ISSN Print: 2394-7500
ISSN Online: 2394-5869
Impact Factor: 8.4
IJAR 2022; 8(9): 156-160
www.allresearchjournal.com
Received: 10-06-2022
Accepted: 13-07-2022

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Combination therapy of solifenacin and mirabegron vs monotherapy in overactive bladder

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DOI: https://doi.org/10.22271/allresearch.2022.v8.i9c.10148

Abstract
Introduction and Objectives: Overactive bladder (OAB) with symptoms of frequency, urgency with or without urgency incontinence and nocturia is one of the most bothersome symptom affecting the quality of life of both men and women. Antimuscarinics and Beta 3 agonists both play an important role in reducing the bothersome symptoms. In this study we find the efficacy of low dose combination therapy of solifenacin 5 mg with mirabegron 25 mg vs the monotherapy solifenacin 10 mg or Mirabegron 50 mg.
Materials and Methods: It is a prospective study conducted on 150 patients at Madras medical college and were divided into 3 groups. Group A received solifenacin 10 mg/day, Group B received solifenacin 5 mg/day + Mirabegron 25 mg/day and Group C received Mirabegron 50 mg/day. Patients were evaluated for improvement in frequency, urgency, leak episodes, voided volume and improvement in quality of life after a period of 4 weeks and 12 weeks. The three groups were compared using anova test and chi square test and p value was calculated.
Results and Observations: Majority of patients of OAB belong to age group > 50 years and majority were females showing female predilection towards OAB. The mean duration of symptoms was 36.01± 7.91 months. Compared with monotherapy, the combination therapy resulted in a significant improvement in reducing the mean number of micturition/24hr from baseline to End of Treatment (EoT). The frequency of urgency episodes and mean number of nocturia episodes/24hr was significantly reduced in patients taking combination therapy as compared to monotherapy. In all the groups a decrease in mean number of incontinence episodes/24hr was observed from baseline to EoT but was not statistically significant. The frequency of antimuscarinic side effects (dry mouth, constipation, urinary retention) had lower incidence in combination therapy compared with solifenacin group.
Conclusions: Combination therapy of solifenacin and mirabegron demonstrated significant improvement over monotherapy (solifenacin 10 mg & mirabegron 50 mg) in frequency of micturition, urgency and nocturia episodes without increasing bothersome adverse effects associated with antimuscarinic therapy.

Keywords: Solifenacin, mirabegron, monotherapy, overactive bladder

Introduction
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 pathologic or metabolic factors that would account for these symptoms [1]. OAB can significantly interfere with daily activities 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 relaxes the detrusor muscle and reduces 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 which causes an array of anticholinergic adverse events (AEs) such as dry mouth and lack of efficacy which is a prime reason for discontinuation of antimuscarinic drugs by the patient [3]. Three β- adrenoceptor subtypes (β1, β2, β3) in the detrusor muscle and urothelium have been identified, β3 being the predominant β- receptor subtype in human urinary bladder [4-8]. Mirabegron is the first β3 adrenoceptor agonist that causes relaxation of the detrusor muscle during the bladder storage phase and increase bladder capacity [9].

Since both class of drugs have different mechanism of action, combining a β3-adrenoceptor agonist with an Anti-Muscarinic agent may improve efficacy in OAB treatment. Combinations with reduced doses may deliver an improved tolerability profile with reduced adverse events compared with monotherapy, without compromising efficacy [10].

Materials and Methods

It is a prospective study conducted at Institute of Urology, Madras Medical College, Chennai for a period of 6 months (October 2021 to march 2022), after obtaining approval from Institutional Ethics Committee. A total number of 150 patients aged ≥18 years with OAB symptoms attending the urology OPD were included in the study after taking written informed consent. They were divided into 3 groups:

- **Group A:** 50 patients receiving solifenacin 10 mg/day.
- **Group B:** 50 patients receiving solifenacin 5 mg/day plus mirabegron 25 mg/day
- **Group C:** 50 patients receiving mirabegron 50 mg/day.

Patients were followed up after 4 weeks and 12 weeks and change in the parameters from baseline were noted. During the follow up period 12 patients from group A and 8 patients from group C lost to follow up. Patients were assessed for change in mean numbers of micturition, urgency, incontinence, nocturia per 24 hour and quality of life. Patients were asked to maintain a bladder diary for the same.

Inclusion Criteria

- Male or female patient ⩾18 years of age with symptoms of OAB.

