Mirabegron versus tolterodine for the treatment of overactive bladder: A prospective randomized study

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Abstract

Objectives: To assess the efficacy of mirabegron and Tolterodine, comparing both drugs by IPSS score at 12th week of intervention.

Materials and Methods: This prospective randomized observational study was conducted in 40 Patients with overactive bladder over 15 months. Patients are divided into two groups, 20 patients (Group-M) receiving Tab Mirabegron 50 mg OD and 20 patients (Group-T) receiving Tab Tolterodine 4 mg OD.

Results: The difference of urine Frequency episodes per 24 hours at the 12th week in Group-M was 2.75 ± 1.41, while that among the Group-T was 1.15 ± 1.04 with a significant p-value < 0.05. The difference of nocturia episodes at the 12th week in Group-M was 1.45 ± 0.88, while that in Group-T was 0.7 ± 0.65 with a significant p-value < 0.05. The difference of urgency episodes at the 12th week in Group-M was 1.65 ± 0.99, while that among the Group-T was 1 ± 0.79 with a significant p-value < 0.05. The difference in urge incontinence episodes at the 12th week was not significant between the two groups. The difference of IPSS at the 12th week in Group-M was 5.7 +/- 3.65, while that among the Group-T was 3.85 +/- 1.27 with a significant p-value < 0.05.

Conclusion: Mirabegron improved Urgency, the total number of micturition episodes/24 hours, nocturia, IPSS score better than Tolterodine in overactive bladder patients. There is no difference between Mirabegron and Tolterodine in terms of incontinence episodes.

Keywords: Over Active Bladder (OAB); Detrusor Overactivity (DO); International Continence Society(ICS); International Prostate Symptom Score(IPSS)

Introduction

Dr Paul Abramsand Dr Alan Wein in 1997 coined the term "overactive bladder" as a title for a symposium convened to discuss lower urinary tract symptoms and their treatment.[1] Overactive bladder (OAB), as described by the International Continence Society (ICS), is characterized by complex symptoms, which include urinary urgency with or without urge incontinence that is usually associated with frequency and nocturia.[2] The main symptom is urinary urgency, which is a sudden compelling need to void that is hard to postpone. Increased daily frequency is the argument made by the patient who feels that day by day, he or she is voiding too much. Nocturia is the statement made by the person who must wake up one or more times to void at night. Currently, the definition of overactive bladder syndrome is a symptomatic diagnosis.[3]On the other hand, detrusor overactivity (DO) is a urodynamic observation and is characterized by involuntary detrusor contractions during the filling phase, which is spontaneous or provoked.[4]These are not the terms interchanged because patients with overactive bladder syndrome may not have detrusor activity on urodynamic testing.[5]

This study aims to assess the efficacy of tolterodine and mirabegron, comparing both drugs by IPSS score, micturition episodes per 24 hours (frequency), nocturia, urgency, urge incontinence at the 12th week of intervention among the patients who presented with predominantly storage LUTS.

Materials and Methods

This prospective observational study was conducted on forty patients with overactive bladder who attended our outpatient department over 15 months, from January 2019 to March 2020. All overactive bladder patients willing to participate in the study and who had failed the conservative management were included. Patients with stress urinary incontinence as a predominant symptom at the screening, urinary stone, urinary tract infection, interstitial cystitis, patients with significant PVR (post-void residual), diabetes mellitus, clinically ill patients were excluded. A detailed history was taken, and a thorough physical examination was done. IPSS score was taken. Routine blood investigations were done. A complete

urine examination was done to rule out Urinary Tract Infection. Uroflowmetry (UFR) and Ultrasound Abdomen were done along with pre-void and post-void residual (PVR) volume measurement. After satisfying the inclusion and exclusion criteria, patients were enrolled in the study. Patients were randomly divided into two groups, one group receiving Tab Tolterodine 4mg once daily and another receiving Tab Mirabegron 50 mg daily. Patients were reviewed at the 12th week with IPSS score, the total number of micturition episodes, urgency episodes, urge incontinence episodes, nocturia episodes. Any side effects were also noted.

