

Manuscript ID
DOIZUMJ-1908-1401 (R1)
10.21608/zumj.2020.15654.1401

ORIGINAL ARTICLE

Safety and Efficacy of Propiverine Hydrochloride Versus Mirabegron in Treating Storage Symptoms in Patients with Benign Prostatic Hyperplasia

⁽¹⁾Safwat Elsayed AbouHashem,⁽¹⁾Ahmed Ragab Ali,⁽¹⁾Ibrahem Ismail Elsayed and⁽²⁾Muneer Abdullah Masoud⁽¹⁾Department of Urology, Faculty of Medicine – Zagazig University, Egypt.⁽²⁾Department of Urology, Faculty of Medicine - Garyan University, Labya

Corresponding author

Muneer Abdullah Masoud

E-mail:

muncertarife34@gmail.com

Submit Date 2020-07-01

Revise Date 2020-09-03

Accept Date 2020-09-28

ABSTRACT

Background: Overactive bladder (OAB) is a condition marked by discomfort, with or without urinary incontinence, typically with an elevated incidence during the day or at night. Overactive bladder is a very prevalent condition in both female and male patients and is more common in older adults than in the general population. This study aimed to evaluate the safety and efficacy of mirabegron compared to propiverine for managing storage symptoms in benign prostatic hyperplasia patient.

Methods: This clinical prospective, randomized comparative study was to compare the clinical efficacy and safety of Mirabegron at Urology outpatient clinic, Faculty of medicine, Zagazig University from October 2018 and April 2019. 60 patients were randomly allocated in two groups; Group (A): Patients receive (mirabegron 50mg) once daily for three months. Group (B): Patients receive (Propiverine HCL 30mg) once daily for three months.

Results: Propiverine and mirabegron exert similar efficacy for OAB symptoms in patients with BPH. However, mirabegron seems more efficacious than Propiverine. It also represents a reasonable alternative to antimuscarinics as well as a good option for patients who should avoid potential antimuscarinic adverse effects.

Conclusions: Mirabegron can be considered as a drug with the better balance between efficacy and safety than Propiverine.

Keywords: Overactive bladder, Propiverine Hydrochloride, Prostatic hyperplasia, Mirabegron.



INTRODUCTION

Lower urinary tract symptoms (LUTS) are one of the most common clinical complaints in adult males [1]. Overactive bladder (OAB) is a condition characterized by discomfort, with or without urinary incontinence, usually with an elevated frequency during the day or at night. OAB is a very prevalent condition in both female and male patients and is more common in older adults compared to the general population [2].

The key pathological symptom of urgency is a sudden desire to undo the sensation associated with abnormal bladder function during the filling phase of the urination, leading to changes in other elements of the OAB symptom complex: increased frequency of urination, incontinence and nocturnal symptoms [3]. Although preclinical studies suggest that antimuscarinic agents may act by reducing the ability of the muscle detrusor to

contract, a review of clinical evidence concluded that they exert their therapeutic action on sensation-related variables. All five muscarinic receptor subtypes in humans (M1 to M5) exist within the bladder. [4].

Because muscarinic receptors are also found in other regions, including salivary glands, gastrointestinal smooth muscle and ciliary and iris sphincter muscles, 5 blockages are responsible for common anticholinergic side effects, such as dry mouth, constipation and blurred vision [5].

Though antimuscarinics are the current cornerstone of oral pharmacotherapy, they exhibit a variety of relative binding affinities for each subtype of muscarinic receptors [6].

Antimuscarinics differ in their pharmacokinetic properties, and it is clear that the incidence and/or severity of anticholinergic side effects vary between them. Discontinuation levels for antimuscarinic care are high because of efficacy

and tolerability standards [7]. A systematic literature review published prior to 2010 revealed discontinuation rates of up to 31 per cent in 12-week clinical trials and up to 83 percent in 30-day medical claims studies. [8]. Long-term research showed low adherence, and up to 91% of patients discontinued treatment in 4 years [9]. The expression and function of β_3 -adrenoceptors in the muscle and urothelium of the bladder, and their limited distribution elsewhere in the human body, established these receptors as a possible therapeutic target for OAB [10].

In the sympathetic system, β_3 -adrenoceptors are thought to be responsible for relaxing the detrusor smooth muscle during the storage process, resulting in increased bladder capacity without altering micturition pressure, post-voidable residual volume (PVR), or voiding contraction [11]. Propiverine was the most commonly prescribed agent in Japan until solifenacin and tolterodine were present. Propiverine is an antimuscarinic agent with a mixed mode of action in the treatment of symptoms of accumulation and in the blocking of muscle detrusive receptors, which also inhibits cellular calcium inflows, thus reducing muscle spasm. [12].

