ORIGINAL ARTICLE

Mirabegron Versus Tolterodine in BPH Patients with ED and LUTS

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Abstract

Background: ***Erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) resulting from benign prostatic hyperplasia (BPH) share similar risk factors, suggesting that LUTS/BPH and ED may have similar pathophysiological and underlying mechanisms. Consequently, there are currently common therapeutic strategies being investigated for these two conditions.***

Aim and objective: ***To assess the value of mirabegron over tolterodine on erectile function in patients having ED concomitant with irritative LUTS due to BPH.***

Patients and methods: ***A prospective randomized study was conducted among 78 patients suffering from ED and irritative LUTS suggestive of BPH. It included sexually active patients above 50 years of age who were randomized into two groups in a 1:1 ratio of 39 participants each. Group (A): Patients were prescribed (mirabegron 50 mg) plus (doxazosin 2mg) orally once daily for 12 weeks. Group (B): Patients were prescribed (tolterodine 4 mg) plus (doxazosin 2mg) orally once daily for 12 weeks. A follow-up was done at the 4th and 12th weeks.***

Results: ***Regarding sexual parameters, IIEF-15 total score median (IQR) improved from (median= 38 and IQR, 34 – 45) at baseline to reach (median= 52 and IQR, 47 – 56) and (median= 54 and IQR= 50 – 58) at 4th and 12th weeks ($p < 0.001$), respectively in mirabegron group, meanwhile in tolterodine group, IIEF-15 total score didn't show significant difference either at 4th or 12th weeks (P>0.05). Regarding urinary parameters, both groups achieved significant improvement in all urinary parameters.***

Conclusion: ***Mirabegron, a β3 agonist, outperforms tolterodine in improving ED concomitant with irritative LUTS due to BPH.***

Keywords: ED; Irritative LUTS; BPH; Mirabegron

1. Introduction

Erectile dysfunction (ED) and lower urinary tract symptoms (LUTS) resulting from benign prostatic hyperplasia (BPH) share similar risk factors, suggesting that LUTS/BPH and ED may have similar pathophysiological and underlying mechanisms.[1] Consequently, there are currently common therapeutic strategies being investigated for these two conditions.[2]

Mirabegron is the first drug approved by the FDA as a selective β3 adrenoceptor agonist for treating LUTS. It has been proven that β3 adrenoceptors are the most common adrenoceptors in the urinary bladder, which is believed to play an important role in mediating detrusor muscle relaxation.[3]

The smooth muscle cells of human corpora cavernosa (HCC) have been shown to contain β3 adrenoceptors. The vascular smooth muscles of HCC can be relaxed by activating β3 adrenoceptors. Therefore, β3 adrenoceptors are a potential target for treating ED.[4]

A previous study assessed the effect of mirabegron on rats and human corpora cavernosa specimens in vivo and in vitro and found that mirabegron can significantly relax both rats and human corpora cavernosa.[5]

The study's objective is to assess the value of mirabegron over tolterodine on erectile function in patients having ED concomitant with irritative LUTS due to BPH.

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2. Patients and methods

This was a prospective randomized study performed at Al-Azhar University Hospitals during the period from July 2023 to June 2024. It included sexually active patients above 50 years of age who presented to the outpatient clinics with ED and irritative LUTS suggestive of BPH.

Exclusion criteria encompassed patients with prostate cancer, urethral disease, urinary bladder mass or stone, neurogenic disorders that may impact urinary and erectile functions, penile fibrosis or severe Peyronie's disease, history of priapism or penile surgery, high PVR urine (PVR>150), and patients who have contraindications for the medications included in the study (severe HTN systolic BP ≥180 mmHg, diastolic BP ≥110 mmHg, or both and severe narrow-angle glaucoma).

