International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 5(E); May 2018; Page No. 12560-12564
DOI: http://dx.doi.org/10.24327/ijcar.2018.12564.2211

Research Article

EFFICACY AND TOLERABILITY OF TREATMENT WITH MIRABEGRON COMPARED WITH SOLIFENACIN IN THE MANAGEMENT OF OVERACTIVE BLADDER SYNDROME: A PROSPECTIVE COMPARATIVE STUDY

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A R T I C L E I N F O

Article History:

Received 6th February, 2018
Received in revised form 20th March, 2018 Accepted 8th April, 2018
Published online 28th May, 2018

Key words:

Mirabegron, overactive bladder, quality of life, solifenacin, urge urinary incontinence, urodynamic testing.

A B S T R A C T

Aim: The aim of this study is to compare the efficacy and tolerability of solifenacin and mirabegron in patients with overactive bladder (OAB) syndrome.
Methods: We carried out a prospective randomized double blind comparative analysis in 342 women affected by OAB syndrome; 168 were treated with solifenacin 5 mg/daily and 174 with mirabegron 50 mg/daily. A clinical evaluation, 3-day voiding diary, and urodynamic testing was performed. Patients completed the Overactive Bladder Questionnaire - Short Form and the Patient Global Impression of Improvement questionnaire. The adverse effects were evaluated. The two groups were compared at baseline and at 12 weeks.
Results: After 12 weeks, a significant reduction in the mean number/24 h of voids and urgent micturition episodes/24 h was observed in both groups. Detrusor overactivity decreased from 58.3% to 13.1% in the solifenacin group and from 58% to 11% in the mirabegron group. Twenty (12%) and 18 (10.7%) patients taking solifenacin reported constipation and dry mouth, respectively, versus four (2.3%) and five (2.9%) patients taking mirabegron, respectively, but there was no difference between the groups in the change in vital signs.
The Overactive Bladder Questionnaire - Short Form did not demonstrate significant differences and the abandonment rates in the solifenacin and mirabegron groups were 25.5% and 20%, respectively.
Conclusion: Solifenacin and mirabegron showed the same efficacy in the treatment of OAB but solifenacin had more adverse effects.

INTRODUCTION

Overactive bladder (OAB) syndrome, consisting of urgency, with or without urgency incontinence, often with frequency (voiding more than eight times in a 24- h period) and nocturia (need to wake up one or more times per night for urination), is a highly prevalent disorder with a significant impact on quality of life (QoL).[1] The National Overactive Bladder Evaluation program estimated OAB prevalence in the USA at 16.5%, with similar findings in the corresponding European study.[2,3] It is estimated that by 2018, as much as 20% of the worldwide population will suffer from OAB, with the prevalence increasing with female age.[4]

The causes of OAB are multifactorial and may be neurogenic, myogenic, or idiopathic.[5] The current pharmacologic approach to treating OAB mainly involves antimuscarinic agents, but the use of these agents is limited in some individuals because of suboptimum efficacy or bothersome adverse events, which cause a high rate of abandonment.[6] Mirabegron, a first-in-class selective β3-adrenoceptor agonist, represents an alternative to antimuscarinic therapy and has a unique mechanism of action and a low side-effect profile.[7] In the published work, there are several studies comparing drugs for the treatment of over active bladder with placebo but there are still few studies comparing two specific drugs. Especially, there are no further data on the comparison between mirabegron and solifenacin in terms of subjective and objective care and the impact on QoL. The aim of this study was to compare the efficacy and tolerability of solifenacin and mirabegron in overactive bladder (OAB) syndrome patients.

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METHODS

From January 2017 to January 2018, 412 consecutive women affected by OAB syndrome were referred to our department and were considered for the study. Of these, 33 (8%) refused treatment and 37 (9%) underwent treatment but were lost to follow-up. The remaining 342 patients (83%) were enrolled in this study. The present study is prospective randomized double blind comparative analysis. In our urogynecologic clinic, the visit and urodynamic examination are the standard care at

baseline and then at 12 weeks after the treatment. Patients who fulfilled all inclusion criteria at baseline were randomized 1:1 to receive double-blind mirabegron 50mg or solifenacin 5mg once daily 12weeks.The Institutional Review Board approved the study. We consider solifenacin and mirabegron to be at the same therapeutic level in patients with OAB; therefore, the choice of the prescribed drug does not depend on the patient's clinical characteristics as we extrapolated the data of patients with the same anamnesis and demographic characteristics taking either of these drugs as first therapy for OAB. None of the patients had previously taken antimuscarinic or other drugs for OAB treatment before our prescription.