Mirabegron is a selective agonist β_3 -adrenoceptor approved for storage symptom therapy. It has been approved for β_3 -adrenoceptor stimulation in Japan (Betanis®, Astellas Pharma Inc, Tokyo, Japan) US (Myrbetriq®, Astellas) and Europe (Betmiga®, Astellas). [13].

AIM OF THIS WORK

This study aimed to evaluate the safety and efficacy of mirabegron compared to propiverine for managing storage symptoms in benign prostatic hyperplasia patient.

PATIENTS AND METHODS

This is a prospective, randomized comparative study that has been held at Urology outpatient clinic, Faculty of medicine, Zagazig University from October 2018 to April 2019. 60 patients complaining from storage symptoms that related to benign prostatic hyperplasia (BPH), presenting with moderate to severe Lower urinary tracts symptoms (LUTS) with no contraindication to medical treatment were enrolled in this trial. Patients were randomly allocated in two groups, Group A, Patients receive (mirabegron 50mg) once daily for three months. Group B, Patients receive (Propiverine HCL 30mg) once daily for three months [14,15].

Inclusion criteria: Male Patients with storage symptoms for ≥ 3 months associated with benign prostatic hyperplasia. Age adult from 35 to 60 years old. Patients were excluded from the study if

they were having prostatic cancer, bladder cancer, previous irradiation, history of lower urinary tract pathology, neurogenic disease that affect the bladder, absolute indications for surgery.

Written Informal consent was obtained from the patient and relative in order to participate in the study. The approval for the study was obtained from the Urology Departments of Zagazig University Hospitals after the approval of the Institutional Review Board (IRB). The work was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Pre-treatment evaluation: Patients were subjected for a full urologic history and clinical examination, Overactive bladder symptom score (OABSS) score is the standard questionnaire, Prostate-specific antigen (PSA), pelvi-abdominal ultrasound, Digital rectal examination (DRE), uroflowmetry and residual urine estimation were applied for every patient. Patients were given either, Mirabegron daily, or Propiverine daily, for 3 months treatment period.

Post-treatment evaluation: Monthly follow up for individual OABSS score, physical examination, Uroflowmetry and post voided residual urine estimation. Patients in both groups were followed for 3 months and were evaluated at 4th week & 8th week & 12th week and on demands regarding overactive bladder symptom score (OABSS) Uroflowmetry, PVR.

STATISTICAL ANALYSIS:

Data collected over the course of the history, basic clinical examination, laboratory investigations and outcome measures are coded, entered and analyzed using Microsoft Excel software. Data was then imported into the Analysis Software Statistical Package for Social Sciences (SPSS version 20.0) (Statistics Package for Social Sciences). Depending on the type of qualitative data represented by number and percentage, the quantitative continuous group represented by mean \pm SD, the following tests were used to test differences for significance. Difference and association of the qualitative variable by the Chi square test (X^2) or the Fisher test. Differences between quantitative independent groups by t-test paired with t-test. The P value was set at < 0.05 for significant results and < 0.001 for high significant results.

RESULTS

In this study 60 patients were randomly allocated in two groups; group A: mean age was (49.65 \pm 10.09) received mirabegron for three months. The age of patients ranged from 35 to 60 years old (8 patients of them escaped and two patients was missed during the follow up of the

study so the study was completed by 20 patients in mirabegron arm) & group B Mean age was (48.2±5.94) receiving propiverine for three months (9 patients escaped and one patients was missed from the 1st follow up of the study so only 20 patients completed the study in propiverine arm). **Figure 1.**

There was no significant difference between groups regard Post-void residual (PVR) at pretreatment (56.5±15.65 vs, 58.65±16.8 p= 0.696) but there was significant difference between both groups after **first** (57.95±12.8 vs, 62.25±16.2 p= 0.033, **second** (59.2±11.8 vs 66.0±17.2 p=0.006), and **third** (61.2±10.0 vs 68.0±12.3 p=0.001) months. **Table (1)**

There was no significant difference between groups in peak flow rate (Q_{max}) distribution pre or post treatment along the three months p>0.05. **Table (2)**

There was no significant difference between groups regard the OABS at pretreatment or first month (p>0.05) but Mirabegron was significantly **Table (1): PVR distribution at different times in each visit.**

	Mirabegron	Propiverine	t	P
PVR-pre treatment	56.5±15.65	58.65±16.8	-0.394	0.696
PVR-1m	57.95±12.8	62.25±16.2	-1.206	0.033*
PVR-2m	59.2±11.8	66.0±17.2	-0.933	0.006*
PVR-3m	61.2±10.0	68.0±12.3	-0.959	0.001**

Table (2): Q_{max} distribution at value in each visit for both groups.