Initial Assessment:

Patients who met the study criteria were requested to participate in this study and were asked to sign an informed consent form. A thorough urinary and sexual history and clinical assessment was done including International Prostate Symptom Score (IPSS), QoL, International Index of Erectile Function (IIEF-15) questionnaire and erection hardness score (EHS) questionnaire. Patients were investigated by CBC, S.creatinine, RBS, LFTs, Serum PSA, midstream urine analysis, pelvi-abdominal ultrasonography (PAUS) and uroflowmetry.

The closed envelope approach was used for randomization, and 78 eligible patients were divided into two groups in a 1:1 ratio of 39 participants each. Group (A): Patients were prescribed (mirabegron 50 mg) plus (doxazosin 2mg) orally once daily for 12 weeks. Group (B): Patients were prescribed (tolterodine 4 mg) plus (doxazosin 2mg) orally once daily for 12 weeks.

Follow-up- program:

Follow up was done at 4th and 12th weeks through clinical assessment of sexual parameters including IIEF-15 and EHS questionnaires, urinary parameters including IPSS, QoL, pelvi-abdominal US and uroflowmetry. In addition, any possible side effects were noted during the study.

Outcome measures:

The primary outcome was to evaluate the changes in sexual functions measured by the IIEF-15 total score at 4th and 12th weeks. We judged a five-point change in IIEF-15 total score (5 out of 75) to be significant; the outcome was classified as improvement, no change, or deterioration. Patients who showed a rise of 5 points or more in their IIEF-15 total score were considered "improved." Those who showed a drop of 5 points or more were considered "deterioration." Meanwhile, "no change" was labelled for patients who had less than a 5-point rise or drop in their total IIEF-15 score.

The secondary outcomes were to evaluate the urinary parameters at 4th and 12th weeks using the IPSS questionnaire and QoL. PVR and Q max were used to evaluate the urinary parameters objectively. The safety of drugs was evaluated by comparing side effects in the two groups.

Statistical analysis

Data were analyzed using the Statistics Package for Social Sciences (SPSS) version 25. Qualitative data were presented as frequency and percentage. Continuous quantitative data were presented as mean ± standard deviation (Mean ±SD) in normally distributed data or median and Interquartile range (Median with IQR) in abnormally distributed data. An independent sample T-test (T) was used to compare the two groups (for normally distributed data). The Mann-Whitney U test (U) was used when comparing two groups (for abnormally distributed data). The chi-square test (X2) was used when comparing non-parametric categorical data.

3. Results

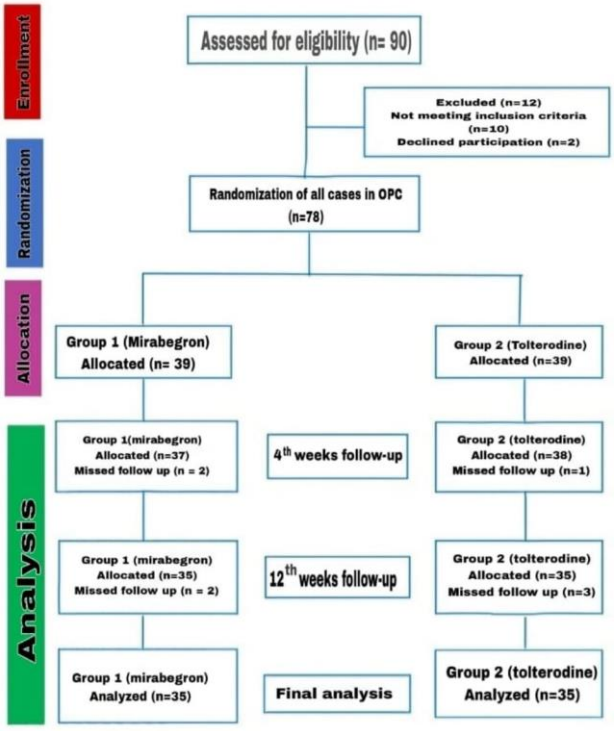

Figure 1. Consort chart for participants in the study

Table 1. Comparison of changes in sexual and urinary parameters of both groups at 4th and 12th weeks.

