAB were allotted to treatment groups based on a computer-generated number strip. They were treated with, combination therapy (Mirabegron 25 mg + Solifenacin 5 mg) once a day versus monotherapy (Solifenacin 5 mg) once a day. Outcomes were studied at 4, 8, 12 weeks from initiation of the treatment. Outcomes

measured were a reduction in, frequency of micturition, episodes of incontinence per 24 hrs, nocturia episodes, and those who became continent.

Variables Recorded

(A) Baseline measurements

- Frequency during 24 hours (8 or > 8 micturitions)
- Urgency episodes
- Incontinence episodes during 24 hour periods
- Episodes of nocturia (1 or >1 micturitions)

(B) Outcomes variables measured at 4, 8 and 12 weeks

- Reduction in frequency over 24 hours (< 8 micturitions)
- Reduction in episodes of incontinence (> 50% reduction)
- Reduction in episodes of nocturia
- Reduction in urgency episodes

Statistical Analysis

Frequency, Urgency, Incontinence & Nocturia at different follow up periods were contemplated as primary outcome variables. The study group (Solifenacin alone vs. Mirabegron + solifenacin) was considered as the primary explanatory variable. Age and gender were other explanatory variables.

SPSS version 22 was used for data entry and analysis. Quantitative variables were demonstrated as mean and standard deviation. Frequency and proportion were obtained for categorical variables. Non normally distributed quantitative variables were summarized by the median and interquartile range (IQR). Data was also represented using appropriate diagrams like a bar diagram, pie diagram, and box plots. Shapiro-Wilk test was conducted to assess normal distribution for quantitative variables. Shapiro-Wilk test p-value of >0.05 was considered as a normal distribution.

Students t-test or Mann Whitney test was used to test for the difference of mean values for quantitative variables. The Chi-square test was used to test for differences in proportion between 2 groups.

For non-normally-distributed Quantitative parameters, Medians and Interquartile range (IQR) were compared between study groups using Mann Whitney u test (2 groups). Categorical outcomes were compared between study groups using the Chi-square test. p-value <0.05 was considered statistically significant.

A total of 48 subjects were included in the final analysis.

Results

Patient demographics and baseline characteristics.

In all, the total number of patients with symptoms of OAB who attended the outpatient services were evaluated. In that 48 patients with primary OAB were included in the study, 24 in each study group. No attrition was observed in any of the two study groups (Figure 1).

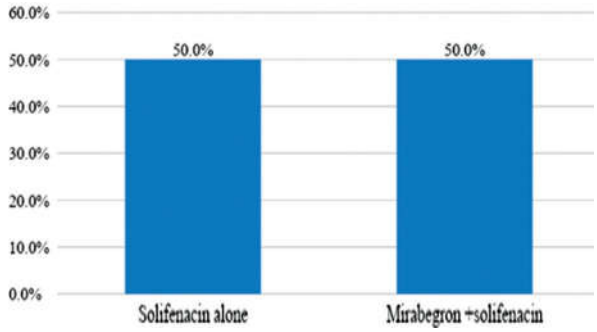

Fig. 1: Bar chart of study group in the study population (N=48).

The mean age of patients in the Solifenacin alone group was 44.29 ± 10.21 years and 38.33 ± 11.25 years in the Combination group. Both groups had a female preponderance (S-75% C-79%). Both the groups were comparable concerning for age (p0.061) and gender (p 0.731) (Figure 2).

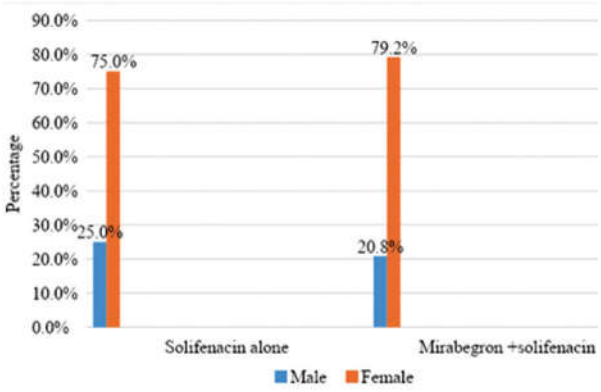

Fig. 2: Cluster bar chart of comparison of gender between study groups (N=48).

The duration and severity of OAB in both groups were more than 3 months. More than 50% of the study population in both groups had no physical comorbidities. The physical comorbidities noted were Diabetes Mellitus, Hypertension, Hypothyroidism, and Ischemic Heart Disease (Table 1).

