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A Comparative Analysis of Efficacy, Safety and Effect on Quality of Life of Mirabegron versus Solifenacin in Patients with Overactive Bladder

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ABSTRACT

Introduction: Anticholinergics, like Solifenacin, have been the mainstay of treatment for Overactive Bladder (OAB). Mirabegron, a new in class β-3 agonist has shown promising results in treating OAB without having typical anticholinergic side effects.

Objectives: To study efficacy, safety and effects on quality of life (QOL) of Mirabegron and Solifenacin in patients of OAB.

Methods: 60 patients having OAB were randomized into two groups of 30. Group I was given Mirabegron 50 mg OD, and Group II was given Solifenacin 5 OD for 12 weeks. Efficacy was measured by assessing micturition episodes/day, and incontinence episodes/day, using a 3-day bladder diary. To measure safety, changes in vital signs, and recording of treatment induced ADRs were done. QOL was assessed using Patient Perception of Bladder Condition (PPBC) scale. All the parameters were statistically analysed and compared within, as well as, between the two groups.

Results: At the 12th week, improvements in micturition episodes/day, and incontinence episodes/day were observed within the groups, but not between the groups. PPBC scale also showed improvements in both the groups, and not between the groups. At the 12th week, unlike Group I, Group II observed higher frequency of constipation and dry mouth from the baseline.

Conclusion: Mirabegron has similar efficacy, and effects on QOL as compared to Solifenacin in patients with OAB. However, having lower incidence of anticholinergic related ADRs like dry mouth, and constipation, which are more likely to be observed in patients taking Solifenacin, Mirabegron stands advantageous when safety of the treatment is concerned.

Keywords: Overactive bladder; mirabegron; solifenacin; incontinence; anticholinergics; β-3 agonist.

INTRODUCTION

Overactive bladder (OAB) is characterised by urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology. It is a distressing and stressful condition which shows higher prevalence as age advances. For treatment of OAB, long-term therapy is usually necessary.[1] The overall prevalence of OAB was reported to be 11.8% in five countries, including Canada, Germany, Italy, Sweden, and the United Kingdom.[2] In Japan, it is estimated that 8.1 million adults (12.4%) aged ≥40 years are affected by OAB out of which, 37% of the patients are expected to be aged ≥80 years.[3] In Spain

as well, the prevalence of OAB is approximately 21.5% in patients ≥40 years of age; significantly higher in women (25.6%) than men (17.4%).[4] An estimated 10.7% of the 2008 worldwide population (4.3 billion) is affected by OAB[5] with the overall prevalence being greater in women than men.[6] OAB is most common in the elderly population.[7] Health-related quality of life (HRQoL) is highly affected in patients who experience OAB. Aspects of life affected by OAB symptoms include sexual health, personal relationships, performing daily activities, employment, and productivity in the workplace. Urgency Urinary Incontinence which is present in approximately one-third of OAB cases—has the greatest negative impact on HRQoL and productivity.[8] The annual worldwide healthcare cost for OAB is enhanced from €1.4 trillion to € 3.2 trillion by 2018. [9]

Mechanism of normal micturition is a complicated one. During the time of storage of urine in the bladder, noradrenaline released by sympathetic pathway acts on β-3 Adrenergic Receptors (β-3 AR) on the detrusor muscle of the urinary bladder leading to its relaxation. Meanwhile, the external urethral sphincter gets contracted due to action of noradrenaline on α-1 Adrenergic Receptors (α-1 AR). Inversely, during micturition, the bladder contracts due to action of acetylcholine released by parasympathetic nerve on muscarinic-3 receptors (M-3 receptors), on detrusor muscles and also cause the urethral sphincter to come into relaxation mode, resulting in to the discharge of urine. The bladder has M1, M2 (80%) and M3 (20%) cholinergic receptor types, but only M3 cholinergic receptors are responsible for the parasympathetic detrusor contraction.[9] Therefore, to alleviate symptoms of OAB, the role of anticholinergic drugs, and β-3 agonist drugs is logical.