	Mirabegron	Propiverine	t	P
Q _{max} -pre treatment	14.54±2.54	15.12±1.98	0.413	0.685
Q _{max} -1m	14.33±1.3	15.58±1.44	0.417	0.695
Q _{max} -2m	14.5±0.96	15.75±1.15	0.522	0.439
Q _{max} -3m	14.84±0.83	15.68±0.62	0.532	0.437

Table (3): OABS score distribution at during follow up in different follow up visit.

	Mirabegron	Propiverine	t	P
OABS score pre treatment	9.45±3.1	9.6±2.4	0.674	0.504
OABS-score-1m	9.4±2.64	9.55±2.4	-0.438	0.664
OABS-score-2m	7.75±2.65	9.3±1.83	-2.148	0.038*
OABS-score-3m	5.3±1.66	7.35±2.66	-2.820	0.008*

Table (4): OABS score distribution before and after treatment among mirabegron group.

	Before	After 1 m	t	P
OABS score	9.45±3.1	9.4±2.64	1.04	0.114
	Before	After 2 m		
OABS-score	9.45±3.1	7.75±2.65	2.48	0.008*
	Before	After 3 m		
OABS-score	9.45 ± 3.1	5.3 ± 1.66	3.25	<0.001**

Table (5): OABS score distribution before and after treatment among propiverine group.

	Before	After 1 m	t	P
OABS score	9.6±2.4	9.55±2.4	0.543	0.211

lower at second (7.75±2.65 vs 9.3±1.83 p= 0.038) and third (5.3±1.66 vs 7.35±2.66 p=0.008) months. **Table (3)**

There was no significant difference between OABS score distribution before and after 1 month of treatment among mirabegron group (p>0.05) while there was significant difference OABS score distribution before and after 2 and 3 months of treatment. **Table (4)**

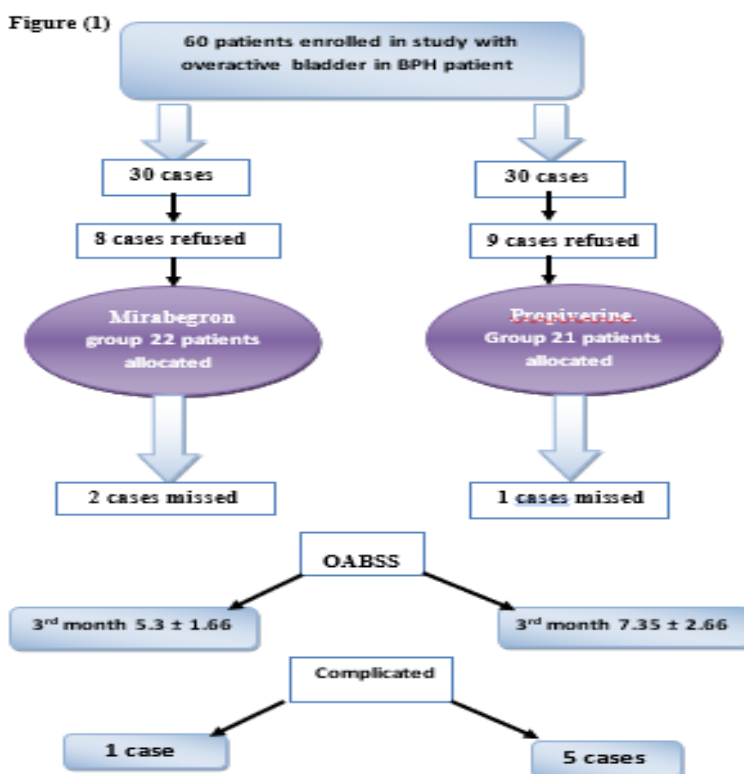
There was no significant difference between OABS score distribution before and after 1 and 2 months of treatment among propiverine group (p>0.05) while there was significant difference between OABS score distribution before and after 3 months of treatment. **Table (5)**

Side effects, Propiverine was significantly associated with Blurred vision and Constipation, **p<0.05** but **Mirabegron** group showed only one case of hypertension as adverse effect at 2nd month. Both drugs were associated with tolerable side effects and none of patients had to discontinue trial because of side effects. **Table (6)**