VARIABLE		MIRABEGRON GROUP (N= 35)	TOLTERODINE GROUP (N= 35)	P VALUE**
SEXUAL CHARACTERISTICS				
IIEF-15	Baseline	38 (34 – 45)	42 (40 – 44)	0.124
TOTAL	4 weeks	52 (47 – 56)	41 (38 – 44)	<0.001
SCORE	12	54 (50 – 58)	42 (39 – 45)	<0.001
MEDIAN	weeks			
(IQR)	P value*	<0.001	0.721	
EF DOMAIN	Baseline	14 (11 – 17)	16 (14 – 18)	0.331

MEAN ± SD	4 weeks	21 (18 – 24)	16 (13 – 18)	<0.001
	12 weeks	23 (20 – 26)	16 (14 – 17)	<0.001
	P value*	<0.001	0.623	
OF DOMAIN MEDIAN (IQR)	Baseline	8 (7 – 9)	8 (7 – 9)	0.333
	4 weeks	8 (8 – 9)	8 (7 – 9)	0.054
	12 weeks	9 (8 – 9)	8 (7 – 9)	0.011
	P value*	<0.051	0.542	
SD DOMAIN MEDIAN (IQR)	Baseline	7 (7 – 8)	7 (6 – 8)	0.081
	4 weeks	8 (7 – 8)	7 (6 – 7)	<0.052
	12 weeks	8 (7 – 9)	7 (6 – 7)	<0.051
	P value*	0.052	0.441	
IS DOMAIN MEDIAN (IQR)	Baseline	5 (4 – 5)	6 (5 – 7)	0.251
	4 weeks	8 (7 – 8)	6 (5 – 6)	<0.001
	12 weeks	8 (8 – 9)	6 (5 – 6)	<0.001
	P value*	<0.001	0.844	
OS DOMAIN MEDIAN (IQR)	Baseline	4 (3 – 4)	4 (3 – 4)	0.336
	4 weeks	5 (5 – 6)	4 (3 – 5)	<0.054
	12 weeks	6 (5 – 7)	4 (3 – 5)	<0.001
	P value*	<0.001	0.096	
EHS MEDIAN (IQR)	Baseline	2 (1 – 2)	1 (1 – 2)	0.336
	4 weeks	2 (2 – 3)	1 (1 – 2)	<0.050
	12 weeks	3 (2 – 3)	1 (1 – 2)	<0.001
	P value*	<0.001	0.322	
URINARY CHARACTERISTICS				
IPSS TOTAL SCORE MEDIAN (IQR)	Baseline	17 (15 – 19)	17 (14 – 19)	0.543
	4 weeks	11 (10 – 13)	14 (11 – 16)	0.003
	12 weeks	10 (9 – 12)	12 (10 – 15)	0.053
	P value*	<0.001	<0.001	
STORAGE DOMAIN MEDIAN (IQR)	Baseline	8 (7 – 10)	8 (7 – 9)	0.093
	4 weeks	5 (4 – 7)	6 (5 – 7)	0.110
	12 weeks	4 (3 – 6)	5 (4 – 6)	0.257
	P value*	<0.001	<0.001	
VOIDING DOMAIN MEDIAN (IQR)	Baseline	9 (7 – 11)	10 (8 – 12)	0.211
	4 weeks	7 (5 – 8)	7 (6 – 9)	0.102
	12 weeks	6 (5 – 8)	7 (5 – 9)	0.052
	P value*	<0.001	<0.001	
QOL DOMAIN MEDIAN (IQR)	Baseline	3 (2 – 4)	3 (2 – 4)	0.761
	4 weeks	1 (1 – 2)	2 (1 – 3)	0.027
	12 weeks	1 (1 – 2)	1 (1 – 2)	0.732
	P value*	<0.001	<0.001	
Q MAX (ML/SEC) MEDIAN (IQR)	Baseline	12 (10 – 13)	14 (11 – 17)	0.421
	4 weeks	14 (12 – 15)	15 (12 – 18)	0.862
	12 weeks	16 (15 – 17)	16 (13 – 19)	0.303
	P value*	<0.001	0.024	
PVR (ML) MEDIAN (IQR)	Baseline	15 (10 – 20)	17 (14-23)	0.142
	4 weeks	10 (5 – 15)	13 (10-15)	0.017
	12 weeks	5 (0 – 9)	9 (6-13)	<0.001
	P value*	<0.001	<0.001	

* P value: statistical difference between 12 weeks and baseline results at the same group.