The first line treatment for all OAB patients should be behavioural therapies, however, combining behavioural and pharmacological therapy wherever necessary give better results in managing OAB.[10] Antimuscarinic agents are very commonly used as the pharmacological therapy for OAB but have lower compliance rates. The reason for the same is anticholinergic side effects including drowsiness, dry mouth, dry eyes, constipation, blurred vision, urinary hesitancy, and confusion.[11] Solifenacin exhibits relatively higher affinity and specificity for the muscarinic M3 subtype than the M1 and M2 subtypes, thus showing pharmacological selectivity in the bladder relative to other tissues such as the salivary gland.[12] Mirabegron is the first β-3 AR agonist for the treatment of OAB. Mirabegron was first approved in 2011 for the treatment of OAB in Japan, is now used worldwide. Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of β-3 AR, which increases bladder capacity.[13]

Antimuscarinics and Mirabegron have comparable efficacy in reducing the frequency of micturition, incontinence, and urgency urinary incontinence episodes in OAB.[14] Mirabegron use is not associated with anticholinergic side-effects, such as dry mouth and constipation. Although, studies have been done comparing antimuscarinics with Mirabegron for treatment of OAB, very few studies compare Solifenacin in particular with Mirabegron in real world clinical settings; none are done in state of Punjab, India. Moreover, there are not much data on the comparison between Mirabegron and Solifenacin in terms of impact on QoL (Quality of Life). Therefore, we aim at comparing the two drugs for their efficacy, safety and effect on quality of life in patients with OAB.

METHODS

In this prospective, open, randomized, parallel group, comparative study, 60 patients of OAB attending the outpatient Department of Urology, Rajindra Hospital, Patiala were included. The patients fulfilling the inclusion criteria and having none of the exclusion criteria were enrolled in the study after obtaining written informed consent. The study was approved by institutional ethics committee,

Inclusion Criteria:

1. Age ≥ 18 years;
2. Gender- male or female;
3. Patient willing to sign informed consent form;
4. Patient willing and able to complete the micturition diary and answer questionnaires correctly;
5. Patients with established diagnosis of OAB with average micturition frequency of eight or more times per 24-h period and at least three episodes of urgency, with or without

Volume 3, Issue 3; May-June 2020; Page No.206-216

incontinence, during a 3-d micturition diary period.

Exclusion criteria:

1. Clinically significant BOO (Bladder Outlet Obstruction);

2. Stress incontinence or mixed stress/urgency incontinence where stress is the predominant factor;

3. An indwelling catheter or practised intermittent self-catheterisation;

4. Severe hypertension (defined as a sitting average systolic blood pressure ≥180 mm g and/or average diastolic blood pressure ≥110 mm g)

5. Patient having average total daily urine volume > 3000ml (as recorded in 3-d micturition diary period);

6. Postvoid residual volume of > 200 mL;

7. Presence of a neurological cause for detrusor muscle overactivity;

8. Evidence of UTI or bladder stones, previous pelvic irradiation, or previous or current malignant disease of the pelvic organs;

9. Any medical condition contraindicating the use of antimuscarinic medication (including narrow-angle glaucoma and urinary or gastric retention);

10. Nonpharmacological treatment for OAB including electrostimulation therapy or start of a bladder training programme during the 2 weeks before or during the study;

11. Diabetic neuropathy, Guillain-Barré syndrome (GBS), human immunodeficiency virus (HIV)-associated neuropathy, chronic inflammatory demyelinating polyneuropathy (CIDP), and amyloid neuropathy;

12. Use of drugs intended to treat incontinence;

13. Use of any drugs with cholinergic or anticholinergic side-effects;

14. Participation in a clinical trial within 30 days before study entry;

15. Women of child-bearing potential who were pregnant or nursing, intending to become pregnant during the study, or who were not using reliable contraceptive methods;

