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Study of mirabegron and solifenacin in the improvement of catheter-related bladder discomfort in patients undergoing transurethral resection

A case–control study

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Abstract

Background: The goal of this study was to see if using mirabegron, solifenacin, or placebo may help patients with transurethral resection avoid catheter-related bladder discomfort (CRBD).

Methods: Patients who underwent transurethral surgery and were given a catheter for 3 days after surgery were chosen for this study. The enrolled patients were separated into 3 groups: mirabegron (M), solifenacin (S), and a blank control group (C). All patients had their overactive bladder symptoms score (OABSS) and blood pressure checked before surgery. The CRBD, blood pressure, and heart rate were measured at 6, 24, 48, and 72 hours after surgery. The OABSS and side effects were documented on the 7th day.

Results: The 104 patients in this trial were randomized into 3 groups at random: M, S, and C. The ultimate follow-up was completed by 99 patients, including 33 in group M, 33 in group S, and 33 in group C. The OABSS, CRBD, and blood pressure in groups M and S were similar before and after surgery ($P > .05$). Groups M and S performed much better on the OABSS and CRBD than group C ($P < .05$). There were no significant differences in blood pressure between the 3 groups ($P > .05$). There were no significant differences in the occurrences of new onset dry mouth ($P = .84$) or constipation ($P = .64$) among the 3 groups.

Conclusion: Mirabegron is comparable to solifenacin as an alternative for the prevention of CRBD, making it a viable option for CRBD prevention.

Abbreviations: BPH = benign prostatic hyperplasia, CRBD = catheter-related bladder discomfort, DBP = diastolic blood pressure, OAB = overactive bladder, OABSS = overactive bladder symptoms score, SBP = systolic blood pressure.

Keywords: catheter-related bladder discomfort (CRBD), mirabegron, solifenacin

1. Introduction

Indwelling catheters will be left in patients after transurethral resection of the prostate (TURP) for urine drainage and monitoring of postoperative bleeding to prevent blood clots.[1,2] The indwelling catheters, on the other hand, frequently cause bladder discomfort in these patients. Catheter-related bladder discomfort (CRBD) is a kind of secondary catheter-related postoperative discomfort in which the patient still feels urine urgency and suprapubic discomfort or pain despite effective catheter draining.[3,4] CRBD will significantly worsen postoperative quality of life by increasing the incidence of postoperative bleeding, discomfort, and dysphoria.[5,6] As a result, preventing or reducing the incidence and severity of CRBD can assist patients' short-term quality of life while also lowering the risk of postoperative complications.

The exact cause of CRBD is unknown. Its symptoms, on the other hand, are comparable to those of overactive bladder

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Before the trial, all patients signed an informed consent form.

The authors have no conflicts of interest to disclose.

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

The study was approved by the Ethics Committee of the Beijing Chao-Yang Hospital, Capital Medical University.

This is a randomized clinical trial, registered at the China Clinical Trial Center (ChiCTR1900028650).

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(OAB), which is produced by involuntary detrusor contraction.[7,8] Anticholinergics, such as solifenacin, which are routinely used to treat OAB, have been successfully utilized to treat CRBD.[4,9,10] However, anticholinergics' major side effects, such as severe dry mouth and constipation, might counteract their therapeutic advantages and lead to therapy discontinuation.[11–13]

The β3-adrenoceptor agonists are a different type of medication that has been used to treat OAB. They control bladder function via a variety of molecular mechanisms.[14] According to the medical claims database, OAB patients who took mirabegron had better treatment continuity than OAB patients who received solifenacin because of the decreased occurrence and severity of side effects.[15,16] Efficacy and side effects of β3-adrenoceptor agonists and antimuscarinics in the treatment of CRBD have not been compared in prior trials. As a result, the goal of this study was to examine the efficacy and safety of mirabegron (a β3-adrenoceptor agonist) and solifenacin (an antimuscarinic medication) in preventing CRBD in patients who had indwelling catheters following transurethral surgery.

2. Materials and Methods

2.1. Trial design

Between January 2019 and February 2020, a prospective, randomized, controlled, single-blind, multicenter study was conducted. The study was approved by the Ethics Committee of the Beijing Chao-Yang Hospital, Capital Medical University. Before the trial, all patients signed an informed consent form. This is a randomized clinical trial, registered at the China Clinical Trial Center (ChiCTR1900028650). After preliminary screening, patients who underwent TURP for benign prostatic hyperplasia (BPH) were included in this study. All patients were catheterized after surgery using a 22F 3-ways Foley catheter with a big inflatable balloon. 40mL normal saline was put into the balloon, and the bladder was continuously irrigated for 1 day. The irrigation was turned off 1 day following the surgery. The saline was aspirated from the balloon until only 20 mL of saline remained. On postoperative day 3, the catheter was withdrawn after determining that there was no risk of future aggressive bleeding or clot retention.