Exclusion Criteria

- Pregnant/lactating Female.
- Neurogenic bladder.
- Patient with significant stress/urgency incontinence
- An indwelling catheter.
- Patient with diabetic neuropathy.
- Evidence of a symptomatic UTI, interstitial cystitis, bladder stones, malignant disease of the pelvic organs.
- Severe renal impairment or End Stage Renal disease.

Statistical Analysis

Statistics have been done using Spss statistics 27.0 using ANOVA test and non-parametric scales. $p< 0.05$ was taken as statistically significant.

Results

Out of 150 patients, 20 patients lost to follow up. Out of 130 patients, majority of patients belong to age group> 50 years as shown in Table 1. Out of 130 cases, 39 (30%) were males and 91(70%) were females as shown in Table 2. The mean duration of symptoms was 36.01±7.91 months. Number of micturitions/24 hour was 9.38±0.548. Baseline data of OAB patients is as shown in Table 3. Mean Change in Frequency of Micturition/24hr among different drug groups is shown in Table 4. The combination therapy resulted in a significant improvement in reducing the mean number of micturitions/ 24 hr from baseline to End of Treatment (EoT). The frequency of urgency episodes was significantly reduced (2.98-0.2) in patients taking combination therapy as compared to the Solifenacin and Mirabegron monotherapy as shown in Fig 1. All three groups showed a decrease in mean number of incontinence episodes/24hr after 4 weeks and 12 weeks of treatment but the reduction was not statistically significant. Change from baseline to EoT in mean number of incontinence episodes/24 hr in all three groups is shown in Table 5. Fig. 2 graph shows statistically significant improvement in mean number of nocturia episodes/24hr in the patients taking combination therapy (1.78- 0.32). The frequency of antimuscarinic side effects (dry mouth, constipation, urinary retention) was significantly lower in combination therapy compared with solifenacin group. Mirabegron group had more incidence of headache compared to other two groups. Fig 3. Shows the adverse effects of monotherapy and combination therapy.

Table 1: Age Distribution of Patients with OAB

Age	No./ percentage of cases
<25 Years	4(3.33%)
25-50 Yrs	33(25.33%)
>50 Yrs	93(71.33%)
Mean Age (Mean + -SD)	51.3+- 12.5

Table 2: Sex Distribution of Patients with OAB

Gender	No./ percentage of cases
Males	39(30%)
Females	91(70%)

Table 3: Duration of symptom and baseline data of OAB patients

Baseline data	Mean±SD
Duration of symptoms(in months)	36.01 ±7.91
Number of micturitions/24 hour	9.38± 0.548
Urgency episodes/24 hr	3.05± 0.204
Incontinence episodes/24 hr	2.01± 0.368
Nocturia/24 hr	2.15± 0.302

Table 4: Mean Change in Frequency of Micturition/24hr among Different Drug Group

	Soli 10 N=38	Soli 5 + mira 25 N=50	Mira 50 N=42
Baseline	9.578± 0.149	9.593±0.189	9.211± 0.354
4th week(1st visit)	8.006± 0.235	7.378± 0.250	7.216± 0.367
12th week(2nd visit)	6.067± 0.020	4.596± 0.146***	5.374± 0.159

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

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

	Soli 10 N=38	Soli5 + mira 25 N=50	Mira 50 N=42
Baseline	1.989± 0.386	2.007± 0.343	2.168± 0.496
4th week (1st visit)	1.122± 0.274	0.552± 0.161	1.216± 0.359
12th week (2nd visit)	0.470± 0.166	0.163± 0.080	0.368± 0.156