16. Patient not willing to give consent.

The study was conducted for a period of 3 months. A thorough history, including past history of urogenital disorders, in combination with physical examination of the genitourinary system and relevant pelvic examinations was performed. Urinalysis, urinary tract ultrasound and measurement of postresidual volume (PVR) were done. A bladder diary, provided to the patient, was recorded by the patient for at least 3 days before the beginning of the study. Bladder diary is a record filled by patients where they would mention details related to micturition episodes, incontinence episodes, time of the events, and details of solid and liquid food intake. Thereafter, patients were divided into two groups of 30 subjects each through simple randomization by coin flip method. In Group I, the patients received Mirabegron 50 mg once a day for 12 weeks. In Group II, the patients received Solifenacin Succinate 5 mg once a day for 12 weeks. During the study, patients developing severe adverse drug reactions and those who were intolerant to the drugs were excluded from the study and treated.

Efficacy assessment: To assess the efficacy of Mirabegron, patients completed a bladder diary for a 3 days period before clinic visits at baseline and at 12th week (final visit). Primary efficacy end points were the change from baseline to final visit in the mean number of incontinence episodes per day (MIE/D), and micturition episodes per day (MME/D).

Quality of life assessment: To assess patient perception of improvement in health-related quality of life (QoL), PPBC scale was used which was filled at the baseline and at the 12th week of the study. PPBC scale is 6-point score system which measures global impact of bladder condition to the patient. The score ranges from 1 to 6, larger the score, more is the negative impact of the treatment on QoL.[15]

Safety assessments: The patients were advised to self report adverse reaction to the investigators, and were also contacted for monitoring of ADRs by investigators on weekly basis. Any ADR was

Volume 3, Issue 3; May-June 2020; Page No.206-216

considered to be severe if it led to hospital admission, required intervention to prevent permanent damage, disability or death. Vital signs including BP measurement and clinical laboratory variables were measured at each study visit. A bladder scan to measure PVR (Post Void Residual) volume was performed at 1st visit and week 12. Notable shifts in PVR volume from baseline to final visit were defined as those >300 ml or those that changed from a baseline PVR volume of <150 ml to >150 ml but <300 ml, which would define urinary retention.

The results of the observations of individual patients were pooled for each group. Data was statistically analysed.

RESULTS:

Total 60 patients were enrolled in the study. The total no. of males who participated in this study were 28 (46.6%) and the total number of females were 32 (53.3%). Gender distribution between two groups was not significant. [Group I was: males 16 (46.67%) and females 14 (53.33%) and in Group II: males 12 (40%) and females 18 (60%)]. Mean age (± SD) calculated in Group I and Group II was 53.80±13.25 years and 55.03±12.79 years, respectively. P-value (0.7197) for the difference in age range between two groups was not significant.

We found that MME/D in Group I, and Group II at the baseline was 13.06±4.91, 13.20±4.70, respectively, at 12 weeks was 8.53±2.78, and 8.76±3.23, respectively. The mean difference of MME/D of the two groups show no statistical significant difference in values. Similarly, the values for MIE/D in Group I, and Group II at the baseline was 5.30±1.86, and 2.60±1.38, respectively, and at 12 weeks was 1.70±1.26, and 0.53±0.62, respectively. The mean difference of MIE/D of the two groups show no statistical significant difference in values [table1], [figure 1], [figure2]. The PPBC score also showed reduction from the baseline in both the groups with mean difference in Group I and II as 0.33 ± 0.33, and 0.26±0.35, respectively. There was no significant difference between the two values [table1], [figure 3].

ADRs observed in Group I were Dry mouth (1 patient), Constipation (1 patient), headache (5 patients), hypertension (8 patients), and urinary retention (1 patient). Similar number of ADRs were also observed in Group II which were not statistically different from Group I, except for dry mouth (16 patients) and constipation (14 patients) [table 2]. There were no incidence of significant increase or decrease from the baseline in SBP, DBP, or HR in both the groups.

