



Original Article

Role of Mirabegron in the Treatment of Overactive Bladder: A Prospective Study

Authors

**Dr Gurpreet Singh Bhangu, Dr Ritansh Bansal, Dr Darpan Bansal*,
Dr Ripudaman Singh, Dr Amrik Singh Bhatia**

Department of General Surgery, Sri Guru Ram Das Institute of Health Sciences and Research, Amritsar

*Corresponding Author

Dr Darpan Bansal

Introduction

Overactive bladder (also known as OAB or OAB Syndrome) is defined as a medical condition having the symptoms of urinary frequency (>8 micturitions/24 hours), urgency with a difficulty to defer and nocturia with or without urge incontinence, in the absence of local pathological or metabolic factors that would account for these symptoms.¹ These symptoms even in the absence of incontinence can have profound and stigmatizing effect on quality of life. However, they are under-reported by a majority of patients in lieu of the mis-beliefs such as incontinence is normal post-partum and with elderly age.²

The international continence society (ICS) has suggested OAB to be a urodynamic diagnosis of Detrusor Over activity (DO). ICS defines this as an involuntary rise in detrusor pressure during filling of the bladder in a laboratory situation in a conscious co-operative patient.

Urinary frequency can be reliably measured by the maintenance of a voiding diary. Conventionally, up to seven micturition episodes during waking hours has been considered normal,⁴ but this number isn't a constant and

varies based upon hours of sleep, fluid intake, comorbid medical conditions and several other factors.

Urgency is defined by International Continence Society as the "complaint of a sudden, compelling desire to pass urine which is difficult to defer."⁵ It is considered to be the hallmark symptom of OAB, however it is difficult to define it for research or clinical purposes.

Nocturia is the complaint of interruption of sleep one or more times because of the need to void.⁵

Urge incontinence is defined as the involuntary leakage of urine, associated with a sudden compelling desire to void.⁶ Incontinence episodes can be measured reliably with a diary, and the quantity of urine leakage can be measured with pad tests.

Mirabegron is an orally active potent β_3 -adrenoreceptor agonist having a potential to treat overactive bladder syndrome. It was originally developed for the treatment of diabetes but was later on refocused to treat OAB.⁷

The beta-adrenoceptors are widely distributed in adipose tissue, heart, vascular systems and the bladder. The β_3 subtype was identified in 1989

and is the predominate adrenoceptor in the bladder and direct stimulation is responsible for mediating detrusor relaxation in humans and can increase bladder capacity.⁸ Although, the presence of β_1 , β_2 , β_3 -adrenoreceptors have been demonstrated in human bladder, β_3 -adrenoreceptors account for more than 95% of all β -adreno receptors in the human bladder and are thought to be the main receptors mediating human detrusor relaxation.

Mirabegron relaxes bladder smooth muscle, increases cyclic adenosine monophosphate (cAMP) concentrations in bladder tissue and shows bladder relaxant effect in urinary bladder due to opening of big conductance calcium activated potassium channels. Mirabegron was developed by Astellas Pharma and was approved in United States in July 2012.⁹

OAB has consequences on physical as well as mental health of an individual, with symptoms such as skin breakdown due to leakage, sleep disturbance, fall-related injuries, depression and prolonged hospital stays.¹⁰ People with OAB are more likely to limit social outings, physical activity, and less often participate in social events and recreational activities.¹¹ Therefore, this study was undertaken to study a newer treatment modality, Mirabegron for the treatment of OAB.

Material & Methods

This prospective study was conducted in the department of General Surgery at Shri Guru Ram Das Institute Of Medical Sciences and Research, Amritsar. A total of 60 cases of overactive bladder were included in this study. The drug treatment with once daily administration of 25 mg of Mirabegron was given for a total of 12 weeks. The signs and symptoms were noted at the beginning of the therapy and then follow up was done at 4, 8, 10 and 12 weeks after administration of the medication to assess the response of the patient's symptoms. The patients were asked to maintain a daily diary of total number of micturitions per day and amount of urine per micturition using a urine pot as well as to note down the episodes of nocturia.

Results

A total of 60 cases of OAB from the age group of 30 to 80 years were included in this study. It was observed that an increased preponderance of OAB was seen in patients of elderly age with maximum number of patients between the age group of 51-60 years.(Table-1)

Table 1- Age wise distribution of patients affected with OAB

Age Distribution	Number of Patients	Percentage
30-40 years	6	10%
41-50 years	9	15%
51-60 years	22	36.67%
61-70 years	14	23.33%
71-80 years	9	15%
Total	60	100%

It was observed that the prevalence of OAB was more in females as compared to males with the female: male ratio being 2.5:1. The gender distribution of the patients included in this study are shown in Table-2.