Table 1: Comparison of comorbidities between study groups (N=48).

Comorbidities	Study Group	
	Solifenacin Alone (N=24)	Mirabegron + Solifenacin (N=24)
Diabetes Mellitus	5 (20.83%)	2 (8.33%)
Diabetes Mellitus/ Hypertension	3 (12.5%)	2 (8.33%)
Diabetes Mellitus/ Hypertension/Ischemic Heart Disease	1 (4.17%)	1 (4.17%)
Diabetes Mellitus/Ischemic Heart Disease	0 (0%)	1 (4.17%)
Hypertension	2 (8.33%)	0 (0%)
Nil	13 (54.17%)	18 (75%)

- No statistical test was performed due to 0 subjects in the cells

Efficacy

Both the study groups demonstrated a decrease in the primary outcome variables. The efficacy for both groups was maintained at the end of 12 weeks.

Frequency

The median frequency episodes reduced from 12.5 (11, 14) at baseline to 6 (6, 7) at 12 weeks for the combination therapy (p<0.001) (Figure 3).

Table 2: Comparison of median of frequency, urgency, incontinence and nocturia baseline and follow-up periods between study groups (N=48).

Frequency	Study group Median IQR		Mann Whitney U test (p-value)
	Solifenacin alone (N=24)	Mirabegron +solifenacin (N=24)	
Baseline	13(12, 14.75)	12.50(11,14)	0.237
At 4 weeks	11(10,12)	10(8.25, 11)	0.002
At 8 weeks	9.50(9, 10.75)	7.50(7, 8.75)	<0.001
At 12 weeks	8(8,9)	6(6,7)	<0.001
Urgency			
Baseline	4(3.25, 5)	6(5,7)	<0.001
At 4 weeks	3(2,4)	3(3,4.75)	0.127
At 8 weeks	2(2,2)	1(1,2)	0.018
At 12 weeks	1(1,1)	1(0.50,1)	<0.001
Incontinence			
Baseline	3 (3,3.75)	4 (3,5)	0.001
At 4 weeks	2 (2,2)	2 (2,3)	0.333
At 8 weeks	1 (1,2)	1 (1,1)	0.015
At 12 weeks	1 (0,1)	0 (0,0)	<0.001
Nocturia			
Baseline	5 (4,6)	5.5 (4.25,7)	0.223
At 4 weeks	3 (2,3)	2 (1,2)	<0.001
At 8 weeks	4 (3,4)	3 (2.25,4)	0.260
At 12 weeks	2 (1.25,2)	1 (1,1)	<0.001

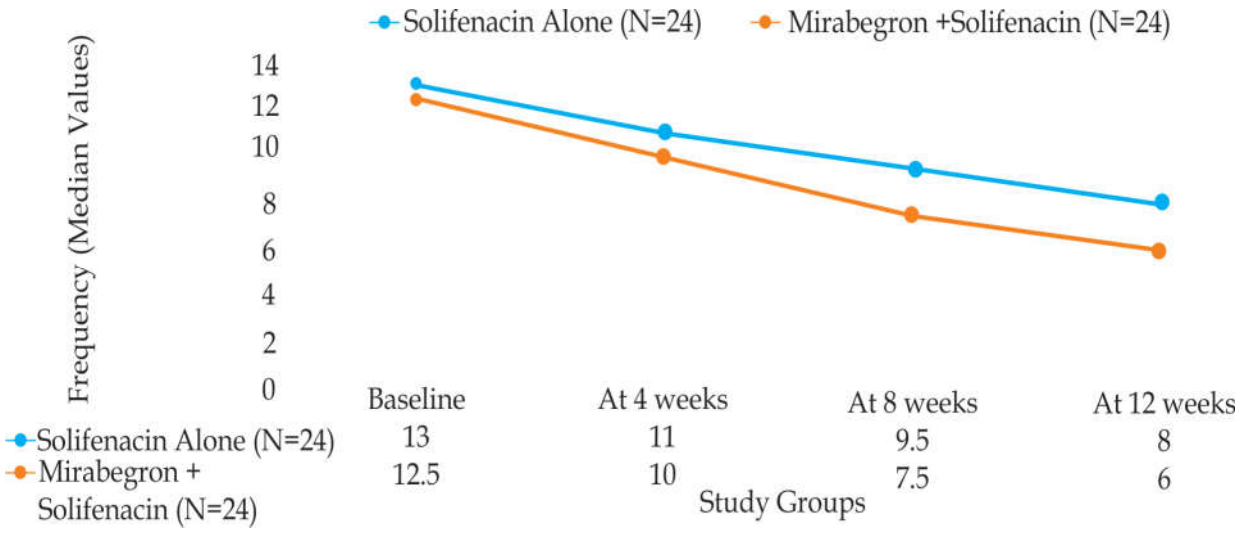

Fig. 3: Comparison of median of frequency baseline and follow-up periods between study groups (N=48).