DISCUSSION

Oral antimuscarinic agents like Solifenacin, are associated side-effects (including dry mouth and constipation) affecting quality of life of the patients. Mirabegron, a first in class β-3 agonist agent, has shown to be an effective treatment for OAB which is also free from typical side effects of anticholinergic agents, but might have some of ADRs arising from its mechanism of action on adrenergic receptors, especially on cardiovascular system. In present study, we aimed at comparing Mirabegron with Solifenacin to assess their efficacy, safety and effect on quality of life of the patients with OAB. The study was done in 12 weeks at Government Medical College, Patiala/Rajindra Hospital, Patiala, Punjab, India. This was a prospective, open labelled clinical trial where 60 patients of age 18 years and above having OAB were enrolled and randomly allocated into two study groups after taking informed consent of the patients. The patients of Group I received tablet Mirabegron 50 mg, once a day for 12 weeks, and patients in Group II received tablet Solifenacin 5mg, once a day for 12 weeks. All the patients were investigated for various health parameters including Blood pressure, Blood sugar, Urinary bladder Ultrasound and urinalysis. Bladder diary, in which record of patient's fluid intake, micturition episodes, incontinence episodes, and nocturia incidents can be kept, was provided to each patient to fill for 3-days at the baseline and at the end of the study period. To measure safety profile of the drugs, the patients were encouraged to report on their own any adverse events during the course of the treatment as well as contacted on weekly basis by investigators. We assessed the effect of the treatment on patients' quality of life using the PPBC scale at the baseline, as well as at 12th week of the study.

In our study, total female and male patients were 32 and 28, respectively. The two groups did not show significant difference between number of cases of males and females (p= 0.44). As the age of the patients advanced, the percentage of patients with

Volume 3, Issue 3; May-June 2020; Page No.206-216

symptoms of OAB also increased. The age group 50-69 years contributed to have the highest percentage (Group I:56.7% and Group II: 60 %) of patients with OAB in both the groups as compared to other age groups. However, in both the groups, there was a downward trend in number of patients presenting with OAB having age > 70 years. Milsom I, et al, in a study published in 2001, complied results from six different countries and showed that overall, 15.6% of men, and 17.4% of women reported symptoms suggestive of OAB. The prevalence of OAB increased with advancing age and was the highest in patients of age ≥75 years.[16] The overall prevalence of OAB was reported as 16.9% in women and 16.2% in men was shown by Stewart, et al, in a year 2003 study. The study also showed that the prevalence by age increased by approximately the same slope in both men and women. [17] As mentioned before, our study also showed increase in prevalence of OAB in both men and women as age advanced, age more than 70 years, however, had only 10% of the cases. This could be a chance finding.

In our study, both Group I (Mirabegron) and Group II (Solifenacin) showed significant reduction in MME/D when compared with the baseline. MIE/D at 12th week also showed significant reduction when compared with baseline. Efficacy of Solifenacin and Mirabegron has been demonstrated in many previous studies which show similar results as observed by us. One such study, the VENUS trial, is done by Serels SR, et al, in 2010, which showed similar trend for efficacy of Solifenacin.[18] In 2012 by Orešković S, et al, deminstrated that the patients treated with solifenacin for OAB significantly improved MME/D after four weeks compared to placebo group.[19] Efficacy of mirabegron observed in our study can also be confirmed through a study published in 2013 by Herschorn S, et al. Changes in MIE/D, and MME/D assessed in patients with OAB given Mirabegron 50 mg showed significant reduction in both the parameters.[20] The results were not different for Wagg A, et al. study done in elderly patients in 2014.[21]

Comparing the mean reduction of efficacy parameters of both the groups, our study showed no significant difference in the values. We can observe similar results in a study by Wang J, et al. in which five RCTs were comparing Solifenacin with mirabegron were included in a metanalysis. The results showed reduction in MME/D, MIE/D, and mean number of urgency episodes per 24 h. The efficacy of Mirabegron was similar to that of Solifenacin in all the parameters mentioned above.[22] Another study establishing our finding is a study published in 2018 by Schiavi M, et al. The authors found that number of voids (24 h) and MIE/D had no significant difference between Mirabegron 50mg group and Solifenacin 5 mg group.[23]

