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Effectiveness of Antimuscarinics and Beta-3 Adrenoceptor in Adult Female with Overactive Bladder

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ABSTRACT

Background: Overactive bladder (OAB), a clinical condition with chronic, complex symptoms that negatively affect quality of life (QoL) and affects a large section of the population. Beta-3 adrenergic agonists that provides a different mode of action and are still in the early stages of development, are being used more frequently than antimuscarinics to treat OAB.**Aim:** To compare between antimuscarinics and a beta-adrenergic agonist (mirabegron) regarding efficacy and side effects in treatment of adult female with overactive bladder.

Patients and methods: This prospective trial was carried out in the Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig University on 82 female patients with OAB. Patient groups were divided into two groups (mirabegron 50 mg n = 41 and tolterodine 4 mg n = 41).

Results: There was a significant difference between each group's baseline and final assessment in terms of post-void residual urine, number of micturitions, urgency episodes, incontinence episodes, and urgency incontinence episodes/24 h, volume voided/micturition, number of nocturia episodes, and number of incontinences. The only significant difference between the two groups was a lower number of nocturia episodes in mirabegron than tolterodine.

Conclusion: In the Egyptian population, with a low incidence of side effects, mirabegron 50 mg and tolterodine 4 mg are efficient therapies for OAB symptoms.

Keywords: Antimuscarinics, Beta-3 adrenoceptor, Overactive Bladder.

INTRODUCTION

An overactive bladder (OAB) is defined as the presence of urine urgency, typically accompanied by frequency and nocturia, with or without urgent urinary incontinence, in the absence of a urinary tract infection or other obvious pathology [(1)]. The two primary current ideas for its multifactorial pathogenesis are enhanced afferent signaling (the urothelium-based theory) and aberrant detrusor excitability (myogenic hypothesis) [(2)]. OAB impairs sexual function, mental health, sleep quality, and quality of life (QoL) while being regarded as a benign illness [(3)].

Due to disappointed expectations or unacceptable side effects, many patients choose to stop receiving OAB treatment despite many advancements. Even though antimuscarinic medications were effective as the first line of treatment for OAB, unfavorable side effects continue to prevent patients from complying with their prescriptions as recommended [(4)].

The management of OAB symptoms and enhancement of health outcomes require pharmacotherapy [(5)]. Despite the effectiveness of antimuscarinic medications in controlling OAB, compliance and adherence to antimuscarinic therapy are negatively impacted by negative symptoms such constipation, fatigue, blurry vision, dry mouth, and cognitive impairment [(4, 6)]. According to numerous studies, low effectiveness and a significant incidence of unfavorable events cause antimuscarinic therapy adherence to be low and to decline over time [(7, 8)].

Mirabegron, an alternative to antimuscarinic drugs, has been shown to reduce overactive bladder symptoms such frequency, urgency, and urgency incontinence after antimuscarinic therapy [(9)]. Although nasopharyngitis (3.4%), urinary tract infections (3%), and hypertension (7.3%) are among the most frequently reported side effects of mirabegron therapy, mirabegron nevertheless has a higher drug adherence and persistence tolerability rate than antimuscarinics. Selective agents and various administration methods have the potential to improve adherence, but these advantages have not been demonstrated in clinical settings, preventing many patients from accessing appropriate treatment [(6, 10)].

So, we aimed to compare between antimuscarinics and a beta-adrenergic agonist (mirabegron) regarding efficacy and side effects in treatment of adult female with overactive bladder.

PATIENTS AND METHODS

This prospective trial was carried out in the Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig University on 82 female patients with OAB. Patient groups were divided into two groups (mirabegron 50 mg n = 41 and tolterodine 4 mg n = 41).

The study comprised patients who had overactive bladders (OAB), were female only, and were older than 18 years old. Patients with claims for two or more OAB products on the same day (data for combinations of mirabegron with antimuscarinics or the use of two or more different antimuscarinics were not captured), diabetic patients, people with congenital renal diseases, people with neurogenic bladders, and people with all cases of genitourinary tract cancer were excluded from the study.

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All patients were subjected to the following:

- Informed consents were obtained from all participants.
- Record-keeping (Age, gender, occupation, prior surgery and medical history).
- Comprehensive clinical evaluation.
- Common laboratory tests, such as (Complete blood picture, kidney function tests, urine analysis).
- Bladder X-ray.