OAB diagnosis was assessed clinically with the following anamnestic criteria: urgency and frequent urination (eight or more times during the daytime and twice or more at night) in the absence of pathologic or metabolic conditions that may cause or mimic OAB, such as urinary tract infections, polyuria, transitional cell carcinoma of the bladder, and underlying neurologic abnormalities.[8]

The inclusion criteria were as follows: symptoms of OAB (for at least 12 weeks) and/or urgent urinary incontinence; no previous administration of other drugs for OAB; and signed informed consent.

The exclusion criteria were as follows: stress urinary incontinence or mixed urinary incontinence confirmed by urodynamic testing, neurological disease and neurogenic bladder, urinary tract infection, bladder lithiasis, genital prolapse higher than stage II on the Pelvic Organ Prolapse Quantification system, uncontrolled narrow angle glaucoma, severe cardiac disease, hypertension, pelvic tumors, post-void residual urine ≥ 100 mL, previous radiation therapy, previous antimuscarinic agents, antidepressants, and antianxiety agents.[9] All women underwent a detailed clinical evaluation, including a complete history, physical examination, 3-day voiding diary, and urodynamic testing. The study was performed with a transurethral 6-Fr, double-lumen catheter into the bladder and a balloon catheter inserted into the rectum to measure abdominal pressure, with a filling rate of 50 mL/min and the patient in the sitting position.Urinary symptoms related to OAB were evaluated with a voiding diary, and the Symptom Bother and Health-Related Quality of Life scales of the Overactive Bladder Questionnaire (OAB-Q) were used to measure the subjective degree of OAB symptoms and impact on QoL. We used a validated short version of the OAB-Q (the OAB-Q Short Form [SF]) at baseline and after 12 weeks.[10] The impact of incontinence on patients' QoL was evaluated with subjective global improvement was measured with the Patient Global Impression of Improvement (PGI-I) questionnaire after 12 weeks of treatment.[11,12] One hundred and sixty-eight patients treated with solifenacin 5 mg/daily (group 1) and 174 patients treated with mirabegron 50 mg/daily (group 2) were evaluated and compared. Adverse effects were evaluated at the end of treatment. No analyzed patient abandoned the drug before 12 weeks. The primary end-points were the change from baseline to the end of treatment in the mean number of voids in 24 h, mean number of urgent micturition episodes in 24 h, mean number of urinary incontinence episodes in 24 h, and mean number of nocturia episodes within the treatment groups and between the two treatment groups. The secondary end-points included improvement in OAB symptom bother (measured with the OAB-Q SF) and improvement in OAB health-related QoL (measured with the OAB-Q SF) after 12 weeks within the treatment groups and between the two treatment groups. Adverse effects were also considered and compared. Urodynamic parameters were compared between the two study groups. The PGI-I after 12 weeks of treatment was compared between the two treatment groups.

Statistical analysis was carried out with the Wilcoxon matched pairs test for the continuous variables and the $\chi 2$-test for the frequency data. Quantitative data are expressed as mean _ standard deviation in the tables. The paired t-test was used to compare the difference in the values between baseline and after treatment. To demonstrate the differences, the Student's t-test and Mann-Whitney U-test were used. Matched t-test was applied to determine the change in OAB Symptoms Score (QABSS) values. Treatment differences were summarized using least squares means and two-sided 95% confidence intervals for mean changes from baseline within the treatment groups and between the treatment groups. The primary method for analyzing count data (i.e., incontinence episodes, urgency incontinence episodes, nocturia episodes) used a mixed-effects Poisson regression model. All analyses were conducted using SPSS 22.0 for Mac. Significance was set at a P-value of <0.05.

RESULTS

A total of 342 patients were enrolled in the study. One hundred and sixty-eight patients were treated with solifenacin (group 1) and 174 were treated with mirabegron (group 2). The baseline demographic and clinical characteristics of the patients are shown in Table 1.

Table 1 Demographic characteristics of 342 patients

variables	Solifenacin(n=168)	Mirabegron(n=174)	P
Age,years(mean±SD	58.34±6.14	59.12±5.23	0.21
BMI(mean±SD)	26.06±3.42	26.34±2.98	0.42
Menopausal patients,n(%)	94(54.97)	101(59.06)	0.72
Parity n(range)	2(0-3)	2(0-4)	0.24

BMI, body mass index; SD, standard deviation.