In our study, very few candidates had treatment emergent ADRs. We found that in Group I, most commonly reported ADR were hypertension (8 patients), headache (5 patients), constipation (1 patient), urinary retention (1 patient) and dry mouth (1 patient) which were not significantly greater than baseline. The safety and tolerability of Mirabegron has been good when previous studies are reviewed. Herschorn S, et al, in 2013 demonstrated that overall incidence of treatment-emergent adverse events (TEAEs) by Mirabegron was similar to placebo. The study also supports our finding related to most commonly observed ADRs, that were, hypertension and headache.[20] The incidence of TEAEs associated with Mirabegron was low and of mild severity in a study done by Liao C, et al in 2018. Hypertension, nasopharyngitis, and UTI were the most common treatment-emergent AEs. Our study did not find any case showing ADRs like nasopharyngitis and UTI, however, hypertension was one of the few observed ADRs. [24]

We observed very few ADRs related to treatment with Solifenacin, most of them (blurred vision, headache, tachycardia, urinary retention, and hypertension) were not significantly higher than baseline values. However, two of the ADRs showed statistically higher frequencies at the end of the treatment. They were dry mouth ($p < 0.0001$), and constipation ($p < 0.0002$). Both of these ADRs can be attributed to antimuscarinic activity of Solifenacin and have also been observed in many previous studies. A systemic review to evaluate safety profile of antimuscarinics and Mirabegron in patients of OAB was conducted by Rosa G, et al, which focused on cardiovascular events related to treatment. The authors concluded that increased HR may be associated with the use of fesoterodine, propiverine, tolderodine and trospium, while the other antimuscarinic drugs like Solifenacin do not present this AE. On the other hand, Mirabegron reported

Volume 3, Issue 3; May-June 2020; Page No.206-216

fewer AEs among which either modest hypertension or a slight increase in HR were most commonly observed ADRs. This review supports findings of our study as no major cardiovascular events were observed in both the groups.[25]

A study to evaluate efficacy and tolerability of Mirabegron versus Solifenacin was published by Schiavi M, et al, in 2018. After 12 weeks of treatment, the results of the study showed that the two treatments did not have significant difference in change of vital signs of patients within the group, as well as between the groups. They also found that patients taking Solifenacin reported two major ADRs, constipation and dry mouth. which were significantly higher in Solifenacin group as compared to Mirabegron group. Our study also found no differences in vital signs among patients. Constipation (14 patients) and dry mouth (16 patients) were the two most common ADRs observed among patients receiving Solifenacin in our study. Therefore, the findings related to safety profile of Solifenacin and Mirabegron used in this study demonstrate remarkable similarities with results of our study.[23]

The results of our study showed that the change in PPBC score in Group I (Mirabegron) was 4.1± 1.42 at baseline, which reduced to 2.46±1.36 at 12 weeks, having mean difference of 1.633±1.402 scores. Statistical analysis of the result confirmed significant reduction in PPBC score when patients of OAB were treated with Mirabegron ($p < 0.0001$). This reduction in PPBC score directly means better quality of life at the end of the study as compared to baseline.

In Group II (Solifenacin), PPBC score at baseline was 4.43± 1.16, and at 12th week was 2.73± 1.36. Just like Group I (Mirabegron), the PPBC score reduction in Group II (Soilifenacin) was also statistically significant, having mean difference of 1.700±1.489 scores. ($p<0.0001$).

The reduction in PPBC scores of both the groups were compared with each other. We found that there was no significant difference between the two groups in terms of reduction of PPBC score ($p>0.05$). Having found that, we can say that both Mirabegron and Solifenacin improve quality of life in patients with OAB in the similar manner. Many published studies show similar results when QOL is assessed in patients treated with either Mirabegron or Solifenacin. A study which was published in 2014 by Han JY, et al, showed that 77.1% of the patients having frequency without urgency, and 76 % of the patients having frequency with urgency had ≥1 point improvement in PPBC score.[26] Schiavi M, et al, published a study in 2018 to compare various aspects of Mirabegron and Solifenacin. In contrast to PPBC scale used by us, to evaluate impact on QOL of treatments, King's Health Questionnaire (KHQ) and Patient Global Impression of Improvement (PGI-I) questionnaire were used after 12 weeks of treatment. Regardless of this, no significant difference between the group when impact on QOL was evaluated.[23] Herschorn S, et al, in 2018 published PREFER study between Mirabegron and Tolterodine (antimuscarinic drug). The authors found that both Mirabegron and Tolterodine were associated with similar mean improvements in PPBC scores. In our study, the antimuscarinic drug used was Solifenacin instead of Tolterodine, which also showed non- significant difference between improvement in PPBC scores when compared with Mirabegron.[27]