2.2. Inclusion criteria and exclusion criteria

Inclusion criteria: Patients aged 50 or older who willingly engaged in this trial, had been preoperatively diagnosed with BPH, and planned to undergo TURP and keep the indwelling catheter for 3 days after surgery met the following criteria.

Exclusion criteria: Patients with liver or kidney dysfunction, patients with anticholinergic contraindications, patients with asthma, patients who were pregnant or breastfeeding, patients with central nervous system disorders, patients with drug abuse, patients with chronic pain, patients with cardiovascular disease, and patients with any mental illness were all excluded from the study.

2.3. Sample size calculation

According to the literature, 70% of people have CRBD.[17] The efficacy analysis at the significance level $\alpha = 0.05$ (1-sided) and β efficacy = 0.8 was used to calculate the sample size based on the hypothesis that the incidence of CRBD would fall to 30% after treatment with β3-adrenoceptor agonists or antimuscarinics. Each group required at least 25 patients, according to the sample size estimation. We decided to enroll at least 90 patients for all 3 groups, notwithstanding the chance of withdrawal, and we eventually recruited 104 patients.

2.4. Method of grouping and drug administration

According to a computer-generated random number table, the enrolled patients were randomly assigned to 1 of 3 groups: mirabegron (group M), solifenacin (group S), or a blank control group (group C) (Fig. 1). No β3-adrenoceptor agonists, antimuscarinics, antispasmodics, or analgesics were given to patients in group C. Patients in group S were given 5 mg solifenacin orally 1 hour before anesthesia induction and once daily for a 1-week regimen. Patients in group M were given 50 mg mirabegron orally once a day for 1 week, starting 1 hour before anesthesia induction. (In China, Mirabegron is only available in 1 dose form: 50 mg/T, which cannot be taken separately).

2.5. Observational indicators

Detection of primary efficacy indicators: the incidence of CRBD was assessed by nonparametric tests between the 3 groups at 6, 24, 48, and 72 hours postoperatively. Detection of secondary efficacy indicators: analysis of change in overactive bladder symptoms score (OABSS) questionnaire scores. The OABSS was examined for all patients before surgery to acquire baseline values, and the OABSS was assessed again for all patients 7 days after surgery; At 6, 24, 48, and 72 hours after surgery, CRBD conditions were reported. Painless, mild pain (decided only following consultation), moderate pain (spontaneous complaints), and severe discomfort were used to grade the severity of CRBD (dysphoria, loud complaints, and attempting to remove the catheter); At 6, 24, 48, and 72 hours after surgery, the systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were monitored and recorded; Other postoperative safety markers were known antimuscarinic side symptoms (such as dry mouth and constipation) and known β3-adrenoceptor agonist adverse effects (such as palpitations and tachycardia).

2.6. Statistical analysis

The Kolmogorov–Smirnov test was used to determine whether numerical variables were normal. The mean (M) and standard deviation (SD) of normally distributed numerical data are used (SD). Numbers and percentages are used to represent category data. Analysis of variance was used to compare patient age, preoperative OABSS, postoperative OABSS, SBP, DBP, and heart rate between groups. The Kruskal-Wallis test was used to evaluate the sex distribution, surgical method, incidence and severity of CRBD, and the incidence of dry mouth and constipation between groups. The paired *t*-test was used to compare the preoperative and postoperative OABSS within each group. Repeated-measures analysis of variance was used to examine intragroup changes in SBP, DBP, and heart rate over time. Statistical significance was defined as a P value of < 0.05. The information was evaluated using statistical software GraphPad Prism version 6.0.

3. Results

3.1. General information of the patients

Twenty patients were eliminated from the trial after preliminary examination because they did not match the inclusion criteria or were unwilling to participate. A total of 104 patients were enrolled in the study. They were divided into 3 groups at random and then analyzed using a random number table. Two patients from group C, 2 from group S, and 1 from group M were lost to follow-up (Fig. 1). The final follow-up was completed by 99 patients (33 patients in each group) (Fig. 1). The average age in groups C, S, and M was 64.67 ± 14.20, 68.55 ± 6.57 and 65.79 ± 11.81, respectively. There were no significant variations in preoperative age among the 3 groups ($F = 1.026$, $P = .362$).