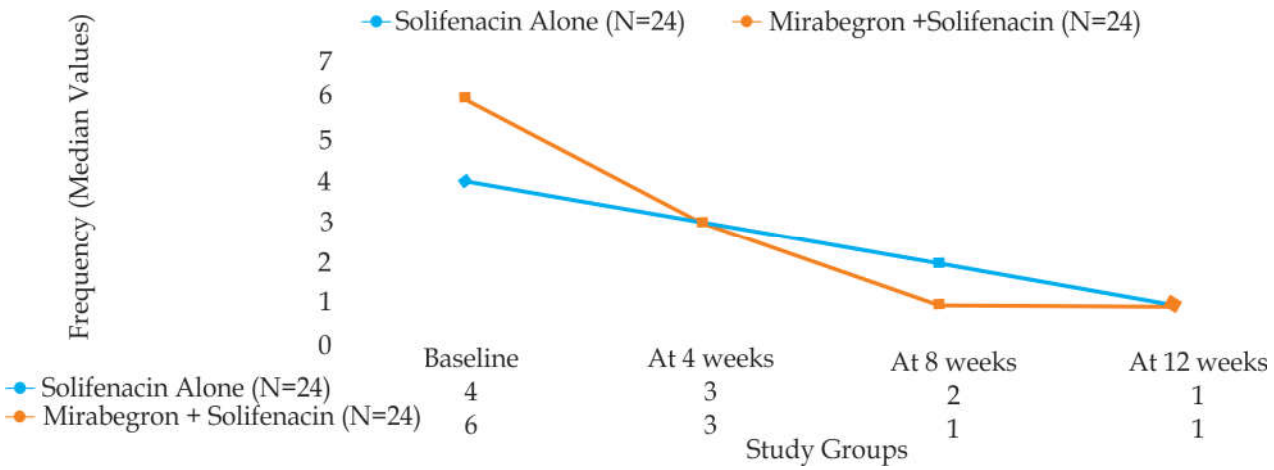

Fig. 4: Comparison of median of urgency baseline and follow-up periods between study groups (N=48).

Urgency

The median urgency episodes reduced from 6 (5, 7) at baseline to 1 (0.5, 1) at 12 weeks for the combination therapy ($p<0.001$) (Table 2) (Figure 4).

Number of Incontinence episodes

The median number of incontinence episodes reduced from 4 (3, 5) at baseline to 0 (0, 0) at 12 weeks for the combination therapy ($p<0.001$) (Table 2).

Nocturia

The median nocturia episodes reduced from 5.5 (4.25, 7) at baseline to 1 (1, 1) at 12 weeks for the combination therapy ($p<0.001$) (Table 2). Overall, the combination group showed significant improvements in urgency, frequency, and the number of incontinence episodes at the end of the 12 weeks.

Safety

The tolerability profile in both the study groups was comparable and not significant. ≈66% of the patients in both the study groups experienced Grade 1 side effects. Most common adverse effect reported by patients was dry mouth and giddiness (Table 3).

Table 3: Comparison of Side effects (SE) between study groups (N=48).

Side effects (SE)	Study Group		Chi square	p-value
	Solifenacin Alone (N=24)	Mirabegron +Solifenacin (N=24)		
Grade 1	15 (62.5%)	16 (66.7%)	0.091	0.763
Grade 2	09 (37.5%)	08 (33.3%)		

Discussion

Primary OAB has always been a difficult condition to treat. The symptoms of OAB are indistinguishable from the lower urinary tract symptoms. It is important to rule out other causes producing similar symptoms such as benign prostatic hyperplasia, vesical calculus, urethral stricture, vaginal prolapse, atrophic vaginitis, interstitial cystitis, neuropathic process, urinary tract infection or genitourinary malignancy before concluding OAB as the primary diagnosis. The symptom of QAB import marked turbulence in the quality of life of the patients.[10]

