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Original Article

Treating overactive bladder symptoms after transurethral prostatic surgery for benign prostatic hyperplasia – Which medication to choose?

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Abstract

Objectives: Overactive bladder (OAB) symptoms are often encountered in patients after transurethral resection of the prostate (TUR-P) or transurethral incision of the prostate (TUI-P) for benign prostatic obstruction (BPO). Either antimuscarinics or β-3 agonist has been found effective in relieving OAB symptoms. However, urologists usually do not prescribe such medication immediately after TUR-P or TUI-P to avoid an increase in postvoid residual and risk of urinary tract infection. If OAB medication can be used and adverse events (AEs) can be reduced to minimum, patients' quality of life after bladder outlet obstruction surgery could be improved. This study compared the safety and efficacy between solifenacin and mirabegron in men undergoing TUR-P or TUI-P. **Materials and Methods:** This prospective, randomized trial compared the safety and efficacy of OAB medication on the reduction in Urgency Severity Score (USS), OAB Symptoms Score (OABSS), International Prostate Symptom Score, and urgency urinary incontinence episodes in men with BPO undergoing surgical intervention. All patients could void smoothly after catheter removal and were randomly received daily solifenacin 5 mg, mirabegron 50 mg, or no interventions for 4 weeks. At 2 and 4 weeks postoperatively, participants' OAB symptoms and AEs were evaluated. **Results:** A total of 57 men were enrolled in this study with a mean age of 70.8 ± 6.1 years. At 2 weeks postoperatively, USS (1.56 ± 1.72 vs. 2.39 ± 1.72 vs. 2.26 ± 1.73, $P < 0.011$) and OABSS (5.33 ± 3.65 vs. 7.67 ± 4.19 vs. 8.58 ± 4.31, $P < 0.000$) were significantly reduced in patients taking solifenacin, mirabegron, or control, respectively. Two patients in the solifenacin group developed urinary retention. However, the changes of variables at 4 weeks postoperatively were insignificant among the three groups. **Conclusion:** Solifenacin and mirabegron are two different drug classes both equally effective in treating immediate OAB symptoms after TUR-P or TUI-P. However, OAB symptoms could be relieved at 4 weeks without any medication. Considering AEs, β-3 agonist has a more favorable safety profile than antimuscarinics.

Keywords: *Benign prostatic hyperplasia, Mirabegron, Overactive bladder, Solifenacin, Transurethral resection of the prostate*

Introduction

Benign prostatic obstruction (BPO) is highly prevalent in aging men and often contributes to lower urinary tract symptoms (LUTS). Transurethral resection/incision of the prostate (TUR-P/TUI-P) with different energy modalities has been and probably remains the gold standard to manage bothersome LUTS resulting from BPO when medical treatment failed to relieve [1]. Although with its advantages of high efficacy and safety profile, TUR-P/TUI-P, on the other hand, is still associated with some degree of adversity. Apart from postoperative bleeding, urinary tract infection (UTI), clot retention, and urinary retention, early storage symptoms (i.e. frequency, urgency, and nocturia with or without urge urinary incontinence [UUI]) are by far the most common unwanted adverse events (AEs), which were reported in 30%–40% of patients [2,3].

Antimuscarinics and β-3 agonists have been widely prescribed alone or in combination for alleviating overactive bladder (OAB) symptoms [4]. The troublesome symptoms

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after TUR-P/TUI-P are similar to those of idiopathic OAB, although their underlying pathophysiology may be completely different. From animal models and human subjects, accumulating evidence suggests that obstruction at the bladder outlet can lead to morphological changes in epithelial and detrusor muscle cells [5,6]. It not only alters its ultrastructure but also causes interference within neuronal networking. Such a transformation, resulting in decreased capacity, low contractility, poor compliance, and hyperactive bladder, may persist even after surgical relief of BPO.

Dry mouth, constipation, urinary retention, UTI, and cognitive impairment are often linked to anti-OAB drugs. The risk of developing such AEs increases with age [7]. The use of these OAB medications in postoperative care immediately after TUR-P or TUI-P can be problematic, especially in the elderly population. Hence, we conducted this study to evaluate the therapeutic efficacy and safety of solifenacin 5 mg (SOL, an antimuscarinic agent) mirabegron 50 mg (BET, a ß-3 agonist), or control (PLB) on the early OAB symptoms after TUR-P/TUI-P following catheter removal during a 4-week study period.

