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Efficacy And Tolerability Of Mirabegron In Women With Overactive Bladder

Dr Kriti[1], Dr Pushpa Nagar[2], Nivesh[3], Dr Prachi Sharma[4], Dr Aakriti Chandra[5]
[1,4,5]Resident, [2]Senior professor and unit head, [3]Intern
Department of Obstetrics & Gynaecology, SMS Medical College and Hospital, Jaipur

***Corresponding Author:**
Dr. Pushpa Nagar
Senior Professor and Unit Head
Department of Obstetrics & Gynaecology, SMS Medical College and Hospital, Jaipur

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Abstract

Background:

Overactive bladder (OAB) is a prevalent, chronic symptom complex that has a significant negative impact on the social, psychological, financial and sexual aspects of quality of life. Mirabegron is the first b3-adrenoceptor selective agonist approved for the treatment of OAB. The aim of our study is to evaluate the efficacy and tolerability of mirabegron as treatment option for OAB and to identify if any patient characteristics predicted patients response to therapy.

Method:

It was a prospective observational study conducted on 89 women (11 loss to follow up) with OAB, between June 2019 to May 2020. Patients were prescribed Mirabegron 50 mg once daily for 6 weeks. They were assessed at the initial appointment and at 6 weeks using validated questionnaires. The primary outcome measure was defined using the International Consultation of Incontinence Modular Questionnaire Female Lower Urinary Tract Symptoms long Form(ICIQ- FLUTS LF).

Results:

100 women were prescribed mirabegron and 89 (89%) completed 6 weeks of drug therapy. Of those completing the course, There was significant symptom improvement based on the ICIQ-FLUTS long form scores from 20.13 to 9.00 ($p < 0.001$). Four (4%) patients discontinued mirabegron prematurely due to side-effects. Three (3%) did not attend follow up and four (4%) decided against taking the medication and did not use their prescription.

Conclusion:

Mirabegron is a treatment option for patients with overactive bladder. Treatment benefits are remarkable and the discontinuation rate for side effects are low.

Keywords: NIL

INTRODUCTION

International Continence Society (ICS) defines Overactive bladder syndrome as a clinical syndrome characterized by lower urinary tract dysfunction, including symptoms of urgency, with or without urge incontinence, usually accompanied by increased frequency of urination and nocturia in the absence of associated metabolic factors, infectious or local causes. Urinary incontinence, although not a dangerous condition, detrimentally affects the psychological health of women and negatively affects quality of life. Although highly under-reported, epidemiological data suggest that the prevalence of OAB in women is 16.9% and comparably increases with age.2,3 Because of patients failing to report

symptoms to their physician, the physical and economic burden of OAB is under-reported but is estimated to be up to 50% of women.4,5 Thus, it is significant to evaluate and treat this "silent" problem that affects so many women who do not discuss it.

Overactive bladder is a debilitating disease, which can substantially impede the quality of life, resulting in low self -esteem, anxiety, depression, impairment of work productivity and increased incidence of sexual problems, sometimes with personal distress and social cut off. The aim of treatment is to reduce overactive bladder symptoms in women and thereby improve the quality of life.

The main therapeutic modalities employed include non-pharmacological and pharmacological treatment. Non-pharmacological clinical treatment includes general measures, behavioral treatment and physical therapy.

On the other hand, the mainstay therapy for overactive bladder syndrome is pharmacological. Currently, anticholinergic agents are the drugs most often used for managing this disease. However, some patients have a suboptimal response to antimuscarinics or may experience adverse effects such as dry mouth or constipation. Therefore, a high proportion of patients discontinue antimuscarinic therapy, with fewer than 25% remaining on treatment at 1 year.6

Recent advances in the understanding of the physiopathology of OAB have identified three subtypes of b-adrenoceptor (b1, b2, and b3) in the detrusor muscle and urothelium.

Mirabegron a new FDA approved drug is the first b3-adrenoceptor agonist to enter clinical practice. It improves the storage capacity of the bladder, without impairing bladder contraction during voiding.7 Mirabegron does not have the same adverse effects as anticholinergic agents and, thus may be more tolerable in some individuals who experience side effects with anticholinergics.

Mirabegron has high intrinsic activity for b3-adrenoceptors and very low intrinsic activity for b1 and b2 adrenoceptors. Stimulation of b3-adrenoceptors elicits direct relaxation of detrusor smooth muscle; mediated by the increase intracellular levels of cyclic adenosine monophosphate.