3.2. Comparison of the 3 patient groups before and after surgery

Preoperatively, there were no significant variations in OABSS across the 3 groups ($F = 0.413$, $P = .813$), but there was a significant difference after surgery ($F = 45.13$, $P < .001$). The OABSS in groups S and M was considerably lower than that in group C (both $P < .001$), and it was similar between groups S and M ($P > .999$) in the postoperative intergroup comparison (Table 1). Furthermore, the intragroup comparison revealed that while the postoperative OABSS was not substantially lower than the preoperative OABSS in group C ($T = 1.382$, $P = .176$), it was significantly lower in groups S ($T = 7.829$, $P < .001$) and M ($T = 9.692$, $P < .001$).

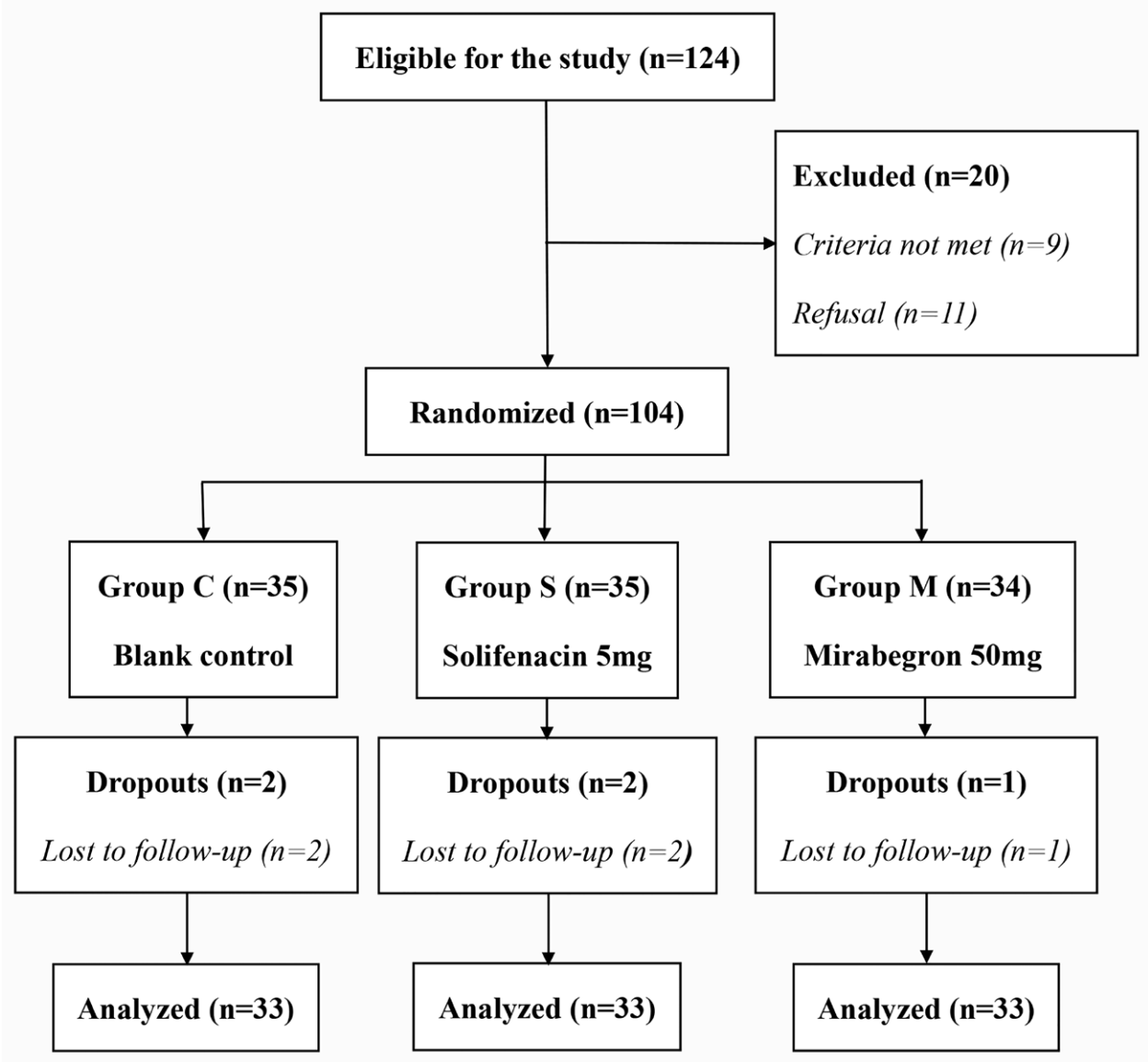

Figure 1. Flow chart of patient enrollment and randomization.