Materials and Methods

Study design and population

This study was a prospective, randomized, and controlled trial, which was conducted in the Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Hualien, Taiwan, between January 2019 and January 2020. This study was approved by our institutional review board (IRB no: TCGH107-115-A; ClinicalTrials.govidentifier: NCT03632772).

Men with symptomatic BPO who underwent TUR-P/TUI-P were screened for eligibility. Exclusion criteria in the preoperative state included overt neurological diseases such as cerebrovascular disease, senile dementia, or spinal cord injury. Those with uncontrolled medical illnesses, were in bedbound state, had a known history of prostatic cancer, or had active infection were also precluded.

Surgical procedure and randomization

TUR-P or TUI-P was performed under standard technique using monopolar, bipolar, or laser devices. An 18 Fr. 3-way Foley catheter was indwelled at the completion of surgery. Once hematuria had resolved, the Foley catheter was removed on the postoperative day 2 or 3. Based on the 3-day voiding diary, for those who had newly developed OAB symptoms after operation, participants with a maximum flow rate (Qmax) ≥15 mL/s or any improvement from the nadir and without evidence of retained blood clot and infection nor postvoiding residual (PVR) volume >150 mL were enrolled. On discharge, each individual was numbered consecutively using permuted block randomization table, allocated into one of the three groups, and prescribed with corresponding medication. Randomization was performed in a 1:1:1 ratio (SOL 5 mg QD, BET 50 mg QD, and control, respectively).

Primary and secondary endpoints

Each participant was assessed for primary endpoint Urgency Severity Score (USS), and secondary endpoints including OAB Symptom Score (OABSS), IPSS (International Prostate Symptom Score), Qmax, and PVR, by calculating the score differences at early postoperative (V-0), 2nd week (V-1), and 4th week (V-2). Patient's subjective satisfaction was compared using the quality of life (QoL) index and AEs were documented between the SOL, BET, and PLB groups. CONSORT flow diagram of the study design is shown in Figure 1.

Statistical analysis

Continuous variables were represented as means ± standard deviations, and categorical data were represented by numbers and percentages. Statistical comparisons between the groups were tested using the Chi-square test for categorical variables and the Wilcoxon rank-sum test for continuous variables. Statistical assessments were considered statistically significant when $P < 0.05$. Statistical analyses were performed using SPSS 15.0 software (SPSS Inc., Chicago, IL, USA).

Results

A total of 57 men were enrolled in this study with a mean age of 70.8 ± 6.1 years (range 55–80) and randomly divided into three groups (SOL, $n = 19$; BET, $n = 19$; and PLB, $n = 19$). Table 1 summarizes the basic characteristics of all participants. All 57 participants completed a 4-week follow-up. There was no significant difference among the three groups at V-0 in terms of age and subjective parameters, including the mean number of micturition events: frequency, urgency, nocturia, and UUI episodes per 24 h, Qmax, voided volume, and PVR.

At the V-1 visit, patients in both SOL and BET groups reported significant decrements in immediate USS, OABSS, and IPSS-storage subscore; and their QoL index was also improved (all $P < 0.05$). For daytime frequency, urgency, and UUI episodes, a substantial reduction was observed in those