After treatment, the percentage of patients with urodynamic detrusor over activity (DO) decreased from 58.3% to 13.1% (P < 0.0001) in group 1 and from 58% to 11% (P < 0.0001) in group 2, but we observed no significant difference between the two study groups. The first voiding desire at urodynamic evaluation increased in both groups after 12 weeks (group 1: 88.83 _ 19.34 vs 153.21 _ 20.87 mL, P < 0.0001; group 2: 87.53 _ 20.49 vs 157.39 _ 19.79 mL, P < 0.0001) without a statistically significant difference between the two groups. The maximum cystometric capacity increased in the solifenacin group (276.51 _ 71.51 vs 379.56 _ 87.24 mL, P < 0.0001) and in the mirabegron group (257.77 _ 81.88 vs 386.46 _ 90.32 mL, P < 0.0001); the detrusor pressure at peak flow (cmH2O) also decreased in both groups (group 1: 19.52 _ 5.57 vs 10.76 _ 5.31, P < 0.0001; group 2: 20.90 _ 4.97 vs 11.23 _ 5.11, P < 0.0001) but we observed no significant difference between the two groups. The urodynamic data are shown in Table 2.

According to the statistical analysis, at the end of 12 weeks of treatment, a reduction in the mean number in 24 h of voids (9.78 _ 2.52 vs 6.23 _ 1.54, P < 0.0001), urgent micturition episodes/24 h (5.32 _ 1.54 vs 1.32 _ 1.21, P < 0.0001), nocturia episodes (2.94 _ 0.85 vs 1.09 _ 1.21, P < 0.0001), and urinary incontinence episodes / 24 h (0.75 _ 0.86 vs 0.28 _ 0.56, P = 0.003) was observed in the solifenacin group.

Table 2 Pre- and post- (12-weeks) urodynamic evaluation

Urodynamic data	Solifenacin (n=168)			Mirabegron(n=174)			Solifenacin vs mirabegron
	Baseline	12wks	P	Baseline	12wks	P	P
Peak flow(ml/s)	20.76±2.64	25.49±4.97	<0.0001	19.85±3.12	24.91±4.75	<0.0001	0.27
Flow time(ml/s)	26.44±4.76	27.84±5.37	0.011	25.89±5.12	26.23±4.11	0.50	0.002
Post-void residual volume(ml)	20.37±7.38	18.45±7.52	0.018	21.45±8.22	18.10±7.88	<0.0001	0.67
First voiding desire(ml)	88.83±19.34	153.21±20.87	<0.0001	87.53±20.49	157.9±19.79	<0.0001	0.06
Maximum cystometric capacity(ml)	276.51±71.51	379.56±87.24	<0.0001	257.77±81.88	386.46±90.32	<0.0001	0.47
Detrusor pressure at peak flow (cmH2O)	19.52±5.57	10.76+5.31	<0.0001	20.90±4.97	11.23±5.11	<0.0001	0.40
Patients with detrusor overactivity (%)	98(58.3)	22(13.1)	<0.0001	101(58)	19(11)	<0.0001	0.74

In the mirabegron group, we observed a reduction in the mean number of voids in 24 h (9.21 _ 1.87 vs 5.97 _ 1.67, P < 0.0001), urgent micturition episodes/24 h (5.11 _ 1.89 vs 1.45 _ 1.11, P < 0.0001), nocturia episodes (3.13 _ 0.87 vs 0.94 _ 1.13, P < 0.0001), and urinary incontinence episodes / 24 h (0.82 _ 1.07 vs 0.30 _ 0.64, P < 0.0001), but no significant differences were observed between the two groups. No difference was reached even for the change in vital signs within the groups or between the two groups after 12 weeks of treatment (Table 3).

As shown in Table 4, no statistically significant difference was found for other adverse events. After 12 weeks, the PGI-I revealed the patients' satisfaction rates of 78.9% in the solifenacin group and 80.7% in the mirabegron group without a statistically significant difference between the two groups (Table 5). No patients abandoned therapy during the 12 weeks of treatment but after 12 weeks, the abandonment rate was 25.6% (43 patients) in the solifenacin group and 20% (35 patients) in the mirabegron group (P = 0.38).