	Before	After 1 m	t	P
	Before	After 2 m		
OABS-score	9.6±2.4	9.3±1.83	0.348	0.501
	Before	After 3 m		
OABS-score	9.6 ± 2.4	7.53 ± 2.66	3.25	<0.001**

Table (6): Side effects distribution between studied groups

Side effects	No	Group		X ²	P
		Mirabegron	Propiverine		
No	N	19	15	2.12	0.14
	%	95.0%	75.0%		
Blurred vision	N	0	2	8.1	0.004*
	%	0.0%	10.0%		
Constipation	N	0	2	8.1	0.004*
	%	0.0%	10.0%		
Dry mouth	N	0	1	3.2	0.07
	%	0.0%	5.0%		
Hypertension	N	1	0	3.2	0.07
	%	5.0%	0.0%		
Total	N	20	20		
	%	100.0%	100.0%		



DISCUSSION

Overactive Bladder Symptom Score (OABSS) was used to evaluate subjective symptoms. Ultrasonography was used to measure the estimated post-void residual (PVR) urine volume. Treatment efficacy was evaluated not only by changes in the IPSS but also by minimal clinically significant changes in the OABSS total score defined as ≥ 3 point decrease from baseline score[16].

In our study there was no significant difference between both groups regard pre OABSS at pre or one month after treatment but Mirabegron was significantly lower at the 2nd and third month. This finding similar to study of **Kobayashi, et al.,[17]** who assessed treatment efficacy of antimuscarinics and mirabegron as spectrum of symptoms determined by OABSS of Mirabegron was significantly lower at two and three month it was distributed as 7.34 ± 3.25 and

6.54 ± 3.69. Similar finding reported by **Otsuki et al., [18]** as Mirabegron for newly diagnosed OAB showed significant decreases in scores for total OABSS, OABSS daytime and nighttime frequency, urinary urgency, emergency incontinence.

On the other hand, **Huang et al. [19]** reported that forty-five OAB patients who did not respond sufficiently to antimuscarinic agents had been switched to mirabegron and evaluated for OABSS daytime and nighttime frequency, urinary urgency, emergency incontinence score, no significant difference for reduced OABSS scores was observed at 8 weeks ($p = 0.47$).

Another study conducted by **Khullar et al. [20]** to investigate the efficacy of mirabegron in patients with OAB who cannot be treated with antimuscarinics and men with BPH-related OAB showed significant decreases in overall OABSS scores, OABSS comparison between mirabegron group and control group. The decrease in OABSS total score (a) was significant between baseline, 4 and 8 weeks in both groups.

In our research, Propiverine was successful for emergency, duration, and emergency incontinence, indicating that it contributes to improve overall OAB symptoms, in particular by improving episodes of urgent and urgent incontinence; The OAB's Overactive Bladder Symptom Score (OABSS) was slightly lower at two and three months when it was measured at 9.6 ± 2.4 and 7.35 ± 2.66 , respectively, as compared to 3 months earlier. **Gotoh et al., [21]**, reported that Propiverine's capacity to boost nocturia has been demonstrated, although the possibility of urinary retention remains contentious. Many clinical trials have shown that propiverine is clinically beneficial in men with OAB.

OABSS and post-empty residual urine volume (PVR) have also been determined by **Gotoh** and his colleagues before and after 4 and 12 weeks of treatment. Enrolled (29 male patients with an average age of 71), OABSS improved significantly with Propiverine (9.0 at baseline, 6.2 at 4 weeks, 6.3 at 12 weeks ($p < 0.001$)) [21].

In our study there was no significant difference between groups regard PVR at pre and post treatment, but both group there were significantly increased from pre to 3 months For mirabegron group PVR was in the first month after medication 57.95 ± 12.8 and became 61.2 ± 10.0 at the 3rd month for Propiverine group PVR was in the first month after medication 59.25 ± 16.2 and became 62.0 ± 12.3 at the 3rd month.

Similar finding reported by **Otsuki et al., [18]** Those who reported that PVR was 32.1 and 34.8 ml before and after mirabegron, respectively, and

the difference was not significant ($p = 0.51$). PVR increased slightly from 26.2 ml to 31.3 ml after antimuscarinic therapy, but this was not a significant difference ($p = 0.14$).