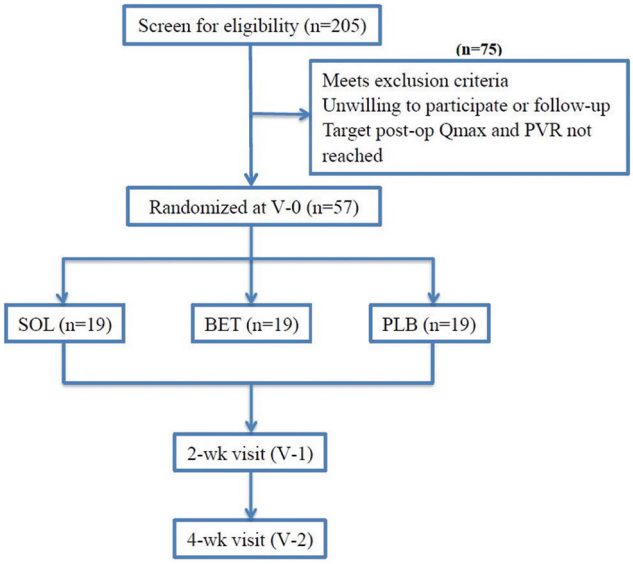

Figure 1: Study design flow chart. Qmax: Maximal flow, PVR: postvoiding residual, SOL: Solifenacin, BET: Mibegron, PLB: Control, V-1: Two weeks after Foley catheter removal, V-2: Four weeks after Foley catheter removal

who have been taking SOL for 2 weeks ($P < 0.05$). Qmax and PVR in both BET and PLB groups remained unchanged at 2-week follow-up. On the contrary, two patients in the SOL group developed urinary retention with a PVR >150 mL.

At 4 weeks postoperatively, all groups showed a continuous decline in USS, OABSS, and total IPSS scores compared to their baseline data [Figure 2]. With regard to the changes in subjective symptoms, the SOL group demonstrated significant benefit in reducing OABSS and USS compared to the BET and PLB group [all $P < 0.01$, Table 2]. A mean number of frequency, urgency, and UUI episode at V2 were also lowest in the SOL group [Table 3]. Nevertheless, there was a relatively high incidence of dry mouth (3/19, 15.8%) and UTI episode (5.3%) in the SOL group, and 2 (10.5%) patients developed intolerable AE, namely urinary retention. However, the difference of the overall QoL index in the SOL, BET, and PLB groups was insignificant.

Discussion

To our knowledge, this was the first prospective, randomized, and controlled trial on the efficacy and safety of antimuscarinic agent, β-3 agonist, and no treatment in treating OAB symptoms after TUR-P or TUI-P. This study concludes that both medications of daily solifenacin 5 mg and mirabegron 50 mg can effectively alleviate early urinary OAB symptoms; however, mirabegron seems to be a preferable option while considering their potential AEs.

Urinary frequency, urgency, and UUI are commonly encountered in patients after TUR-P or TUI-P for BPO. It is estimated that approximately one in every three patients can experience storage symptoms after BPH surgery, and these symptoms can lead to dissatisfaction after surgery as well as have a negative impact on QoL despite the disappearance of obstructive symptoms after the operation [3]. The causes of postoperative OAB symptoms might be complex and often multifactorial. From preexisting detrusor overactivity (DO) before surgery, perioperative hyper-activated afferent input due to acute inflammation and to a temporary weak urethral sphincter which results in urinary incontinence at the bladder capacity [6].

There were 40.3% of participants in our study diagnosed with some degree of diabetes. From *in vivo* and *in vitro* streptozotocin-induced diabetic rat models, studies have demonstrated that there is an overexpression and overactivity of Rho-kinase and CPI-17 proteins involved in calcium sensitization in smooth muscle resulting involuntary contraction [8]. A recent national-based study revealed

Table 1: Basic characteristics of the patients in the solifenacin, mirabegron, and control groups

	Solifenacin (*n*=19)	Mirabegron (*n*=19)	Control (*n*=19)
Age (years)	70.26±6.76	71.37±6.43	71.16±5.37
Prostate size (mL)	44.06±19.22	53.85±37.31	49.18±27.49
Transitional zone	0.49±0.26	0.48±0.16	0.45±0.13
PSA (ng/dL)	2.43±2.12	2.87±3.31	2.65±2.45
Energy device, *n* (%)			
Monopolar (*n*=52)	17 (89.5)	18 (94.7)	17 (89.5)
Bipolar (*n*=2)	2 (10.5)		
Laser (*n*=3)		1 (5.3)	2 (10.5)
Comorbidities, *n* (%)			
HTN	11 (57.9)	13 (68.4)	11 (57.9)
DM	7 (36.8)	8 (42.1)	8 (42.1)
COPD	2 (10.5)	1 (5.3)	0