Table 1

OABSS among 3 groups.

OABSS	Control (n = 33)	Solifenacin (n = 33)	Mirabegron (n = 33)	*F* value	*P* value
Pre-operation	7.91 ± 2.04	7.61 ± 3.05	7.76 ± 3.13	0.413	.813
Post-operation	7.46 ± 2.90	3.30 ± 1.69	3.33 ± 1.43	45.13	<.001
T-value (post–pre)	1.382	7.829	9.692		
P-value (post–pre)	.176	<.001	<.001		
	Pre-	Post-			
C vs S	>.999	<.001			
C vs M	>.999	<.001			
S vs M	>.999	>.999			

Data are presented as mean ± SD.

C = control group, M = mirabegron, OABSS = overactive bladder symptoms score, S = solifenacin.

At 6 hours, 24 hours, 48 hours, and 72 hours after surgery, the incidence of CRBD was significantly lower in groups S [respectively, 54.5% ($P = .005$), 51.5% ($P < .001$), 39.4% ($P < .001$), and 36.4% ($P < .001$)] and M [57.6% ($P = .025$), 60.6% ($P = .011$), 57.6% ($P = .035$), and 51.5% ($P = .040$)]. At 6 hours ($P > .999$), 24 hours ($P > .999$), 48 hours ($P = .392$), and 72 hours ($P = .650$), the incidence of CRBD was not statistically different between groups S and M (Table 2).

At all 4 postoperative time points, the severity of CRBD was considerably higher in group C than in groups S (all $P < .001$) and M ($P = .003$ at 6 hours; $P < .001$ at 24 hours, 48 hours, and 72 hours). Three patients in group C developed severe CRBD at 6 hours, 4 patients at 24 hours, 4 patients at 48 hours, and 3 patients at 72 hours. At any of the 4 postoperative time points, neither group S nor M experienced severe CRBD (Table 3 and Fig. 2), and the severity of CRBD was not significantly different between the 2 groups ($P > .999$ at 6 hours; $P > .999$ at 24 hours; $P = .647$ at 48 hours; $P = .983$ at 72 hours).

3.3. Adverse effects

The most common adverse effects were documented. Dry mouth developed suddenly in 6 (18.2%) of group C patients, 8 (24.2%) of group S patients, and 7 (21.2%) of group M patients. There were no significant differences in the incidence of new-onset dry mouth among the 3 groups ($H = 0.359$, $P = .836$). New-onset constipation occurred in 5 (15.2%) of group C patients, 8 (24.2%) of group S patients, and 6 (18.2%) of group M patients. There were no significant differences in the incidence of new-onset constipation among the 3 groups ($H = 0.903$, $P = .637$).

3.4. Blood pressure and heart rate

Blood pressure and heart rate were measured at 4 postoperative time points to compare the common side effects of β3-adrenoceptor agonists. At any of the 4 postoperative time points, no significant changes in SBP ($F = 2.487$, $P = .089$ at 6 hours; $F = 0.425$, $P = .655$ at 24 hours; $F = 0.728$, $P = .485$ at 48 hours; $F = 0.420$, $P = .658$ at 72 hours), DBP ($F = 1.082$, $P = .343$ at 6 hours; $F = 1.851$, $P = .163$ at 24 hours; $F = 0.928$, $P = .399$ at 48 hours; $F = 2.714$, $P = .071$ at 72 hours), or heart rate ($F = 2.553$, $P = .083$ at 6 hours; $F = 2.230$, $P = .113$ at 6 hours; $F = 0.982$, $P = .378$ at 48 hours; $F = 0.747$, $P = .477$ at 72 hours) were seen between groups C, S, and M, as shown in Table 4. Our findings revealed that the incidences of elevated blood pressure and palpitations were the same in all 3 groups. Mirabegron was found to have less severe side effects and the same level of safety as solifenacin in all studies.

4. Discussion

70% of patients who had postoperative catheterization might have CRBD, and it's most common in people who had TURP for BPH.[18,19] The significant incidence of preoperative OAB in these

Table 2

Prevalence of CRBD among 3 groups.