Table-2 Gender Distribution of patients affected with OAB.

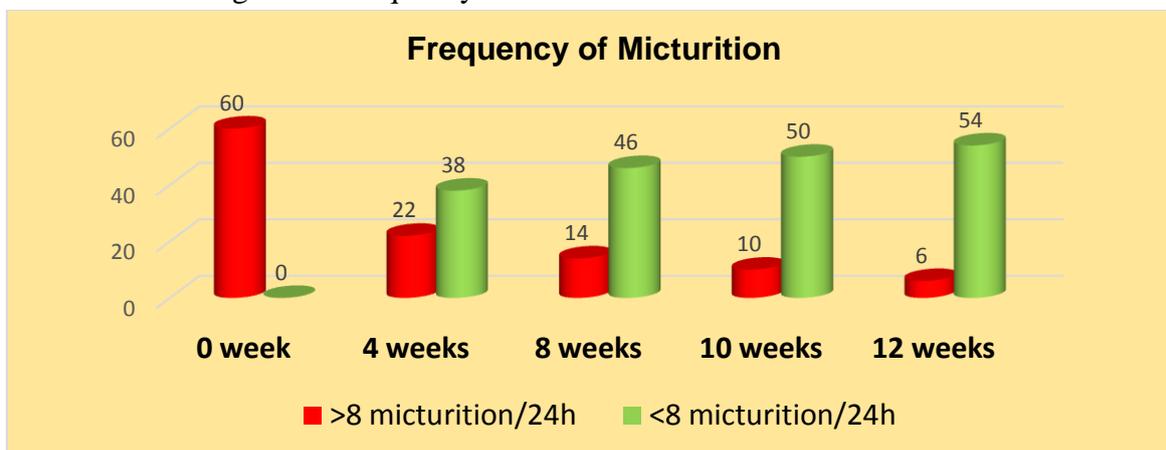
Gender	No. of patients	Percentage
Male	17	28.33%
Female	43	71.67%
Total	60	100%

Mirabegron was found to be effective in the treatment of the symptoms of OAB in a majority of the patients. Firstly, the symptom of Increased frequency of micturition was evaluated. As stated by ICS, more than 8 episodes of micturition were considered as increased frequency of micturition. It was observed that 90% of the patients were relieved of this symptom by the end of therapy as depicted in Table-3, Figure-1

Table-3 Effect of Mirabegron on Frequency Micturition/24 hour at various time intervals

Time Period	Number of Patients with <8 micturition/24h	Percentage	Number of Patients with >8 micturition/24h	Percentage
0 weeks	0	0%	60	100%
4 weeks	38	63.33%	22	36.67%
8 weeks	46	76.66%	14	23.43%
10 weeks	50	83.33%	10	16.67%
12 weeks	54	90%	6	10%

Figure-1 Effect of Mirabegron on Frequency of Micturition/24 hour at various time intervals



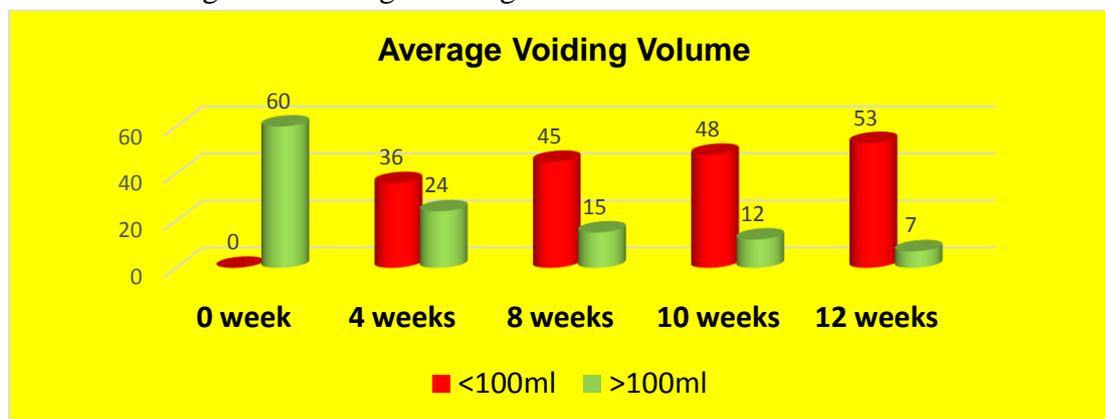
Thereafter, the symptom of average voiding volume was evaluated in all the 60 patients. An average voiding value of more than 100ml was considered to be efficaciously treated for OAB. In our study we observed that 60% of the patients

were effectively treated by mirabegron therapy as early as 4 weeks while 88.33% of patients were effectively treated by the end of the study period as shown in Table-4, figure-2.