Individuals who participated in the trial and finished it and had on average ≥8 micturitions/24 h and ≥1 urgency episode/24 h and/or ≥1 urgency incontinence episode/24 h, confirmed using 3-day urination diaries, were separated into two groups based on the type of medical therapy they received:

Group (A): the antimuscarinics (tolterodine ER 4 mg) for 12 weeks.

Group (B): beta-3 adrenoceptor agonist (mirabegron 50 mg) for 12 weeks.

To ensure safety, a two-week post-treatment observation follow-up period was set up. The research lasted for 14 weeks in total.

Using patient micturition diaries, we analysed the volume and the amount of incontinence, periods of urgency, and voids per micturition each occurring once every 24 hours.

The variation in the average number of urinations per day between the baseline and final assessment served as the primary efficacy variable. Based on the difference between the baseline and final assessment, secondary efficacy variables included the average number of nocturia episodes, average number of urinary incontinence episodes per 24 hours, average volume of pee passed per micturition, and average number of urgency episodes per 24 hours. For the three days prior to the designated appointments, a patient's micturition diary was completed (baseline and final assessment).

The safety assessment was carried out based on adverse events (AEs), laboratory examinations (hematology, blood chemistry, and urine analysis), vital signs, and post-void residual urine volume (patients who took the study medication at least once during the treatment period). Treatment-related adverse events (AEs) were referred to as adverse drug reactions (ADRs) to be connected to the study treatment. Vital signs (such as seated pulse rate and blood pressure) and routine laboratory tests were evaluated at baseline and again at the follow-up.

Ethical approval:

Informed written consent was taken from every patient. The trial was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Zagazig University.

Statistical analysis

With SPSS software version 18 (IBM, USA), data were examined. The parametric data were shown as mean ± SD or as number and percentage. We used the unpaired Student's t-test for parametric data as well as the Chi square test for categorical data. Non parametric data were represented as median (Range), and analyzed using Mann Whitney test and Wilcoxon test The significance level was calculated at $P<0.05$.

Results

There was no significant difference between both groups regarding demographic and baseline data (Table 1).

Table 1: Demographic and baseline data of the studied groups

Variables		Mirabegron (N=41)	Tolterodine (N=41)	t/ X^2	P
Age		52.1 ± 8.1	52.9 ± 8.4	-0.4	0.7
Weight (Kg)		62.1 ± 7.1	63.09 ± 9.1	-0.5	0.6
Height (cm)		156.8 ± 4.1	156.8 ± 4.2	0.02	1
Comorbidities	None	9 (22%)	10 (24%)	X2 =0.48	0.9
	Hypertension	23 (56%)	24 (59%)		
	DM	7 (17%)	6 (15%)		
	COPD	2(5%)	1 (2%)		
Duration of illness (months)		72.2 ± 6.9	70.8 ± 6.7	0.95	0.3
Previous medication	0	18 (44%)	15 (37%)	X2 =0.46	0.5
	1	23 (56%)	26 (63%)		
OAB severity (mean number of micturitions)	<10	17 (41%)	12 (29%)	X2 = 1.41	0.5
	≥10 to ≤15	19 (46%)	22 (54%)		
	>15	5 (12%)	7 (17%)		
Type of incontinence	Absence	3 (7%)	4 (10%)	X2 = 0.31	0.9
	Urgency incontinence	24 (59%)	25 (61%)		
	Mixed incontinence	14 (34%)	12 (29%)		

Data are represented as mean ± SD and number (%). Data are analyzed by independent t test or chi square test. There was significant difference between post-void residual urine, number of micturitions, urgency episodes, incontinence episodes, urgency incontinence episodes/24 h, volume voided/micturition, number of nocturia episodes and number of incontinences at baseline and final treatment in each group, while there was no significant difference between both groups except number of nocturia episodes at final assessment that was lower in mirabegron than tolterodine (Table 2).