At the other hand, after 8 weeks of antimuscarinic therapy, **Kobayashi and Minoru [17]** PVR increased dramatically while mirabegron had little effect at PVR, resulting in a small difference between antimuscarinic and mirabegron which was comparable in effectiveness to initial OAB treatment. But mirabegron tends to have a comparative advantage over antimuscarinics in terms of efficacy and effect on improvement in PVR.

In present study showed that Propiverine sig associated with (two cases of blurred vision 10%), (two cases 10% Constipation) and (one case of dry mouth 5%). Although none of our patients had to discontinue trial because of adverse effect but, dry mouth and constipation are the key reasons for discontinuation of antimuscarinic adverse event-related treatment [22].

This in match with study conducted by **Kobayashi et al., [17]** reported that there were significant increases in dry mouth and accompanying symptoms while unremarkable change was seen in stool condition during mirabegron treatment. And the degree of dry mouth and constipation in the antimuscarinic group was substantially higher than in the mirabegron group.

Four studies involving 2042 participants (1139 in the treatment group and 903 in the control group) on the possible adverse effects of propiverine hydrochloride for overactive bladder; have reported that there was no clinical disparity in blurred vision ($P = 0.12$) based on latest study, but there was substantially greater rise in dry mouth and constipation in the propiverine group than in the control group ($P < 0.00001$), yet their frequency was usually mild [23].

At the other hand, adverse effects such as dry mouth and constipation arising from blockage of the muscarinic receptor are another factor that adversely affects the efficacy of antimuscarinic therapy and Constipation worsened dramatically during antimuscarinic treatment, although mirabegron had no impact on these symptoms, resulting in a remarkable tolerability difference as an initial therapy. That's why many patients were forced to avoid antimuscarinic treatment, although none of the mirabegron patients stopped treatment due to adverse effects [17].

Mirabegron tends to be more helpful to men with OAB with BPH unresponsive to prior antimuscarinic therapy [17]. Also, **Otsuki et al., [18]** Suggests that Mirabegron was also successful

for antimuscarinic-resistant OAB patients and that offers a broader variety of treatment choices for OAB. In addition, the present study demonstrated the efficacy of BPH-related storage symptoms in males, resulting not only in male wet OAB improvement under α 1-blocker combination therapy, but also in improved storage symptoms.

The main limitation of this study is the relatively small number of patients short period for follow up mirabegron is a new medicine in Egypt, Some patients rejected mirabegron and others preferred to end mirabegron at week 8 also drop out of patient.

CONCLUSION:

For managing storage symptoms in benign prostatic hyperplasia patients, Mirabegron can be considered a drug with better balance between efficacy and safety than Propiverine.