Results

The Mirabegron group (Group-M) had 15 males and 5 females. The Tolterodine group (Group-T) had 13 males and 7 females. There was no significant difference between the two groups. The mean age of Group-M was 60.7 ±10.1 years, while that of Group-T was 60 ± 13.63 years. The difference between the two was not significant. The difference of urine frequency episodes per 24 hours at the 12th week in Group-M was 2.75 ± 1.41, while that among the Group-T was 1.15 ± 1.04 with a significant p-value < 0.05. The difference of nocturia episodes at the 12th week in Group-M was 1.45 ± 0.88, while that among the Group-T was 0.7 ± 0.65 with a significant p-value. The difference of urgency episodes at the 12th week in Group-M was 1.65 ± 0.99, while that among the Group-T was 1 ± 0.79 with a significant p-value < 0.05. The difference of urge incontinence episodes at the 12th week in Group-M was 0.45 ±0.69, while that among the Tolterodine group Group-T was 0.25 ± 0.44. The difference in urge incontinence episodes per 24 hours between the groups was not significant with a p-value > 0.05 [Table-1].

The difference of IPSS at the 12th week in Group-M was 5.7 ±3.65, while that among the Group-T was 3.85 ± 1.27 with a significant p-value < 0.05 [Table-2]. As far as side effects are concerned, 7 patients in Group-T had dry mouth compared to only 5 patients in Group-M, which were not statistically significant.3patients in Group-T had constipation compared to only one patient in Group-M, which was again not statistically significant. [Table 3]

Table 1: Effects of Mirabegron vs Tolterodine on lower tract symptoms

Group	IPSS score at the end of the treatment		
	Baseline (Mean +/- SD)	**12th week after intervention (Mean +/- SD)**	**Difference (Mean +/- SD)**
Group-M (n=20)	15.5 +/- 4.81	9.8 +/- 2.12	5.7 +/- 3.65
Group-T (n=20)	18 +/- 3.51	14.15 +/- 4.07	3.85 +/- 1.27
P - Value			< 0.05

Table 2: Adverse effects of the treatment

Side Effects	Mirabegron (No of Patients)	Tolterodine (No of Patients)	P-value pp
Dry Mouth	5	7	> 0.05
Constipation	1	3	> 0.05
Dyspepsia	3	7	> 0.05
Retention	0	1	> 0.05
Head ache	1	3	> 0.05
Palpitation	3	1	> 0.05
Hypertension	3	1	> 0.05

Table 3: IPSS at the end of the treatment

Episodes per 24 hours	Group	Baseline (Mean +/- SD)	12th week after intervention (Mean +/- SD)	Difference (Mean +/- SD	P- value
Frequency	Group M(n=20)	8.2 +/- 1.40	5.45 +/- 1.32	2.75 +/- 1.41	<0.05
	Group T (n=20)	9.2 +/- 1.36	8.05 +/- 1.76	1.15 +/- 1.04	
Nocturia	Group M(n=20)	3.5 +/- 0.76	2.05 +/- 0.75	1.45 +/- 0.88	< 0.05
	Group T (n=20)	2.6 +/- 0.82	1.9 +/- 0.85	0.7 +/- 0.65	
Urgency	Group M(n=20)	4.8 +/- 1.32	3.15 +/- 1.42	1.65 +/- 0.99	< 0.05
	Group T (n=20)	3.55 +/-1.28	2.55 +/- 1.36	1 +/- 0.79	
Urge Incontinence	Group M(n=20)	1.28 +/- 1.49	0.7 +/- 0.92	0.45 +/- 0.69	>0.05
	Group T (n=20)	0.7 +/- 1.03	0.45 +/- 0.68	0.25 +/- 0.44	

Discussion

The number of patients in both groups was equal, thus limiting the chances of discrepant results. Both the groups were age and sex-matched such that there was no statistical significance between these two parameters. Even though the overall prevalence of OAB is similar between men and women, there are sex-specific differences in the majority of different symptoms within the OAB complex.

The anatomical and physiological differences in the lower urinary tract of both males and females help to explain these variations.[6] Overall, OAB prevalence rates in extensive population-based studies range from 7–27% in men and 9–43% in women. In our study, the Mirabegron group had 15 males (75%) and 5 females (25%). The Tolterodine group had 13 males (65%) and 7 females (35%). There was no significant difference between the two groups. However, in our study,70% of the total cases were men,30% were women, probably owing to decreased reporting in Indian women. The mean age of the patients in the study was 60 years, with 62% ranging from 56 to 75 years. The prevalence progressively increases with age, from 4.8% in women under 25 years to 30.9% in those over 65 years.[7]