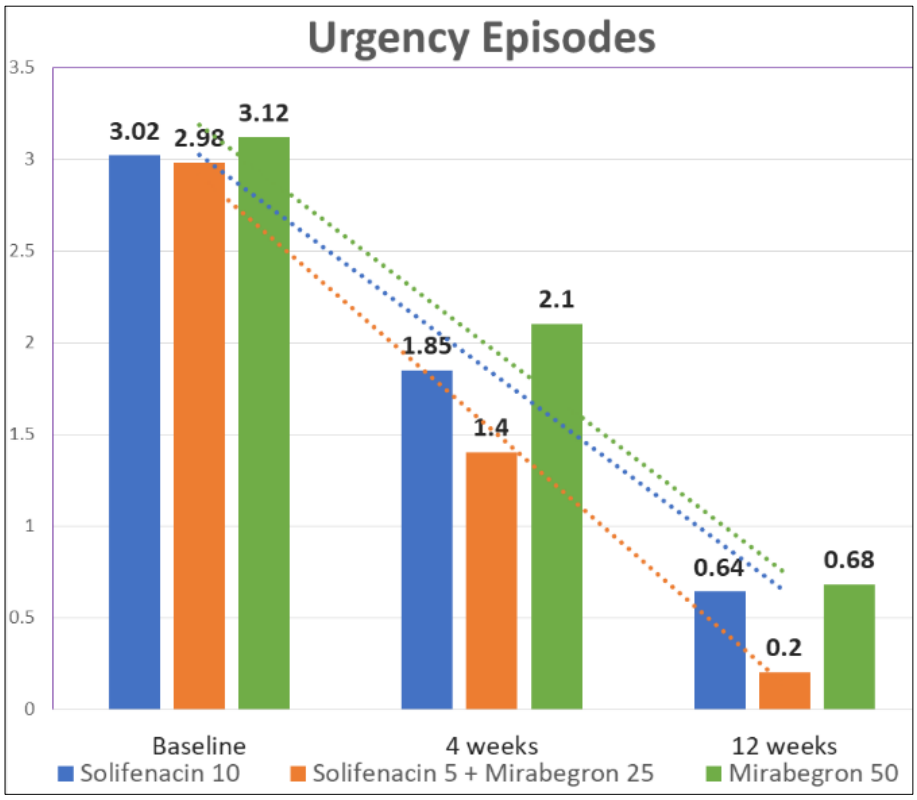

Fig 1: Urgency episodes: Change from baseline to 12 weeks

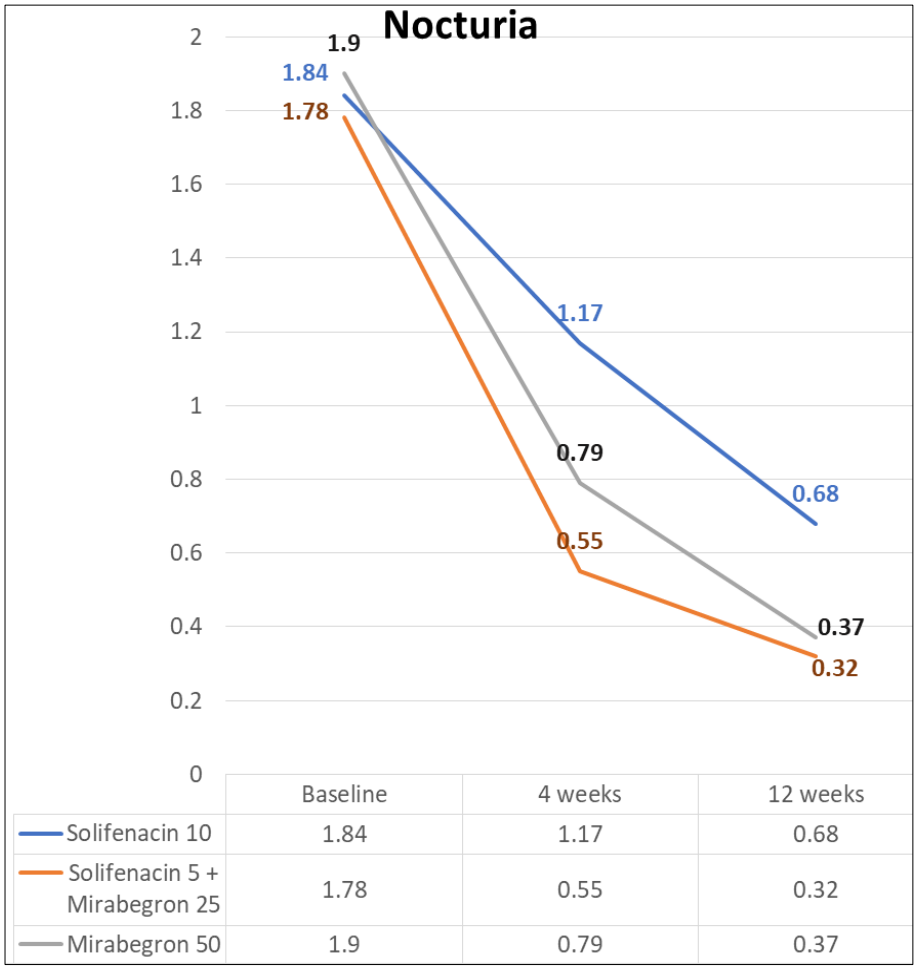

Fig 2: Nocturia Episodes

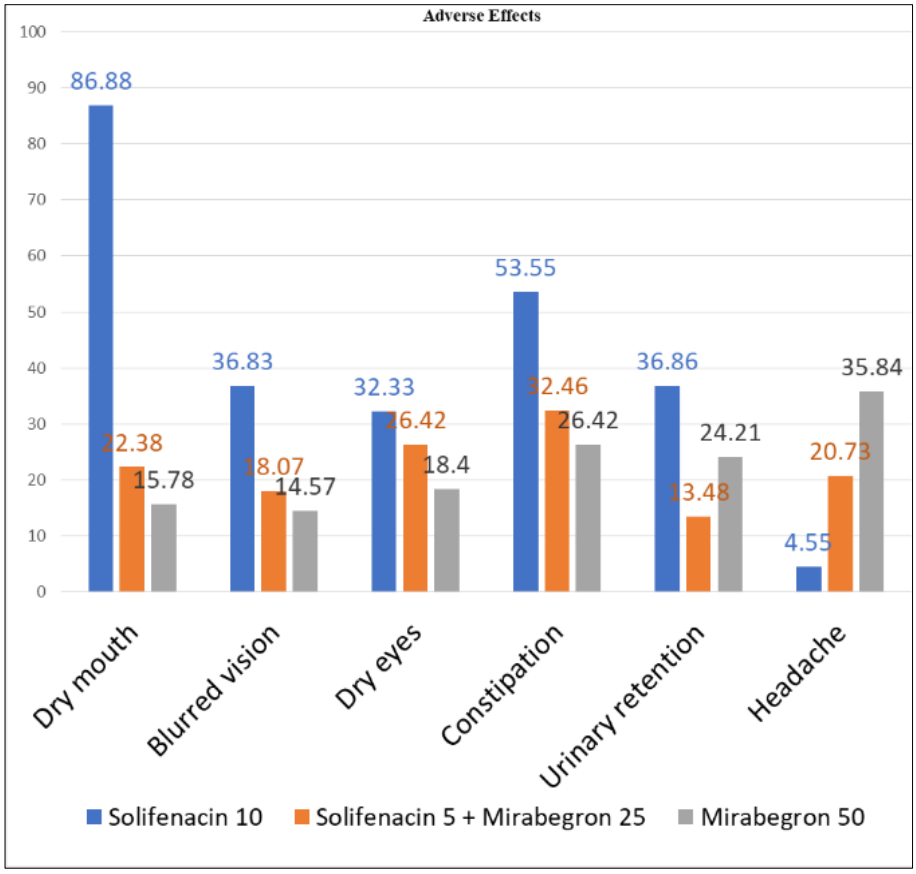

Fig 3: Adverse Effects

Discussion

OAB is a bothersome symptom complex, which significantly affects patient's quality of life [11]. In our study, we found that the mean age of patients developing symptoms of OAB was 51.3 years which corroborates with the study conducted by Abrams *et al*., which showed mean age to be 54.6 years. [12]. This strengthens that OAB is more common in older age group. Majority of the patients encountered were females (70%) which signifies that females are more prone for developing OAB and which is similar to a study done by Khuller *et al*., where female prevalence was 72%. [13]. The mean duration of symptoms in our study was found to be 36.01 months which was comparable to a study done by Paul Abrams *et al*., which showed mean value to be 48.5 months [12]. Our study concluded that combination therapy significantly reduces the mean no. of micturitions/24hr from 9.59 at baseline to 4.59 at 12 weeks (Table 4). A study done by Krauwinkle *et al*., showed that the mean number of micturition was decreased from 10.73 to 8.24 [14]. The mean reduction in urgency episodes/day was from 2.98 to 0.20 in the combination group, which was statistically significant. We found in our study that the mean reductions in incontinence episodes in the combination group was comparable to the other two monotherapies. This finding corroborates with the study done by Christian Gratzke *et al*., [16] In the current study, the mean reduction in number of nocturia episodes was comparable in two groups that is in combination group (1.78 to 0.32) and mirabegron monotherapy (1.9 to 0.37) as shown in Figure 2. There was statistically significant reduction in mean number of nocturia episodes per 24 hr in combination group. This finding was in agreement to study done by Yamaguchi *et al*., [15] 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.

Conclusion

The 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 has improved efficacy with reduced adverse event profile.

Conflict of Interest

There is no conflict of interest.

Funding source

There are no funding Sources.

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