REFERENCES

- 1- **Martin SA, Haren MT, Marshall VR, Lange K, Wittert GA.** Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. *World J Urol.* 2011; 29(2), 179-84.
- 2- **Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten, U, et al.** The standardisation of terminology in lower urinary tract function: report from the standardisation sub-committee of the international continence society. *Urology,* (2003).61(1), 37-49.
- 3- **Cho KJ, Kim JC.** Alfuzosin for the treatment of storage symptoms suggestive of overactive bladder. *Expert Opin Pharmacother.* 2012; 13(8), 1143-51.
- 4- **Sigala S, Mirabella G, Peroni A, Pezzotti G, Simeone C, Spano P, et al.** Differential gene expression of cholinergic muscarinic receptor subtypes in male and female normal human urinary bladder. *Urology,* 2002; 60(4), 719-25.
- 5- **Jayarajan J, Radomski SB.** Pharmacotherapy of overactive bladder in adults : a review of efficacy , tolerability, and quality of life. *Res Rep Urol.* 2014; 6, 1.
- 6- **Çetinel B, Onal B.** Rationale for the Use of Anticholinergic Agents in Overactive Bladder With Regard to Central Nervous System and Cardiovascular System Side Effects. 2013; 806 -15.
- 7- **Rovner ES.** Patient-reported reasons for discontinuing overactive bladder medication. *Urology,* 2011; 210–1.
- 8- **Sexton CC, Notte SM, Maroulis C, Dmochowski RR, Cardozo L, Subramanian D, et al.,** Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy : a systematic review of the literature. *Int J Clin Pract Suppl.* 2011;65(5), 567–85.
- 9- **Gomes T, Juurlink DN, Mamdani MM.** Comparative adherence to oxybutynin or tolterodine among older patients. *Eur J Clin Pharmacol.* 2012; 68(1), 97–99.
- 10- **Michel M C, Vrydag W.** α 1-, α 2- and β -adrenoceptors in the urinary bladder, urethra and prostate. *Br J Pharmacol.* 2006; 147(S2), S88–S119.
- 11- **Wuest M, Eichhorn B, Grimm MO, Wirth MP, Ravens U, Kaumann AJ.** Catecholamines Relax Detrusor through 2-Adrenoceptors in Mouse and 3-Adrenoceptors in Man. *J Pharmacol and Experimental Therapeutics.* 2008; 328(1), 213–222.
- 12- **Bae JH, Kim SO, Yoo ES, Moon KH, Kyung YS, Kim HJ.** Efficacy and safety of low-dose propiverine in patients with lower urinary tract symptoms/benign prostatic hyperplasia with storage symptoms: a prospective, randomized, single-blinded and multicenter clinical trial. *Korean J Urol.* 2011; 52(4):274–278.
- 13- **Gillespie JI, Palea S, Guilloteau V, Guerard M, Lluet P, Korstanje C.** Modulation of non-voiding activity by the muscarinic antagonist tolterodine and the β 3-adrenoceptor agonist mirabegron in conscious rats with partial outflow obstruction. *BJU int.* 2012; 110(2b), E132-E142.
- 14- **Bae JH, Kim SO, Yoo ES, Moon KH, Kyung YS, Kim HJ.** Efficacy and safety of low-dose propiverine in patients with lower urinary tract symptoms/benign prostatic hyperplasia with storage symptoms: a prospective, randomized, single-blinded and multicenter clinical trial. *Korean journal of urology.* 2011 Apr 1;52(4):274-8.
- 15- **Tubaro A, Batista JE, Nitti VW, Herschorn S, Chapple CR, Blauwet MB, Siddiqui E, Huang M, Oelke M.** Efficacy and safety of daily mirabegron 50 mg in male patients with overactive bladder: a critical analysis of five phase III studies. *Therapeutic advances in urology.* 2017 Jun;9(6):137-54.
- 16- **Reisch R, Rutt R, Dockter M, Sanders S.** Overactive Bladder Symptoms in Female Health Profession Students: Bladder Diary Characteristics and Impact of Symptoms on Health-Related Quality of Life. *J Womens Health.* 2018; 27(2), 156-161.
- 17- **Kobayashi M, Nukui A, Kamai T.** Comparative Efficacy and Tolerability of Antimuscarinic Agents and the Selective β 3-Adrenoceptor Agonist, Mirabegron, for the

Treatment of Overactive Bladder: Which is More Preferable as an Initial Treatment?. LUTS: Lower Urinary Tract Symptoms. 2018; 10(2), 158-166.

- 18- Otsuki H, Kosaka T, Nakamura K, Mishima J, Kuwahara Y, Tsukamoto T.** β 3-Adrenoceptor agonist mirabegron is effective for overactive bladder that is unresponsive to antimuscarinic treatment or is related to benign prostatic hyperplasia in men. *Int Urol Nephrol.* 2013; 45(1), 53-60.
- 19- Huang W, Zong H, Zhou X, Wang T, Zhang Y.** Efficacy and safety of propiverine hydrochloride for overactive bladder in adult: A systematic review and meta-analysis. *Indian J Surg.* 2015; 77(3), 1369-77.
- 20- Khullar V, Amarenco G, Angulo JC, Cambronero J, Høye K, Milsom I, et al.** Efficacy and tolerability of mirabegron, a β 3-adrenoceptor agonist, in patients with

overactive bladder: results from a randomised European–Australian phase 3 trial. *Eur Urol.* 2013; 63(2):283-95.

- 21- Gotoh M, Yokoyama O, Nishizawa O.** Propiverine hydrochloride in Japanese patients with overactive bladder: A randomized, double-blind, placebo-controlled trial. *Int J Urol.* 2011;18(5),365–73.
- 22- Maman K, Aballea S, Nazir J, Desroziars K, Neine ME, Siddiqui E, et al.** Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. *Eur Urol.*2014; 65(4), 755-65.
- 23- Sener NC, Oztur k U, Goktug H N, Gucuk A, Nalbant I, Yesil S, et al.** Efficacy and safety of propiverine and terazosine combination foroney earinmale patients with luts and detrusor over activity. *Int Braz J Urol.* 2013; 39(4):513–8.

How to cite

Masoud, M., abouhashem, S., ali, A., elsayed, I. Safety and Efficacy of Propiverine Hydrochloride Versus Mirabegron in Treating storage Symptoms in Patients with Benign Prostatic hyperplasia. *Zagazig University Medical Journal*, 2023; (49-55): -. doi: 10.21608/zumj.2020.15654.1401