** P value: statistical difference between 4, 12 weeks and baseline results at both groups.

IIEF: International Index of Erectile Function, EF: Erectile Function, SD: Sexual Desire, OF: Orgasmic Function, OS: Overall Satisfaction, IS: Intercourse Satisfaction, EHS: Erection Hardness Score, IPSS: International Prostate Symptom Score, PVR: Post-Voiding Residual, Qmax: Maximum urinary flow rate, QoL: Quality of Life.

Table 2. Comparison of changes in total IIEF-15 score between both groups at 4th and 12th weeks:

IIEF-15 CHANGES		MIRABEGRON GROUP (N= 35)		TOLTERODINE GROUP (N= 35)		P VALUE
AFTER 4 WEEKS						
IMPROVEMENT	No. (%)	27	77.1%	6	17.1%	<0.001
NO CHANGE	No. (%)	6	17.1%	25	71.4%	
DETERIORATION	No. (%)	2	5.7%	4	11.4%	
After 12 weeks						
Improvement	No. (%)	32	91.4%	7	20.0%	
No change	No. (%)	3	8.6%	26	74.3%	<0.001
Deterioration	No. (%)	0	0.0%	2	5.7%	

Treatment-related adverse effects: were recognized in 3 (8.7%) and 6 (17.2%) patients in mirabegron and tolterodine groups, respectively (p > 0.05) as demonstrated in table (3). However, the patients tolerated the side effects and did not discontinue the medications used in the study.

Table 3. Comparison of treatment-related adverse effects in both groups:

SIDE EFFECT	MIRABEGRON GROUP	TOLTERODINE GROUP	P VALUE
CONSTIPATION	1 (2.9%)	0 (0.0%)	
DRY MOUTH	1 (2.9%)	3 (8.6%)	
TACHYCARDIA	1 (2.9%)	0 (0.0%)	>0.05
BLURRING OF VISION	0 (0.0%)	2 (5.7%)	
HEADACHE	0 (0.0%)	1 (2.9%)	
TOTAL	3 (8.7%)	6 (17.2%)	

4. Discussion

β3 adrenoreceptors are the most prevalent β receptors present in the detrusor muscle, and their activation result in detrusor muscle relaxation. Mirabegron, which is a selective β3 adrenoreceptor agonist, has recently received FDA approval for the treatment of LUTS in patients with OAB or BPH. To assess its efficacy in BPH patients who were already on tamsulosin, a recent meta-analysis including 3 RCTs with a total of 1317 participants demonstrated its role and found that mirabegron significantly alleviated LUTS caused by BPH in patients on tamsulosin.[6]

Mirabegron has equivalent efficacy to tolterodine in improving urgency, frequency, and UUI. Furthermore, it has a more bearable side effect profile than any other antimuscarinics, particularly as regards dry mouth, flushing, headache, and the risk of AUR.[7]

Mirabegron and tolterodine both significantly improved IPSS total score, its subdomains, Qmax,

and PVR in our study. However, there was a significant difference between the two groups' values regarding IPSS total score, QoL, and PVR after 4 weeks and Qmax and PVR after 12 weeks.