Our study was fraught with a few limitations. First of all, the duration of the study was limited with limited patient enrolment. The study was conducted only at one region specific site, results of which cannot be generalized to general population. We carried out the study between 50mg dose of Mirabegron and 5 mg dose of Solifenacin, which give us limited knowledge about effect of the drugs in other therapeutic doses. Further, we used micturition diary for evaluation of efficacy of the treatment, which may not be enough to deeply monitor patients' response to the treatment as compared to utilization of urodynamic studies.

Further studies with a larger sample size and longer duration are, therefore, warranted. The studies with a multicentric patient enrolment will help in the generalization of data to larger populations, and improve external validity in the general population and different settings. We also suggest usage of various other measurable parameters to evaluate efficacy of the drugs. The cost effectiveness of the treatment should also be evaluated since it could be a major reason for discontinuation and non-adherence of patients.

CONCLUSION

Mirabegron 50 mg, and Solifenacin 5mg as lead to improvement in signs and symptoms of OAB within

Volume 3, Issue 3; May-June 2020; Page No.206-216

12 weeks of continuous treatment as monotherapy. Both the drugs also improved patients' quality of life. Mirabegron was found to be safer alternative than Solifenacin when treatment induced ADRs were considered. Solifenacin treatment lead to development of dry mouth, and constipation in significantly higher number of patients, which can be attributed to its anticholinergic effects. Adverse events reported in our study were mild in both the groups and no discontinuation of drug was required. Having mentioned that, similar effectiveness, and impact on QOL of Mirabegron, and Solifenacin for treatment of OAB must not be ignored. When prescribing either Mirabegron or Solifenacin as monotherapy for treatment of OAB, physician should have individualized approach based on various aspects like previous treatments, patient's response, compliance, affordability, development of ADRs, and availability of drugs. However, Mirabegron has shown to be a promising treatment of OAB, which has potential to become new first line therapy for OAB.