Table 2: Micturition variables of the studied groups

Variables	Mirabegron (N=41)	Tolterodine (N=41)	t/ X^2	P
Post-void residual urine volume/mL (baseline)	9.3 ± 1.01	9.7 ± 0.98	-1.87	0.06
Post-void residual urine volume/mL (final assessment)	3 (2-5)	2 (2-5)	U=789	0.63
p	W= 861,P<0.0001*	W=865, P<0.0001*		
Number of micturitions/24 h (baseline)	10.4 ± 1.2	10.3 ± 1.08	0.57	0.56
Number of micturitions/24 h (final assessment)	3 (2-5)	3 (2-5)	U=767	0.47
P	W= 863,P<0.0001*	W= 860, P<0.0001*		
Number of urgency episodes/24 h (baseline)	5 (2-6)	4 (2-6)	U=836.5	0.96
Number of urgency episodes/24 h (final assessment)	1 (0-3)	2 (1-3)	U=686	0.11
p	W= 867, P<0.0001*	W=890.5,P<0.0001*		
Number of incontinence episodes/24h (baseline)	2 (1-3)	2 (1-3)	U=838	0.98
Number of incontinence episodes/24h (final assessment)	1 (0-2)	1 (0-2)	U=822	0.84
p	W= 1038,P<0.0001*	W=1023, P<0.0001*		
Number of urgency incontinence episodes/24 h (baseline)	2 (1-3)	2 (1-3)	U=753.5	0.38
Number of urgency incontinence episodes/24 h (final assessment)	0 (0-2)	0 (0-2)	U=766	0.43
p	U= 995 P<0.0001*	W=1079, P<0.0001*		
Volume voided/micturition (mL) (baseline)	157.4 ± 9.7	154.6 ± 9.9	1.29	0.198
Volume voided/micturition (mL) (final assessment)	227.5 ± 25.1	219.5 ± 26.6	1.39	0.16
P	t=-16.1, P<0.0001*	t=-16.07, P<0.0001*		
Number of nocturia episodes (baseline)	2 (1-3)	2 (1-3)	U=779.5	0.54
Number of nocturia episodes (final assessment)	0.4 ± 0.06	0.6 ± 0.09	11.8	<0.0001*
Incontinence (baseline) Absence Present	 12 (29%) 29 (71%)	 15 (37%) 26 (63%)	X^2 = 0.50	0.48
Incontinence (final assessment) Absence Present	 33 (80.5%) 8 (19.5%)	 35 (85.4%) 6 (14.6%)	X^2 = 0.34	0.55
p	X^2 =21.7, P<0.0001*	X^2 =20.5, P<0.0001*		

Parametric data were represented as mean ± SD, and analyzed using independent t test and paired t test
Non parametric data were represented as median (Range), and analyzed using Mann Whitney test and Wilcoxon test
Catagorical data were represented as Number (%) and analyzed using chi square test (X2).
*: Significant

The overall incidence of treatment-related AEs was higher in the tolterodine group (39%) compared to mirabegron (12%) but it did not reach significant difference. There were few mild AEs and none were severe (Table 3).

Table (3): Adverse events of the studied groups

Variables	Mirabegron (N=41)	Tolterodine (N=41)	X^2	P
Adverse events				
None	36 (88%)	25 (61%)		
Dry mouth	3 (8%)	9 (22%)		
Thirst	0 (0%)	2 (5%)		
Constipation	1 (2%)	3 (7%)	8.3	0.08
Erythema	0 (0%)	0 (0%)		
Blurred vision	0 (0%)	0 (0%)		
Fatigue	1 (2%)	2 (5%)		
Urinary retention	0 (0%)	0 (0%)		

Data are represented number (%) and analyzed by chi square test (X^2).

DISCUSSION

According to updated treatment guidelines for OAB, oral beta-3 adrenoceptor agonists or antimuscarinic medications should be used as second-line treatments to reduce OAB symptoms and enhance health outcomes, so long-term medication is necessary [(5)].

The mainstay of the current pharmaceutical strategy for treating OAB are antimuscarinic medications, but their usage is restricted in some patients due to their insufficient efficacy or annoying side effects (AEs), such as diarrhea, blurred vision, and dry mouth [(11)].

Other methods of treating OAB have centered on β -adrenoceptors, which are understood to contribute to regulating how the smooth muscle of the bladder relaxes. Although the human detrusor contains three different types of β-adrenoceptors, it is the 3-adrenoceptor subtype that facilitates detrusor relaxation and urine storage [(12)], and that could potentially inhibit the bladder afferent nerves from activity [(13)].

In total 82 OAB patients were in the present study randomly assigned to receive medication (mirabegron 50 mg n = 41; tolterodine 4 mg n = 41). There were no observable variations between the two groups' baseline demographic data.