Urinary frequency is one of the most studied variables in many trials. In our study, the mirabegron group demonstrated a statistically significant greater reduction in the frequency episodes than the tolterodine group ($p < 0.05$). In the study by Hann-Chorng Kuo et al.[8],the mean difference between the mirabegron and tolterodine groups was −1.41. The mirabegron group demonstrated a more significant reduction in the mean number of micturition per 24 hours than the tolterodine group. The study by Arcangelo Sebastianelli.[9] et al., which included a meta-analysis of Chapple 2013 phase II[10], Chapple 2013 phase III[11], Khullar 2013[12],Kuo 2014[13], Yamaguchi 2014[14], Nitti 2013[15] concerning the reduction in the mean number of micturition per 24 hours, concluded that mirabegron (Weighted Mean Difference, WMD=0.60, $P < 0.0001$), and tolterodine (WMD 0.34, $P = 0.0005$) showed greater efficacy than the placebo. Their meta-analysis, however, did not find any differences when comparing mirabegron with tolterodine (WMD 0.11, $P = 0.12$).

The mirabegron group demonstrated a statistically significant greater reduction in the nocturia episodes than the tolterodine group ($p < 0.05$). Arcangelo Sebastianelli et al.[9], in the meta-analysis on the efficacy and tolerability of mirabegron in comparison with placebo and tolterodine, showed that mirabegron 50mg was associated with a significant reduction of nocturia episodes (WMD 0.13, $P = 0.003$), whereas only a marginally significant reduction was found for mirabegron 100 mg (WMD 0.16, $p=0.05$) when compared with the placebo. Conversely, tolterodine did not prove to be more effective than the placebo in reducing nocturia episodes (WMD 0.05, $P = 0.36$).

The mirabegron group demonstrated a statistically significant greater reduction in the urgency episodes per 24 hours than the tolterodine group ($p < 0.05$). A study by Arcangelo Sebastianelli et al.[9] concerning the reduction of urgency episodes per 24 h said mirabegron 50mg (WMD 0.53, $p<0.0001$), tolterodine (WMD 0.23, $p=0.02$) were associated with significantly greater efficacy compared to the placebo. But no significant differences were observed among both drugs.

There was no difference in urge incontinence episodes per 24 hours between both groups ($p> 0.05$) in our study. But the meta-analysis by Arcangelo Sebastianelli et al.[9] concluded Mirabegron 50mg (WMD 0.38, $p<0.0001$) and Tolterodine (WMD 0.21, $p = 0.02$) were significantly associated with the reduction of incontinence episodes per 24 hours when compared with the placebo. In addition, mirabegron 50mg was statistically equivalent to tolterodine (WMD 0.09, $p = 0.49$) regarding the number of incontinence episodes per 24 h, which means there was no significant difference between the two drugs concerning control of urge incontinence episodes. The results of our study are as per this meta-analysis.

The mirabegron group demonstrated a statistically significant reduction of IPSS at the 12th week compared with the tolterodine group ($p < 0.05$). In the MIRACLE study, Dong gill shin et al. concluded that significantly more significant changes from baseline to 12 weeks were observed in IPSS score in the mirabegron group ($p = 0.01$).[16]

A recent literature review and network meta-analysis compared the relative efficacy and tolerability between antimuscarinics and mirabegron 50 mg in patients with OAB, using peer-reviewed articles.[17] Results from 44 randomized controlled trials (RCTs) accounting for 309 patients showed that mirabegron 50 mg was as efficacious as antimuscarinics for incontinence, micturition frequency and Urge Incontinence episodes. This review corroborated the results of the phase III studies by showing that mirabegron in 50 mg dosage provides a more favourable tolerability profile, significantly lower rates of dry mouth compared with antimuscarinics. Hann-ChorngKuo et al. concluded that the overall incidence of treatment-emergent adverse events (TEAEs) was 42.9% (33/77 patients), 42.4% (36/85), and 49.4% (40/81) in the placebo, mirabegron, and tolterodine groups, respectively.[12]

Conclusion

Mirabegron showed better improvement in urgency episodes per 24 hours, a total number of micturition episodes per 24 hours, nocturia and IPSS score than tolterodine in overactive bladder patients. There was no difference between mirabegron and tolterodine in terms of incontinence episodes. Smaller sample sizes and no long term follow up were the main limitations of our study. So, further studies should be done to evaluate the efficacy of mirabegron compared with other antimuscarinics.

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None.

Conflict of Interest

None.

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