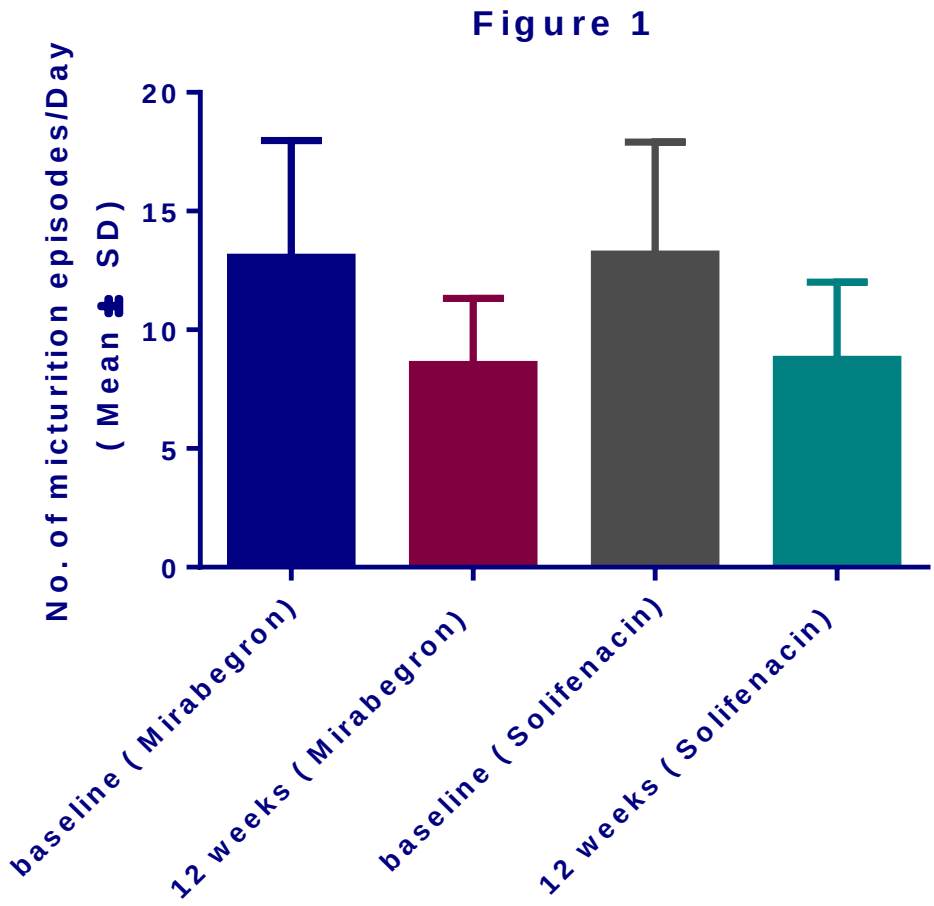

Figure 1: Number of Micturition episodes/day (mean±SD) at the baseline and at the 12th week in group I (Mirabegron), and group II (Solifenacin)

Volume 3, Issue 3; May-June 2020; Page No.206-216

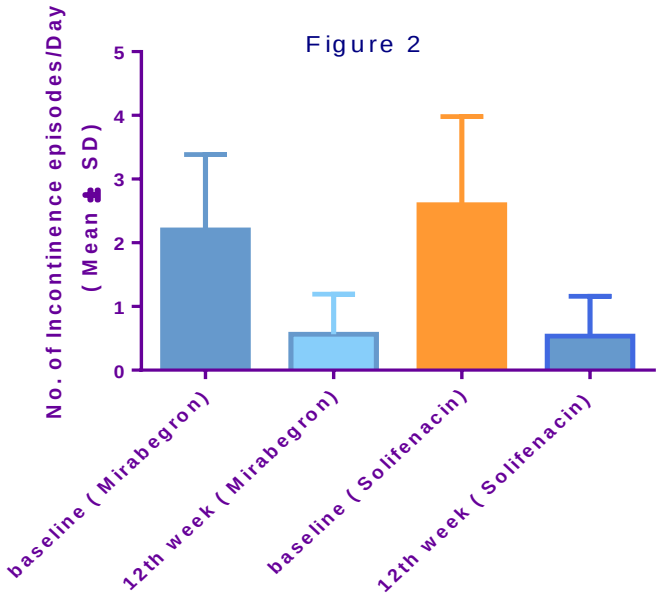

Figure 2: Number of Incontinence episodes/day (mean±SD) at the baseline and at the 12th week in group I (Mirabegron), and group II (Solifenacin)