Time (h)	6 h			24 h			48 h			72 h		
Groups	**C**	**S**	**M**	**C**	**S**	**M**	**C**	**S**	**M**	**C**	**S**	**M**
N. patients CRBD	33	33	33	33	33	33	33	33	33	33	33	33
No	3	15	14	2	16	13	4	20	14	6	21	16
Yes	30	18	19	31	17	20	29	13	19	27	12	17
Percentage (%)	90	54.5	57.6	93.9	51.5	60.6	87	39.4	57.6	81.8	36.4	51.5
H-value	11.53			15.16			16.57			14.24		
P-value (prevalence)	.003			<.001			<.001			<.001		
C vs S	.005			<.001			<.001			<.001		
C vs M	.025			.011			.035			.040		
S vs M	>.999			>.999			.392			.650		

Data are presented as absolute frequency.

C = control group, CRBD = catheter-related bladder discomfort, M: mirabegron, S = solifenacin.

Table 3

Severity of CRBD among 3 groups.

Time (h)	6 h			24 h			48 h			72 h		
Groups	**C**	**S**	**M**	**C**	**S**	**M**	**C**	**S**	**M**	**C**	**S**	**M**
N. patients CRBD	33	33	33	33	33	33	33	33	33	33	33	33
No	3	15	13	2	16	13	4	20	14	6	21	16
Yes	30	18	20	31	17	20	29	13	19	27	12	17
Mild	14	16	17	13	15	19	15	11	16	14	11	16
Moderate	13	2	3	14	2	1	10	2	3	10	1	1
Severe	3	0	0	4	0	0	4	0	0	3	0	0
H-value	23.39			32.10			23.78			22.66		
P-value (severity)	<.001			<.001			<.001			<.001		
C vs S	<.001			<.001			<.001			<.001		
C vs M	<.001			<.001			.002			.001		
S vs M	>.999			>.999			.647			.983		

Data are presented as absolute frequency.

C = control group, CRBD = catheter-related bladder discomfort, M = mirabegron, S = solifenacin.

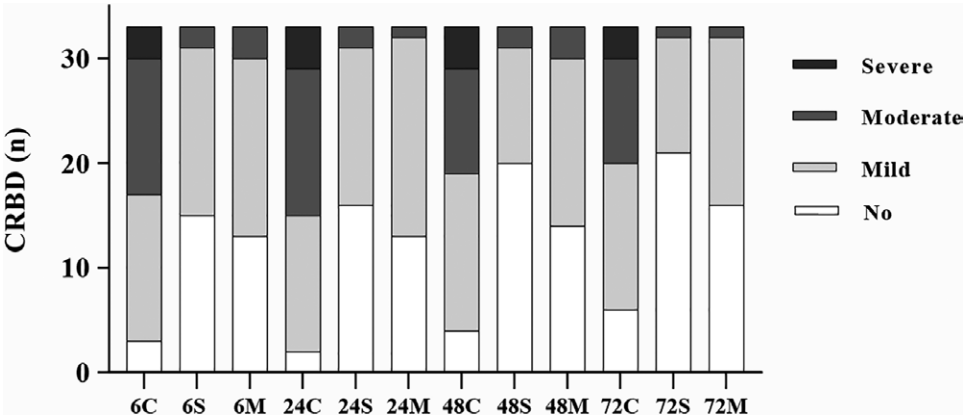

Figure 2. Incidence and severity of CRBD. CRBD = catheter-related bladder discomfort.

Table 4

Blood pressure and heart rate among 3 groups.

Time (h)		Control (n = 33)	Solifenacin (n = 33)	Mirabegron (n = 33)	*F*-value	*P*-value
6 h	SBP	127.5 ± 13.2	128.8 ± 14.9	134.5 ± 12.8	2.487	.089
	DBP	77.3 ± 8.0	76.8 ± 8.0	80.1 ± 12.2	1.082	.343
	HR	74.9 ± 6.8	72.3 ± 9.3	70.8 ± 6.1	2.553	.083
24 h	SBP	127.8 ± 11.3	125.3 ± 15.3	125.0 ± 13.9	.425	.655
	DBP	76.5 ± 8.1	73.5 ± 9.1	72.2 ± 10.3	1.851	.163
	HR	73.2 ± 4.9	72.5 ± 8.7	69.8 ± 6.8	2.230	.113
48 h	SBP	126.2 ± 10.2	126.5 ± 1M5.5	123.0 ± 13.3	.728	.485
	DBP	75.8 ± 6.7	75.2 ± 8.6	73.1 ± 9.7	.928	.399
	HR	73.6 ± 5.4	73.2 ± 5.0	71.9 ± 5.7	.982	.378
72 h	SBP	124.4 ± 10.7	124.6 ± 13.2	126.9 ± 13.1	.420	.658
	DBP	75.4 ± 6.9	73.7 ± 9.4	78.4 ± 8.5	2.714	.071
	HR	72.9 ± 4.2	73.1 ± 5.6	74.3 ± 4.8	.747	.477

Data are presented as either mean ± SD.