In line with our research, **Huang *et al.*** [(6)] revealed that there were no appreciable variations in underlying illnesses between the groups. Also, **Yamaguchi *et al.*** [(14)] proved that the population's demographic and baseline OAB features were determined by their analysis (n = 1105) and no clinically important differences between the therapy groups were found.

Our findings showed that in terms of post-void residual urine, number of micturitions, urgency episodes, incontinence episodes, urgency incontinence episodes/24 h, volume voided/micturition, number of nocturia episodes, and number of incontinence, there was a significant difference between each group's baseline and final treatment, but there was no significant difference between the two groups other than number of nocturia episodes at final assessment that was lower in mirabegron than tolterodine.

In agreement with our study, **Huang *et al.*** [(6)] found that in both treatment groups, the Clinical Global Impression (CGI), a major and trustworthy tool for evaluating treatment outcomes in OAB patients in earlier trials, improved, demonstrating the efficacy of both antimuscarinics and beta-3 adrenoceptor agonists. There was no observable difference in CGI across groups following therapy between the two groups (p = 0.135). Also, their findings revealed no discernible variations in the scores between the two groups in terms of daytime frequency, overnight frequency, urgency, or urge incontinence.

In addition, **Yamaguchi *et al.*** [(14)] showed that at the time of the evaluation, the average number of urinations per day decreased.

considerably from baseline after using mirabegron 50 mg. (P 0.001). Mirabegron experienced significant advancements in the quantity of urgency based on the mean [SD] change between baseline and final assessment for the secondary efficacy factors episodes/24 h (–1.85 [2.555] vs –1.37 [3.191]; P = 0.025); number of incontinence episodes/24 h (–1.12 [1.475] vs –0.66 [1.861]; P = 0.003); number of urgency incontinence episodes/24 h (–1.01 [1.338] vs –0.60 [1.745]; P = 0.008); and volume voided/micturition (24.300 [35.4767] vs 9.715 [29.0864] mL; P < 0.001); but not for number of nocturia episodes (–0.44 [0.933] vs –0.36 [1.062]; P = 0.277). As early as the first evaluation, mirabegron vs. placebo revealed improvements in every variable, and these gains persisted until the final assessment. All treatment groups experienced a comparable change in the volume of post-void residual urine when the evaluation was made in the end.

Wani *et al.* [(15)] revealed that nine research examined the efficacy of these two classes of drugs in their meta-analysis. According to the findings of all the trials, mirabegron is just as effective as any other anticholinergic. Even postvoid residual micturition has been shown to diminish as a result. In one trial, postvoid volumes in females showed improved urodynamics following the switch to mirabegron.

According to the current study, the 3-adrenoceptor is a key target in the treatment of OAB symptoms. In

order to reduce OAB symptoms and enable detrusor relaxation during the storage phase, the 3-adrenoceptor is activated. Activation of the 3-adrenoceptor encourages bladder relaxation that is unique to the storage or filling phase of the micturition cycle, whereas antimuscarinic medications tend to diminish bladder contraction during the voiding phase [16].

The capacity of mirabegron to decrease urothelium and detrusor 3-adrenoceptor-mediated bladder afferent activity is likely what accounts for the observed improvement in lowering urgency in the current investigation [13, 17].

Given that the condition is persistent and antimuscarinic medications are known to have negative effects, medications, tolerability is a crucial factor in the therapy of OAB with these therapies (for instance, constipation, dry mouth, or blurred vision). Tolterodine and mirabegron each experienced 13% more treatment-related adverse events (AEs) overall in the current trial, although there was no statistically significant difference, there were no serious AEs, and the most were minor.

This came in agreement with **Yamaguchi *et al*. [14]** who discovered that the tolterodine group had a greater overall incidence of treatment-related adverse events (AEs) (34.9%) compared to the mirabegron group (24.5%).

Wani *et al*. [15] indicated that five studies analyzed the negative effects of both treatments in their meta-analysis and found that mirabegron has less side effects than antimuscarinics.

CONCLUSION

In the Egyptian population, the two medications tolterodine 4 mg and mirabegron 50 mg work well to treat OAB symptoms with little risk of adverse effects. Mirabegron is an attractive alternative to antimuscarinic therapy in the management of OAB.

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