Mirabegron is a first beta 3 adrenergic receptor agonist to receive approval for the treatment of OAB. It falls under the pharmacotherapeutic group of urological and urinary antispasmodics. Mirabegron is a potent and selective beta 3 adrenergic receptor agonist that acts in contrast to antimuscarinics which act on the parasympathetic pathway. Smooth muscle relaxation during bladder filling is dependent on sympathetic nerve activity and the release of noradrenaline. Beta 3 adrenergic receptors are the predominant beta receptors in the human bladder. Mirabegron induces detrusor muscle relaxation thus allowing for greater bladder filling and reduced frequency of micturition. It does not inhibit bladder emptying which predominantly is effected by parasympathetic control.[10]

For patients with OAB refractory to first-line monotherapy whose symptoms would often progress for invasive therapies, combination therapy offers to be a stand-in treatment. The additive effect is expected to be foreseen when two distinct molecular mechanisms in the regulation of detrusor are targeted. The addition of mirabegron to an antimuscarinic agent conceivably be more effective in controlling urgency compared with antimuscarinic monotherapy alone.[11]

Symphony study had a sample size of 1306 patients with OAB. The study evaluated the efficacy and safety of solifenacin + mirabegron combination therapy (solifenacin 2.5, 5, or 10 mg + mirabegron 25 or 50 mg) compared with each treatment as monotherapy or placebo over 12 weeks. Combination therapy demonstrated significant improvements in mean volume voided (primary endpoint), micturition frequency, and the number of urgency episodes, with minimal adverse effects (with the possible exception of constipation).[12]

Beside study investigated whether the addition of mirabegron to solifenacin 5 mg (combination therapy) was more effective than solifenacin monotherapy in reducing the symptoms of OAB in incontinent OAB patients. The reduction in the mean number of incontinence episodes/24 h was statistically significantly greater with combination therapy (−1.80) compared with solifenacin 5 mg monotherapy (−1.53).[13]

Synergy study evaluated combination treatment with solifenacin 5 mg + either mirabegron 25 mg or 50 mg versus the respective monotherapies or placebo in a large OAB patient population with urinary incontinence. Combination treatment did not achieve a statistically significant effect (p = 0.052) versus mirabegron 50 mg in one of the co-primary endpoints (change from baseline to end of treatment in incontinence episodes/24 h). For the second co-primary endpoint, adjusted change from baseline to end of treatment in micturitions/24 h was greater in the combination therapy groups versus monotherapies, with nominal p values <0.05. Analysis of the mean number of urgency and urgency incontinence episodes showed that the effect size was larger for those who had received OAB treatment before entering the study than for those who were treatment naïve.[14]

Hence this study was undertaken to study the efficacy and tolerability profile of combination therapy of mirabegron and solifenacin in comparison to solifenacin alone. The research about Indian context in the field of OAB has been limited to epidemiological studies. There is a scarcity of evidence related to pharmacological therapies for OAB in the Indian population. Since our study is first of its kind in the Indian population, we found the exploratory open-label study method to be more applicable. The study employed a prospective observational design. The patients of primary OAB were allotted to the two groups using a computer-generated strip to avoid selection bias. The primary outcome variables were assessed for both the groups at baseline, 4 weeks, 8 weeks and 12 weeks. Frequency, Urgency, Nocturia & Incontinence episodes, at different, follow up periods were considered as primary outcome variables. All the endpoints were set in parallel and evaluated comprehensively. All the patients maintained the bladder diary.

Combination therapy demonstrated significant improvements compared with solifenacin monotherapy in all the primary outcome variables. Both treatment arms were well tolerated and concordant with the known safety profile of mirabegron and solifenacin monotherapy. The results of our study are in comparison with the previously conducted randomized trials in terms of efficacy and safety of combination therapy versus solifenacin monotherapy.

The limitations in our study include small sample size, open-label, not having objective measures such as Mean Voided Volume (MVV) as an outcome variable, and recall bias. Nevertheless, our study has demonstrated practical implications that combination therapy is efficacious than monotherapy and the safety profile of combination therapy is in line with monotherapy.

Conclusion

Combination therapy of mirabegron & solifenacin demonstrated significant improvements over monotherapy in all primary outcome variables measured without increasing bothersome adverse effects associated with monotherapy. The combination of mirabegron and solifenacin may provide an attractive therapeutic approach to maximize efficacy and minimize the side effect burden. Further studies with a rigorous randomized control design are warranted to establish a strong database. Cost effect analysis and qualitative studies can also provide unsurmountable support to the treatment evidence for difficult to treat and severe primary OAB cases.

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