Table-4 Effect of Mirabegron on average voiding volume at various time intervals

Time Period	Average voiding volume <100ml	Percentage	Average voiding volume >100ml	Percentage
0 weeks	60	100%	0	0%
4 weeks	24	40%	36	60%
8 weeks	15	25%	45	75%
10 weeks	12	20%	48	80%
12 weeks	7	11.67%	53	88.33%

Figure-2 Effect of Mirabegron on average voiding volume at various time intervals



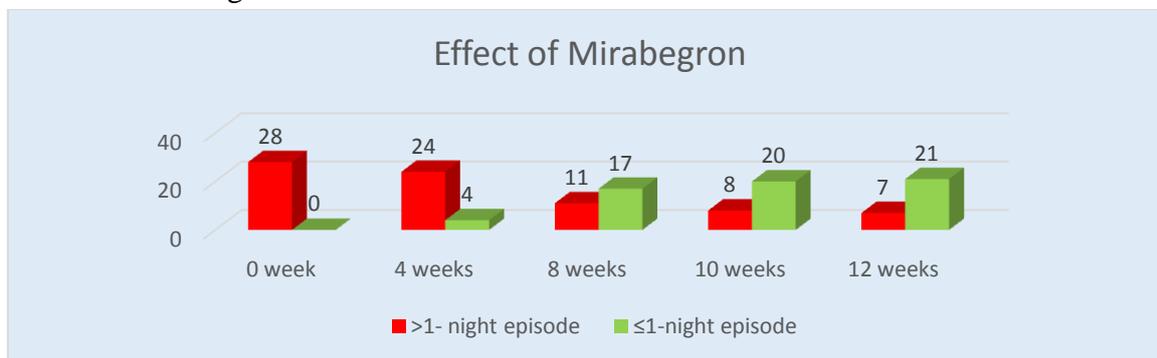
Amongst the 60 patients included in this study, it was observed that only 28(46.67%) patients complained of nocturia. Nocturia was considered to be present if the patient complained of more

than 1 episode of micturition during night. 75% of the patients were cured of nocturia at the end of therapy as depicted in Table-5, figure-3.

Table-5 Effect of Mirabegron on Nocturia at various time intervals

Time Period	Number of Patients with >1-night episode	Percentage	Number of Patients with ≤1-night episode	Percentage
0 weeks	28	100%	0	0%
4 weeks	24	85.71%	4	41.29%
8 weeks	11	39.28%	17	60.72%
10 weeks	8	28.57%	20	71.43%
12 weeks	7	25%	21	75%

Figure-3 Effect of Mirabegron on Nocturia at various time intervals



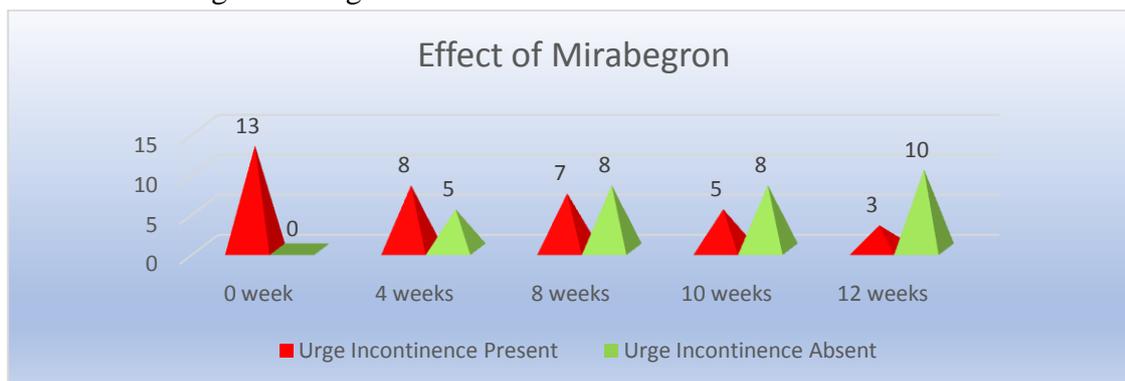
Lastly, the effect of mirabegron on the occurrence of urge incontinence was evaluated. It was observed that amongst a total of 60 cases included in this study, 13 (21.67%) of the patients

complained of nocturia. On treatment with mirabegron, 76.92% of the patients were relieved of the symptom of urge incontinence as depicted in Table-6, Figure-4.