Table 3 Comparison of voiding diary, quality of life questionnaires, and vital signs before and after treatment (12-weeks follow-up)

Variables	Solifenacin			Mirabegron			Solifenacin vs mirabegron
Follow up	Baseline	12wks	P	Baseline	12wks	P	P
Mean number of voids(24h)	9.78±2.52	6.23±1.54	<0.0001	9.21±1.87	5.97±1.67	<0.0001	0.13
Mean number of urgent micturition events(24h)	5.32±1.54	1.32±1.21	<0.0001	5.11±1.89	1.45±1.11	<0.0001	0.30
Mean number of urinary incontinence events(24h)	0.75±0.86	0.28±0.56	<0.0001	0.82±1.07	0.30±0.64	<0.0001	0.76
Mean number of nocturia events	2.94±0.85	1.09±1.21	<0.0001	3.13±0.87	0.94±113	<0.0001	0.24
OAB-Q symptoms	62.21±14.62	22.31±12.84	<0.0001	64.27±13.75	21.45±13.45	<0.0001	0.55
OAB-Q(HRQL)	19.76±9.12	84.45±12.56	<0.0001	18.12±8.88	85.32±13.09	<0.0001	0.53
VITAL SIGNS	Baseline	12wks	P	Baseline	12wks	P	P
Systolic pressure(mean+SD)	125.54±13.42	126.65±12.87	0.43	125.87±12.86	126.64±13.58	0.59	0.95
Diastolic pressure(mean+SD)	84.65±8.67	85.63±9.43	0.32	83.95±9.65	84.43±10.73	0.66	0.27
Pulse rate(mean+SD)	78.23±11.32	79.76±12.43	0.24	77.65±11.23	78.31±12.94	0.65	0.29

HRQL, Health-Related Quality of Life scale; OAB-Q, Overactive Bladder Questionnaire; SD, standard deviation.

At the follow-up visit, 20 (11.7%) and 18 (10.5%) patients taking solifenacin reported constipation and dry mouth, respectively, while these numbers were only four (2.3%) and five (2.9%) in patients taking mirabegron, respectively. However, no patients abandoned treatment before 12 weeks in either of the groups.

DISCUSSION

The present study supports the efficacy and safety of solifenacin and mirabegron in the treatment of OAB patients. After treatment, the percentage of patients with urodynamic DO decreased from 58.3% to 13.1% in the solifenacin group and from 58% to 11% in the mirabegron group.

Table 4 Patients' clinical characteristics at baseline and adverse effects after 12 weeks of treatment

Variables	Solifenacin (n=168) Baseline	Solifenacin (n=168) 12wks	P	Mirabegron (n=174) Baseline	Mirabegron (n=174)12wks	P	Solifenacin vs mirabegron (12wks),p
Dry mouth(%)	0(0)	20(12)	<0.0001	0(0)	4(2.3)	NS	0.0012
Constipation(%)	2(1.2)	18(10.7)	0.0004	3(1.8)	5(2.9)	NS	0.0087
Headache(%)	5(3)	6(3.6)	NS	1(0.6)	3(1.7)	NS	NS
Urinary retention(%)	0(0)	1(0.6)	NS	0(0)	1(0.6)	NS	NS
Vision blurred(%)	0(0)	1(0.6)	NS	0(0)	0(0)	NS	NS
Glaucoma(%)	0(0)	0(0)	NS	0(0)	0(0)	NS	NS
Tachycardia(%)	2(1.2)	2(1.2)	NS	3(1.8)	4(2.3)	NS	NS
Hypertension(%)	1(0.6)	3(18)	NS	1(0.6)	2(1.1)	NS	NS

NS, not significant.

Table 5 Patient Global Impression of Improvement after 12 weeks of treatment

Variables	Solifenacin(n=168)	Mirabegron(n=174)	P
Very much better(%)	95(56.5)	101(58)	NS
Much better(%)	40(23.8)	37(21.3)	NS
A little better(%)	16(9.5)	14(8)	NS
No improvement(%)	13(7.7)	14(8)	NS
A little worse(%)	7(4.2)	5(2.9)	NS
Much worse(%)	0(0)	0(0)	-
Very much worse(%)	0(0)	0(0)	-
SUCCESS(%)	135(80.3)	138(79.3)	NS

NS, not significant.

Guidelines recommend bladder training and lifestyle advice as first-line treatments for OAB, followed by primary pharmacotherapy with antimuscarinic agents (i.e., darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) or β3-adrenoreceptor agonist (mirabegron).[13,14] In this study, solifenacin and mirabegron were compared and efficacy and safety were evaluated.