METHODOLOGY

A prospective study on 100 women with lower urinary tract symptoms attending Gynaecology OPD from June 2019 to May 2020, who fail to respond to conservative treatment or who refuse to accept conservative treatment, was done in department of obstetrics and gynaecology, SMS medical college, Jaipur. Prior to the study, Approval was taken from the ethical board for the drug usage. Informed and written consent was taken from each women of the study group. Then inclusion criteria was implied which comprised of women with symptoms of overactive bladder, including frequency- voiding >8 times/day, urgency – sudden compelling desire to pass urine, urge incontinence- involuntary leakage of urine, nocturia - 2 or >2 times. Women with urinary tract infections, uncontrolled hypertension, cardiovascular disease and on diuretics were excluded. Symptoms were evaluated using the International Consultation of Incontinence Modular Questionnaire Female Lower Urinary Tract Symptoms long Form(ICIQ- FLUTS LF)[8], and catergorised in terms of frequency (F score), voiding (V score) and incontince (I score). Patients were prescribed Mirabegron 50 mg once daily for 6 weeks. Patients were assessed at the initial appointment and reviewed in clinic 6 weeks later using validated questionnaires. Post treatment analysis was done and outcomes were measured. Primary outcome measure was evaluated using the International Consultation of Incontinence Modular Questionnaire Female Lower Urinary Tract Symptoms long form (ICIQ FLUTSLF).

Secondary outcome measures included discontinuation rates and adverse reaction rates.

Statistical analysis was done from the pre and post treatment data using Wilcoxon test, Kruskal wallis test,chi sqaure test and p value(<0.05 taken as significant).

RESULTS

A total of 100 eligible women were enrolled into the study with 89 actually taking the prescribed medication. Some refused, some had side effecs and some were lost to follow up. Hundred patients completed the 6 weeks course of mirabegron.

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As observed from Table 1, the mean F Score (frequency) decreased from a maximum of 8.06 at the Pre-Treatment timepoint to a minimum of 2.70 at the Post-Treatment timepoint. This change was statistically significant (Wilcoxon Test: V = 3916.0, p = <0.001).

Coming to the voiding symptoms, From table 2, the mean V Score (Voiding symptoms) decreased from a maximum of 2.70 at the Pre-Treatment timepoint to a minimum of 1.53 at the Post-Treatment timepoint. This change was statistically significant (Wilcoxon Test: V = 2628.5, p = <0.001).

Next incontinence ,From table 3, the mean I Score (Incontinence) decreased from a maximum of 9.37 at the Pre-Treatment timepoint to a minimum of 4.78 at the Post-Treatment timepoint. This change was statistically significant (Wilcoxon Test: V = 4005.0, p = <0.001).

Overall analysis done from table 4 shows, the mean Total Score decreased from a maximum of 20.13 at the Pre-Treatment timepoint to a minimum of 9.00 at the Post-Treatment timepoint. This change was also statistically significant (Wilcoxon Test: V = 4005.0, p = <0.001). And lastly, Table 5 is the summary of side effects, which shows only 8% had side effects.

DISCUSSION

This study provides us with the information which are statistically confirmed. In our study after a course of 6 weeks, Mirabegron therapy with 50mg OD, a significant improvement in the total ICIQ-FLUTS LF (p<0.001) was observed. When the score is further subdivided, a significant improvement in the filling, incontinence and voiding score was also noted. Similrly, In a BLOSSOM study done by Chapple CR et al(2013)9 mirabegron showed statistically significant improvement versus placebo in the mean change of micturition frequency from baseline to the final visit (p < 0.01). Urgency episodes in 24 hours decreased significantly for mirabegron groups (p < 0.05). Statistically significant improvements in changes in incontinence episodes, urgency incontinence [urge urinary incontinence (UUI)] episodes, and nocturia episodes were also observed.

Similar to our study, In another dose-ranging DRAGON study done by Chapple CR et al(2013)10, the primary efficacy results showed dose-dependent decrease in mean number of micturitions in 24 hours, which were statistically significantly different between the placebo and 50mg, 100mg and 200mg mirabegron groups (p < 0.05). In addition, from baseline to final follow-up visit, the mean improvements in mean voiding volume (MVV), incontinence episodes, UUI episodes, urgency episodes, level of urgency, and nocturia episodes were statistically significant.

Nitti VW et al(2013)11 did ARIES study, which showed statistically significant improvements in MVV, level of urgency number of UUI episodes, urgency episodes, and nocturia episodes in 24 hours from baseline to final visit, and in number of incontinence episodes and micturitions in 24 hours from baseline to Week 4 for both mirabegron groups compared with the placebo group (all p < 0.05) which is also observed in our study.