Table-6 Effect of Mirabegron on Urge Incontinence at various time intervals.

Time Period	Urge Incontinence Present	Percentage	Urge Incontinence Absent	Percentage
0 weeks	13	100%	0	0%
4 weeks	8	61.54%	5	38.46%
8 weeks	7	53.85%	6	46.15%
10 weeks	5	38.46%	8	61.54%
12 weeks	3	23.08%	10	76.92%

Figure-4 Effect of Mirabegron on urge incontinence at various time intervals



Hence, mirabegron was efficacious in the relief of all the symptoms evaluated in this study. A few common side effects associated with the treatment with mirabegron were dry mouth, constipation and headache. However, the magnitude of the symptoms was relatively low and did not affect the compliance in our study.

Side Effects

Out of the total 30 patients treated with 25 mg once daily dose of Mirabegron, -- suffered with the side effect of constipation, -- suffered with dry mouth, and – suffered with ----- . However all these side effects were tolerable and none of the patients left the treatment due to them.

Discussion

Overactive bladder (OAB) is a highly prevalent condition affecting millions of men and women all around the world.¹³ It is a socially embarrassing condition with far-reaching consequences on mental as well as physical well-being. Although, an array of treatment options exists but no single treatment has been proven to be the gold standard approach in curing the disease. Often a combination of pharmacotherapy along with behavioral modifications is required to successfully manage OAB symptoms. Various pharmacological agents have been used for the management of OAB including antimuscarinics, oxybutynin, tolterodine, solifenacin succinate, imipramine, desmopressin, estrogen, vanilloids etc. Behavioral therapy has also been proven to be effective in the management of OAB. In refractory and complicated cases, PTNS, neuromodulation, augmentation cystoplasty and urinary diversion have also been employed for the treatment of OAB. However, pharmacotherapy remains the mainstay of the management for the treatment of OAB. Newer drugs such as mirabegron and darifenacin having specific receptor targets to the urinary bladder have been employed for the treatment of OAB and have proved to be efficacious alone as well as in combination with

other available medications with relatively minimal side effects and high compliance.

In our study we observed an increased prevalence of OAB with increasing age along with female preponderance. Gray MG conducted a study on “Evaluation and management of OAB: strategies for optimizing care” and similarly found out that increasing age is the best known risk factor for the occurrence of OAB and reported more occurrence of OAB in females.¹² Eapen RS conducted a study on the review of epidemiology of OAB and also concluded increasing age to be a confounding risk factor for the occurrence of OAB along with female gender being more oftenly affected.¹³

Warren K et al conducted a study on “Mirabegron in overactive bladder patients: Efficacy review and update on drug safety” and reported Mirabegron to be effective in curing the increased frequency of micturition. In our study, Mirabegron was able to cure increased frequency of micturition in 63.3% of patients at just 4 weeks of treatment and 90% of patients were relieved of the symptoms at the end of the study period i.e. 12 weeks.

Khullar V et al conducted a trial on the efficacy and tolerability of mirabegron vs a placebo and measured post voiding residual volume. They reported mirabegron to be effective in the decreasing the post voiding residual volume.¹⁴ Hesch K et al conducted a study on the agents for treatment of overactive bladder and concluded that darifenacin was effective in relieving the symptom of decreased voiding volume per micturition in more than 90% of the patients.¹⁵ In our study, 60% of patients treated with Mirabegron reported normal average voiding volume at the end of 4 weeks, while 88.3% of them were efficaciously treated at the end of the study period i.e. 12 weeks.

Andersson KE et al conducted a study on the pharmacotherapy of nocturia and described Mirabegron to be an effective agent for the treatment of nocturia associated with OAB based on phase 2 dose-ranging trial of Mirabegron.¹⁶ Herschorn et al conducted a double blind

randomized multicenter trial for the efficacy of Mirabegron in the patients of OAB (PREFER) and found Mirabegron to be effective in relieving the symptoms of urgency in the patients with OAB.¹⁷ We similarly found mirabegron to be effective in the treatment of nocturia and urge incontinence.

Conclusion

It has been concluded that both Mirabegron is highly effective newer treatment option for the management of OAB with minimal side effects. The once daily oral administration of the drug in 25 mg makes it a highly tolerable and compliant treatment modality. The relief of symptoms begins as early as 4 weeks gradually progressing and is retained with no relapses of the symptoms throughout the therapy.

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