PSA: Prostate-specific antigen, HTN: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease

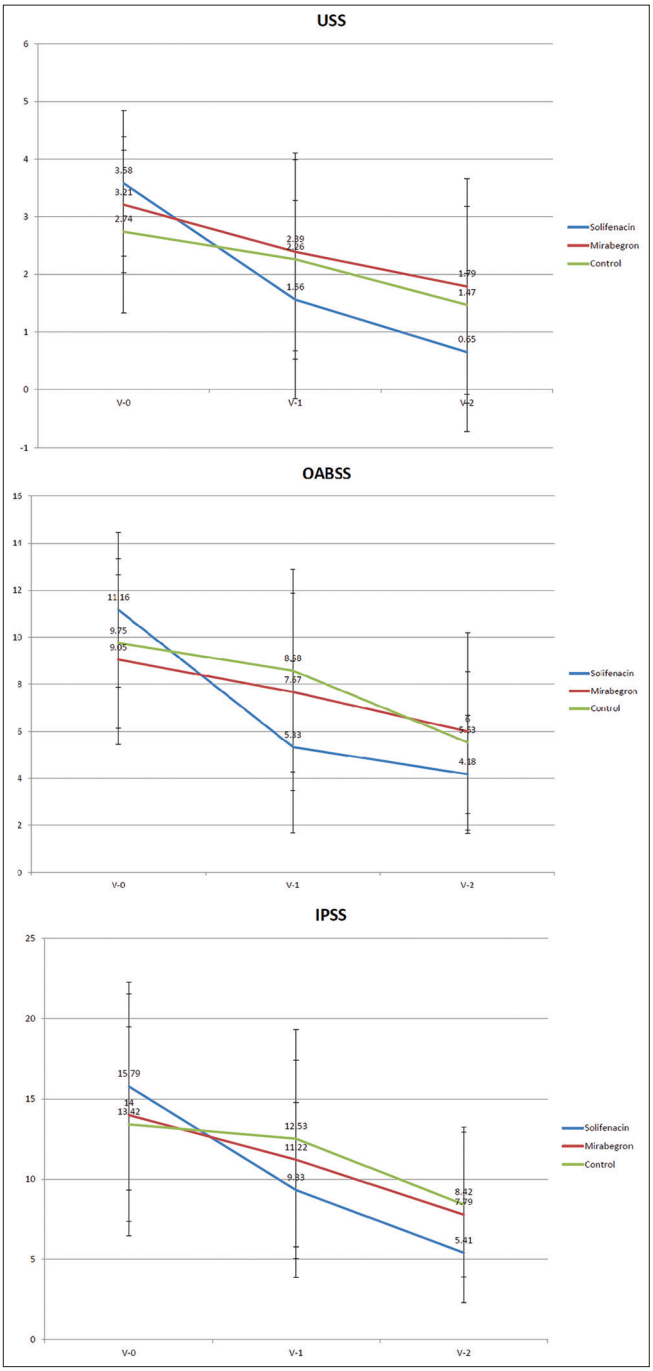

Figure 2: The changes of Urgency Severity Score, Overactive Bladder Symptom Score, and total International Prostate Symptom Score from early postoperative (V-0) to the 2-week (V-1) and 4-week (V-2) visits postoperatively. SOL: solifenacin, BET: mirabegron, PLB: control

Table 2: Changes of Overactive Bladder Symptom Scores and quality of life index from immediate, 2 weeks, and 4 weeks in patients receiving solifenacin, mirabegron, and control after transurethral resection of the prostate/transurethral incision of the prostate