A similar comparative study done by Herschorn S et al (2013) The CAPRICORN study,12 compared with placebo, 50 mg mirabegron demonstrated significantly greater improvements at 4 week in mean number of incontinence episodes in 24 hours (p < 0.001) and micturition in 24 hours compared with the placebo group. Compared with placebo, 50 mg mirabegron also demonstrated statistically significant improvements at this time points in mean level of urgency, number of UUI episodes in 24 hours, and urgency episodes. The 25-mg mirabegron group demonstrated numerically greater improvements on the three urgency assessments than did the placebo group. However, reduction from baseline in the mean UUI episodes in 24 hours was the only urgency assessment with statistical significance.

Side-effect profile and efficacy remain the two most important factors for the success of a drug therapy. Mirabegron has a low side-effect profile with only 8% of the total population reporting any side effects and only 4% discontinuing therapy before the 6-week point due to side effect. Palpitations occurred most frequently at 4%, which is comparable to rates in published literature.

There are certain limitations to this study. The study design did not allow for comparisons of response of Mirabegron versus placebo or antimuscarinic therapy. The study cohort included a mixed pool of

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patients and the drug study group was small. The outcome was assessed using ICIQ-FLUTS . This gives a global assessment of improvement which we felt is a more useful indicator than a change in individual quality of life. This gives valuable data on the proportions of patients that are likely to benefit from drug therapy.

CONCLUSION

Mirabegron is an effective treatment option for treatment of women with overactive bladder. It has a low side effect profile and is well tolerated. This study confirms that mirabegron improves the symptoms and quality of life in women with overactive bladder. And is broadly comparable with other drug therapies.

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Table 1 : Assessment of change in F Score over time (n = 89)

Timepoint	*F Score*			*Wilcoxon Test*	
	Mean (SD)	Median (IQR)	Range	V	P Value
Pre-Treatment	8.06 (3.10)	8.00 (3.00)	2.00 - 16.00	3916.0	<0.001
Post-Treatment	2.70 (1.53)	2.00 (1.00)	0.00 - 8.00		
Absolute Change	-5.40 (2.14)	-5.00 (3.00)	-12.00 - 0.00		
Percent Change	-67.2% (15.5)	-69.2% (12.5)	-100% - 0%		

Table 2 : Assessment of change in V Score over time (n = 89)

Timepoint	*V Score*			*Wilcoxon Test*	
	Mean (SD)	Median (IQR)	Range	V	P Value
Pre-Treatment	2.70 (2.09)	2.00 (3.00)	0.00 - 8.00	2628.5	<0.001
Post-Treatment	1.53 (1.40)	1.00 (2.00)	0.00 - 5.00		
Absolute Change	-1.19 (1.04)	-1.00 (1.00)	-4.00 - 4.00		
Percent Change	-52.2% (24.4)	-50.0% (26.7)	-100% - 0%		

Table 3 : Assessment of change in I Score over time (n = 89)

Timepoint	*I Score*			*Wilcoxon Test*	
	Mean (SD)	Median (IQR)	Range	V	P Value
Pre-Treatment	9.37 (3.33)	9.00 (4.00)	3.00 - 18.00	4005.0	<0.001
Post-Treatment	4.78 (2.04)	5.00 (3.00)	1.00 - 8.00		
Absolute Change	-4.67 (1.77)	-5.00 (2.00)	-10.00 - -1.00		
Percent Change	-50.2% (12.6)	-50.0% (13.4)	-83% - -25%		

Table 4 : Assessment of change in Total Score over time (n = 89)

Timepoint	*Total Score*			*Wilcoxon Test*	
	Mean (SD)	Median (IQR)	Range	V	P Value
Pre-Treatment	20.13 (6.93)	19.50 (8.25)	6.00 - 38.00	4005.0	<0.001
Post-Treatment	9.00 (3.83)	9.00 (6.00)	1.00 - 19.00		
Absolute Change	-11.27 (3.54)	-11.00 (3.00)	-20.00 - -4.00		
Percent Change	-56.6% (9.0)	-57.1% (9.4)	-89% - -36%		

Table 5 : Summary of Side Effects

Side Effects	Present	Absent
Any	8 (8.0%)	92 (92.0%)
Palpitation	4 (4.0%)	96 (96.0%)
Heart Burn	1 (1.0%)	99 (99.0%)
Headache	0 (0.0%)	100 (100.0%)
Abdominal Pain	3 (3.0%)	97 (97.0%)
Urinary Retention	1 (1.0%)	99 (99.0%)
Pruritis	0 (0.0%)	100 (100.0%)
Lethargy	0 (0.0%)	100 (100.0%)

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