There was also no significant difference between the two groups as regards adverse effect profiles. These findings are consistent with two studies that compared mirabegron to tolterodine in 1978 and 2,444 individuals, respectively. [3,8]

Furthermore, in a previous study involving 33 individuals with OAB, mirabegron monotherapy decreased PVR after 12 weeks compared to tolterodine monotherapy, though the difference was not statistically significant.[9]

To our best knowledge, only three clinical trials have established the efficacy of mirabegron on ED in males; two of these studies were conducted on OAB patients and one on BPH patients. The first trial assessed the impact of mirabegron 50 mg on sexual and urinary characteristics in males with OAB/LUTS over 12 weeks [10]

After 4 weeks, most urinary parameters showed significant improvement ($p<0.05$). Furthermore, this improvement was sustained at 12th weeks. OABSS nocturia subscore, QoL, incontinence, and urgency scores improved considerably at 4th and 12th weeks ($p<0.05$). But, neither PVR and Q max, nor OABBSS frequency subscore improved significantly after 4 or 12 weeks.[10]

Surprisingly, the IIEF-5 score decreased during the 4th and 12th week follow-ups. The mean value of IIEF-5 score declined from 16.4±5.5 at baseline to 15.6±5.6 at the 4th week and 14.9±5.9 at the 12th week. [10]

However, the study's significant flaws were the absence of a placebo control and the sample size was insufficient to indicate mirabegron's therapeutic efficacy on alleviating LUTS in patients with OAB and ED.

The second clinical trial, conducted at Tottori University in Japan, included 52 male patients with ED and OAB. During the 16-week trial, only the mirabegron group showed a significant improvement in IIEF-5 score, from 11.1±3 at baseline to 17.2±3.2 at the end ($p < 0.05$).[11] However, the study's limitations include a non-randomized design, a small sample size, and no investigation of the placebo effect.

The third and only clinical study to evaluate the impact of mirabegron on ED in BPH patients involved 47 patients. In this trial, the mirabegron group exhibited significant improvements in sexual parameters after both 4 and 12 weeks, whereas the tolterodine group showed no change in any of the sexual parameters after either 4 or 12 weeks.[12]

Although this was a RCT, it still has some drawbacks by having small sample size and the trial design may be criticized for missing a third arm of PDE5Is.

Our study was done on 78 patients who had ED and LUTS/BPH. The Mirabegron group exhibited significant improvement of all sexual parameters after 4th and 12th weeks. The total IIEF-15 score Median (IQR) improved from (median= 38 and IQR, 34 – 45) at baseline to reach (median=52 and IQR, 47 – 56) and (median= 54 and IQR= 50 – 58) at 4th and 12th weeks, respectively ($p < 0.001$. Meanwhile, in the tolterodine group, IIEF-15 total score didn't show a significant difference either at 4th or 12th weeks ($P>0.05$).

Also, by comparing both groups' values, the mirabegron group showed a significant difference regarding the total IIEF-15 score, its five subdomains, and EHS after 4 and 12 weeks of follow-up. In addition, by setting a cut-off point of change of five points or more from the baseline in total IIEF-15 score, the mirabegron group showed a significant difference in change direction versus the tolterodine group after 4 and 12 weeks. IIEF changes after 4 weeks in the Mirabegron group: there were 6 patients (17.1%) with no changes, improved 27 patients (77.1%), and deteriorated 2 patients (5.7%). While in the Tolterodine group, there were 25 patients (71.4%) with no changes, 6 patients (17.1%) improved, and 4 patients (11.4%) deteriorated. IIEF changes after 12 weeks in the Mirabegron group, there were 3 patients (8.6%) with no changes, and 32 patients (91.4%) were improved. While in the Tolterodine group, there were 26 patients (74.3%) with no changes, 7 patients (20%) improved, and 2 patients (5.7%) deteriorated.

Although this was a randomized trial, there are some drawbacks. The sample size is insufficient to confirm these findings, and the trial design may be criticized for missing PDE5Is as a third arm. So, more multicenter RCTs with a large number of patients are needed to confirm our findings about mirabegron's enhancing effect on sexual characteristics in patients suffering from ED and LUTS/BPH.

4. Conclusion

Mirabegron, a β3 agonist, outperforms tolterodine in improving ED concomitant with irritative LUTS due to BPH.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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