	Solifenacin (*n*=19)	Mirabegron (*n*=19)	Control (*n*=19)	*P* (ANOVA)
Age	70.26±6.76	71.37±6.43	71.16±5.37	-
USS				
BL	3.58±1.26	3.21±1.18	2.74±1.41	
V_1	1.56±1.72*	2.39±1.72*	2.39±1.69	0.004
V_2	0.65±1.37*	1.89±1.88*	1.56±1.72*	0.004
OABSS				
BL	11.16±3.29	9.05±3.60	8.94±3.77	
V_1	5.33±3.65*	7.67±4.19*	8.89±4.21	0.000
V_2	4.18±2.51*	6.33±4.04*		0.001
IPSS-storage				
BL	10.53±3.53	10.32±3.42	10.61±4.18	
V_1	6.28±3.23*	7.61±4.00*	9.56±3.87	0.018
V_2	4.76±2.80*	5.39±2.93*	6.89±3.12*	0.190
IPSS-voiding				
BL	5.26±4.86	3.68±6.24	3.17±4.16	
V_1	3.06±4.21	3.61±4.54	3.39±4.26	0.305
V_2	0.65±1.06*	2.72±3.23	1.78±2.24	0.089
IPSS-total				
BL	15.79±6.46	14.00±7.53	13.78±6.02	
V_1	9.33±5.46*	11.22±6.17	12.94±6.71	0.038
V_2	5.41±3.12*	8.11±5.44*	8.67±4.52*	0.057
QoL				
BL	2.68±1.29	2.74±1.10	2.67±1.24	
V_1	1.72±1.45*	2.11±1.02*	2.72±1.53	0.104
V_2	1.24±1.60*	1.67±0.91*	1.61±1.24*	0.775

*Significant difference of variables between changes from baseline data. BL: Baseline, immediate postoperatively, V_1: 2 week postoperatively, V_2: 4 week postoperatively, USS: Urgency Severity Score, OABSS: Overactive Bladder Symptom Score, IPSS-S: International Prostate Symptom Storage Score, IPSS-V: International Prostate Symptom Voiding Score, IPSS-T: International Prostate Symptom total (S + V) Score, QoL: Quality of life index

Table 3: Changes of frequency volume chart record and uroflow parameters from immediate, 2 weeks, and 4 weeks in patients receiving solifenacin, mirabegron, and control after transurethral resection of the prostate/transurethral incision of the prostate

	Solifenacin (*n*=19)	Mirabegron (*n*=19)	Control (*n*=19)	*P*
Frequency				
BL	11.70±3.75	10.35±2.48	10.21±3.98	
V_1	9.31±3.18*	10.28±2.15	10.72±4.17	0.010
V_2	7.73±2.85*	9.29±2.89	9.53±4.26	0.015
Urgency				
BL	4.83±5.85	3.98±4.70	5.90±6.76	
V_1	1.28±1.89*	3.64±5.00	5.29±6.10	0.129
V_2	0.36±0.64*	2.58±3.97	1.32±3.06*	0.276
Nocturia				
BL	2.71±1.61	2.33±1.30	3.83±1.89	
V_1	2.54±1.68	2.27±1.38	4.03±1.71	0.707
V_2	2.28±1.47	2.17±1.00	2.98±1.12*	0.360
UUI				
BL	1.06±1.50	1.48±2.33	1.04±1.68	
V_1	0.33±0.75*	0.88±1.38	1.02±1.91	0.133
V_2	0.02±0.08*	0.98±1.49	0.31±0.95*	0.716
Qmax (mL/s)				
BL	14.72±12.40	16.71±11.31	13.88±10.3	
V_1	16.57±11.88	12.88±11.17	17.19±9.93	0.079
V_2	18.18±12.46	16.08±10.81	15.37±7.85	0.290
Volume (mL)				
BL	171.18±90.47	163.53±86.87	133.67±52.41	
V_1	224.13±105.58	174.69±144.97	184.53±99.81	0.698
V_2	245.21±102.06*	207.47±125.79	245.43±125.61*	0.356
PVR (mL)				
BL	31.11±28.16	34.26±35.78	39.94±41.03	
V_1	43.2±54.6	19.7±19.7	14.3±13.3*	0.247
V_2	39.4±56.3	12.6±22.1	16.5±25.4	0.287