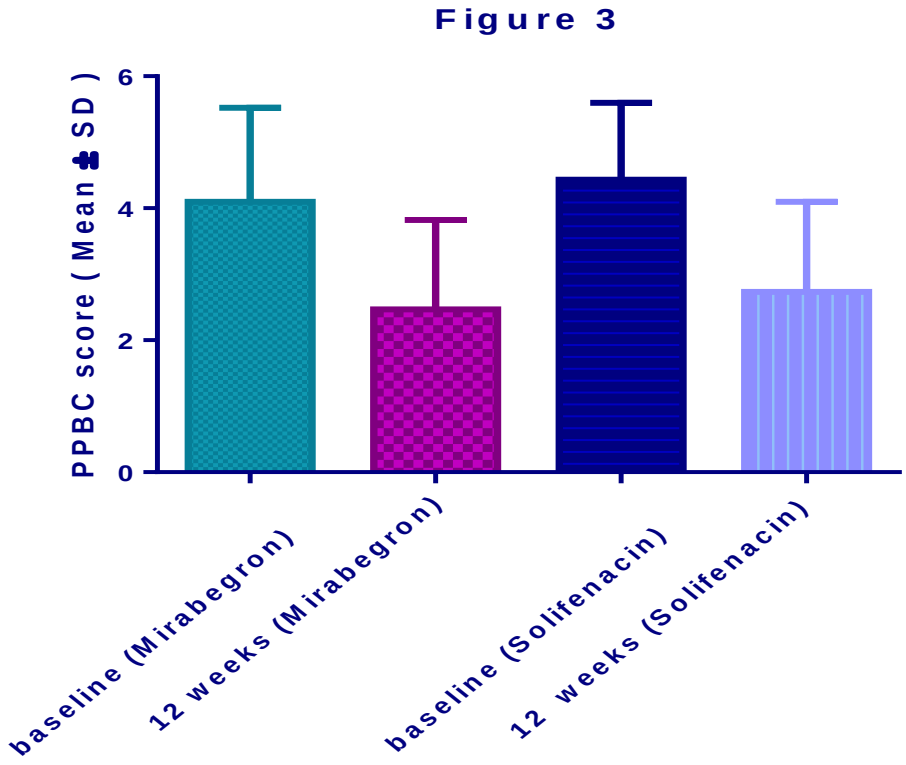

Figure 3: PPBC (Patient Perception of Bladder Condition) score (mean±SD) of group I (Mirabegron) and group II (Solifenacin) at the baseline, and at the 12th week.

Volume 3, Issue 3; May-June 2020; Page No.206-216

Table 1- Summary of efficacy parameters, and PPBC scale observed.

Parameters	Group I	Group II	Means difference	Group I vs Group II
MME/D baseline	13.06±4.91	13.20±4.70	0.13±1.24	0.91 (NS)
MME/D 12 weeks	8.53±2.78	8.76±3.23	0.23 ± 0.78	0.76 (NS)
MIE/D baseline	5.30±1.86	2.60±1.38	0.40 ± 0.33	0.23 (NS)
MIE/D 12 weeks	1.70±1.26	0.53±0.62	-0.03±0.16	0.83(NS)
PPBC baseline	4.10± 1.42	2.46±1.36	0.33 ± 0.33	0.32 (NS)
PPBC 12 weeks	4.43± 1.16	2.73± 1.36	0.26±0.35	0.45(NS)

Abbreviation: MME/D (Mean Micturition Episodes/day); MID/D (Mean Incontinence Episodes/day); PPBC (Patient Perception of Bladder Condition); S (Significant); NS (Non-Significant)

Table 2- Number of ADRs observed at week 12 of the treatment.

ADRs	GROUP I	GROUP II	P value
Dry mouth	1	16	0.0001 (S)
Constipation	1	14	0.0002 (S)
Blurred vision	0	0	NS
Headache	5	6	1.00 (NS)
Tachycardia	0	0	NS
Hypertension	8	8	1.00 (NS)
Urinary retention	1	3	0.6120 (NS)

Abbreviation: S (Significant), NS (Non-Significant)

MAIN POINTS

1. Currently, drug of choice for patients with Overactive bladder (OAB) is Anticholinergic drugs, which have troublesome adverse effects like dry mouth, constipation, urinary retention, etc which lead to some patients discontinuing the treatment.
2. Mirabegron, a β-3 adrenergic receptor agonist, is first in class drug which has is has shown similar efficacy like anticholinergic drugs for treatment of OAB.
3. Our study aimed at establishing the efficacy, safety and effect on quality of life of Mirabegron in patients with OAB in comparison to antiholinergic drug Solifenacin
4. The results of our study confirm that there is no significant difference between Mirabegron and Solifenacin in terms of efficacy and effect on quality of life.
5. As far as safety is concerned, Mirabegron was found to be safer alternative than Solifenacin. Solifenacin treatment lead to development of dry mouth, and constipation in significantly

Volume 3, Issue 3; May-June 2020; Page No.206-216

higher number of patients, which can be attributed to its anticholinergic effects

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Volume 3, Issue 3; May-June 2020; Page No.206-216

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Volume 3, Issue 3; May-June 2020; Page No.206-216