Antimuscarinic agents represent the first-line pharmacological therapy recommended for OAB treatment, but cause common adverse events.[15] They also inhibit muscarinic receptors in different tissues, such as the salivary glands and the brain, as well as those in the bladder. As reported in the published work, this lack of specificity results in adverse events, such as blurred vision, constipation, and above all dry mouth, which are the most common causes of treatment withdrawal. In fact, it is estimated that the discontinuation rate at 12 months for OAB patients treated by antimuscarinics ranges between 65% and 86%.[16] Also, the present study demonstrated constipation and dry mouth in 20 (12%) and 18(10.7%)patients treated by solifenacin. It is an effective muscarinic receptor antagonist with selectivity for M3 receptors in the urinary bladder but there may also be minimal activation in other muscarinic receptors that are expressed in different tissues.[17] In fact, all five muscarinic receptor subtypes (M1-M5) are also expressed in the brain and have been shown to play a pivotal role in learning, memory, movement control, pain reception, and circadian cycle regulation.[18] Antagonism of these receptors is expected to have an impact on cognitive function.[19] Central nervous system side-effects, such as somnolence, fatigue, confusion, delirium, and cognitive impairment, can result when antimuscarinics cross the blood-brain barrier, becoming more permeable in older people.[20] Among the antimuscarinics, fesoterodine has demonstrated favorable central nervous system tolerability, presumably as a result of having the lowest penetration across the blood-brain barrier, although it is less effective and shows more side-effects than solifenacin. [8,21,22] Mirabegron, the first commercially available β3-adrenoreceptor agonist for the treatment of OAB, has a mechanism of action and side-effect profile distinct from that of antimuscarinics.[23] The approval of mirabegron was based on three placebo-controlled phase III studies in which mirabegron 25 and 50 mg significantly and respectively reduced incontinence and micturition episodes.[24] It enhances urine storage through stimulation of bladder β3-adrenoreceptors and has similar efficacy to antimuscarinic therapy, but with improved tolerability, with a lower incidence of dry mouth.[23,24]

In our study, as reported in the published work, mirabegron 50 mg/daily showed improvement in urodynamic parameters and urinary symptoms. In particular, the interesting results of this study were an increase in the maximum cystometric capacity of patients with urodynamic DO treated with mirabegron compared with those treated with solifenacin. This increase may be due to the β3-adrenergic action, which has an affect directly on bladder compliance, relaxing the detrusor muscle during filling.These results were not observed in patients without DO. Only four (2.3%) and five (2.9%) patients taking mirabegron presented with constipation and dry mouth, respectively. Periodic monitoring of blood pressure is recommended because mirabegron could increase blood pressure, especially in hypertensive patients; in fact, it is not recommended in severe uncontrolled hypertensive patients, though mean maximum systolic/diastolic blood pressure increase was 0.5-1 mmHg and occurred in less than 2% of patients.[5] In this study, only four and two patients treated by mirabegron showed tachycardia and hypertension, respectively, and no difference was observed in the changes in vital signs within the individual groups or between the two groups after 12 weeks of treatment. Many studies have been performed to evaluate the efficacy of solifenacin and mirabegron versus placebo, but only one recent study including male and female patients has compared these two treatments, demonstrating similar clinical improvements with a lower incidence of dry mouth with mirabegron.[24]

In this study, clinically relevant improvements in OAB symptoms and QoL were observed in both groups, but, as reported in the published work, the higher incidence of adverse effects of solifenacin compared with mirabegron increased the rate of abandonment after 12 weeks, even if insignificantly. Currently, mirabegron is considered at the same level as solifenacin for the treatment of OAB patients, but the similar cost to solifenacin increases the discontinuation rate, although not having the same side-effects.[21] Therefore, before proceeding with other treatments, such as hormonal or non-hormonal therapy in postmenopausal patients,[25] or second-level therapies, such as sacral nerve neuromodulation or intravesical botulinum toxin, mirabegron can be considered as the drug with the better balance between efficacy and tolerability in the treatment of OAB.[7] Also, our results show that mirabegron may be considered first-line pharmacologic therapy in OAB treatment.

The weak points of this study are the small study; however, the comparison of the subjective and objective responses and the impact of therapy on QoL represent the strengths. Furthermore, considering only patients who had never taken antimuscarinic drugs is another strength. The current study could be useful because the two drugs have been tested on a small number of patients; these results can help clinicians in choosing the treatment for OAB, whose pathophysiology is still debated. Moreover, thanks to its relaxing action on the detrusor muscle, mirabegron could increase the bladder filling capacity in patients with urodynamic DO. This result can be useful after urodynamic testing. However, prospective and randomized controlled clinical trials on a large scale are necessary to obtain conclusive evidence.

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How to cite this article:

Sivasankar Govindaraju *et al* (2018) 'Efficacy And Tolerability of Treatment With Mirabegron Compared with Solifenacin in the Management of Overactive Bladder Syndrome: A Prospective Comparative Study Trial', *International Journal of Current Advanced Research,* 07(5), pp. 12560-12564. DOI: http://dx.doi.org/10.24327/ijcar.2018.12564.2211

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