*Significant difference of variables between changes from baseline data. BL: Baseline, immediate postoperatively, V_1: 2 week postoperatively, V_2: 4 week postoperatively, UUI: Urgency urinary incontinence episodes, Qmax: Maximal flow rate, PVR: Postvoiding residual volume

that diabetes mellitus was associated with a 40%–80% and 30%–80% increased risk of urge incontinence and overflow incontinence, respectively [9]. There was also urodynamic evidence of a high incidence of DO in diabetic patients [10]. In their study, Han *et al*. found a strong correlation between persistent LUTS and a history of medical illnesses such as diabetes and cerebrovascular accident in patients aged 70 years or older after prostate surgery [11]. Above all, it appears relevant that preexisting DO may contribute to ongoing storage symptoms despite surgical treatment of BPO. Similarly, in this study, two-thirds of participants were in their 70s and beyond, with almost 70% of them having some degree of glucose intolerance. This could explain one reason why there is an immediate improvement, mainly in obstructive but not storage symptoms after surgery.

Antimuscarinics and β-3 adrenoceptor agonist are two different classes of drugs often prescribed for OAB. By blocking acetylcholine release from postganglionic axons in the pelvic nerve, antimuscarinic therapy can suppress signal that triggers involuntary bladder contractions [12]. Previous studies have demonstrated that solifenacin significantly reduced episodes of urgency in more than 60% of patients and secondarily reduced other symptoms related to OAB symptoms [13]. At perioperative and postoperative period, it is believed that iatrogenic injury to the prostatic urethra and bladder mucosa, exposure of the detrusor to urine, catheterization, and bladder irrigation can also stimulate the afferent nerves of the bladder, leading to the release of acetylcholine and provoke inflammation which can bring about temporary involuntary contractions of detrusor mediated by muscarinic receptors after TUR-P or TUI-P [5,6,14]. Zhang *et al*. found that SOL can ease inflammation by decreasing the levels of inflammatory cytokines (tumor necrosis factor-α, interleukin [IL]-6, IL-17, and IL-8) and increasing serum levels of IL-2 and extractable nuclear antigen-7. Therefore, SOL improves the urinary symptoms during the early recovery period after TUR-P [15]. Our analysis also demonstrates that solifenacin can significantly relieve irritative symptoms after

TUR-P or TUI-P by reducing OABSS, USS, IPSS, daytime frequency, urgency, and episodes of UUI.

However, antimuscamics might decrease detrusor contractility and result in an increase of PVR volume. Given its known potential side effects, using solifenacin in the postoperative setting can be a concern in elderly patients or for those with poor bladder contractility. β-3 adrenoceptor agonist, mirabegron, on the other hand, can also decrease DO and improve OAB symptoms. β-3 adrenergic agonist was found to improve glucose homeostasis, stimulate lipolysis, regulate mitochondrial biogenesis, and fibrotic gene expression and reduce inflammation of muscles in insulin-resistant subjects [16]. Available literature shows mirabegron does not impair detrusor contractility nor increase PVR. Under this consideration, mirabegron has also been used to treat male LUTS due to BPO [17,18]. However, there has been no clinical trial to evaluate if mirabegron provides benefits in decreasing the OAB symptom severity immediately after TUR-P or TUI-P. Our results revealed that mirabegron could also achieve comparable outcomes to solifenacin with less incidence of AE. Although there was difference in relieving OAB symptoms between OAB medication and control, at 4 weeks after surgery, all groups showed a continuous decline in USS, OABSS, and total IPSS scores compared to their baseline data. This result implies the fact that once the tissue injury or inflammation begins to ease, the OAB symptoms may eventually be resolved on its own, with or without OAB medication.

The limitations of this study were as follows: (1) the study was conducted at a single medical center with a relatively small sample size and short-term follow-up may have unintentionally influenced our results. (2) The diagnosis of *de novo* OAB was made mostly by questionnaire rather than urodynamic evidence of DO in pre- and post-operative period. (3) All participants enrolled in this trial are of Asian descent; hence, the implications may not well apply to other ethnicity.

Conclusion

Both solifenacin and mirabegron are equally effective in treating immediate OAB symptoms in patients who underwent transurethral prostate surgery for BPO. However, given its potential AEs, β-3 agonist has a more favorable safety profile than antimuscarinics.

Data availability statement

The datasets generated during and/or analyzed during the current study are available in the correspondence author on reasonable request.

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Nil.

Conflicts of interest

Dr. Hann-Chorng Kuo, an editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

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