DBP = diastolic blood pressure, HR = heart rate, SBP = systolic blood pressure.

patients may be due to bladder outlet obstruction-induced OAB or advanced age. Their bladders have a proclivity for becoming too sensitive. In addition, intraoperative bladder overfilling and stimulation, postoperative compression of the prostate fossa by a catheter with a big inflatable balloon, bladder stimulation by continuous irrigation, and the size and material of the catheter with a big inflatable balloon all contributed to the higher-than-average incidence and severity of postoperative CRBD in TURP patients.

Several therapies for CRBD have been discovered, including antimuscarinic drugs and painkillers.[4,20,21] Muscarinic receptor antagonists are the most commonly employed among them. The M3 receptor antagonist with great selectivity, solifenacin, has been widely utilized in the treatment of CRBD due to its comprehensive treatment effect and low incidence of side effects. Solifenacin, on the other hand, can cause side effects in the central nervous system and gastrointestinal system due to the widespread expression of muscarinic receptors in the body. Muscarinic receptor antagonists are strictly prohibited in people with narrow-angle glaucoma. The use of muscarinic receptor antagonists is limited in TURP patients because they are elderly and have more or fewer mental or gastrointestinal problems.

The β3-adrenoceptor agonist may be an alternative to muscarinic receptor antagonists for treating CRBD, especially in patients with contraindications to them. Rather than inhibiting involuntary detrusor contraction like muscarinic receptor antagonists do, mirabegron cures OAB by increasing detrusor relaxation during urine storage. Despite this, β-adrenoceptors are found throughout the body, with a concentration in the cardiovascular system. As a result, increased blood pressure, tachycardia, and palpitations are common side effects of β-adrenoceptor agonists.

The incidence of CRBD 6 hours after TURP was reduced from 90.1% (group C) to 54.5% (group S) after oral dose of solifenacin 1 hour before surgery, and the incidence and severity of CRBD at other 3 time points significantly decreased. Furthermore, after oral administration of solifenacin, the OABSS was dramatically reduced 7 days after surgery. These findings suggest that solifenacin may help to alleviate the irritative symptoms associated with catheter removal. The findings are consistent with earlier research. Zhang et al[21] found that giving patients 5 mg solifenacin 6 hours before surgery reduced the incidence of CRBD after transurethral excision of bladder tumors by about 25%. They also evaluated the severity of CRBD with and without solifenacin medication, finding that even if CRBD occurred after solifenacin treatment, the symptoms were modest at all postoperative time points, with no severe symptoms.

The same considerable efficacy was reported in patients treated with mirabegron. The incidence of CRBD after 6 hours postoperatively was similarly reduced after oral administration of mirabegron 1 hour before surgery, from 90.1% (group C) to 57.6 % (group M). Treatment efficacy did not differ significantly between groups M and S. The other 3 postoperative time points yielded similar results. The degree of CRBD in group M was largely mild, similar to that of group S, and both groups showed similar improvements in OABSS 7 days following surgery. As a result, mirabegron's efficacy in treating CRBD in patients who had TURP was not inferior to that of solifenacin.

In this investigation, the incidence of new-onset dry mouth in 3 groups (18.2% in group C, 24.2% in group S, and 21.2% in group M) was > those reported by Srivastava et al (10% in the control group and 16.7% in patients treated with solifenacin).[8] This could be related to the fact that elderly individuals, who made up a large component of our sample, had impaired salivary gland function. Although group S had a higher number of patients with dry mouth than group C, the difference was not significant. This result is in line with the conclusion of Srivastava et al[8] Mirabegron had identical side effects to solifenacin, and the incidence of dry mouth in group M was not substantially higher than in group C. Constipation, like dry mouth, was common in all 3 groups (15.2% in group C, 24.2% in group S, 18.2% in group M). On the 1 hand, this outcome could be owing to M3 receptor antagonists' high selectivity, as adverse effects from M3 receptor antagonists are substantially fewer than those from low-selectivity muscarinic receptor antagonists. This conclusion, on the other hand, could be owing to the patients' advanced age, as elderly individuals are more responsive to muscarinic receptor antagonists than younger patients. The frequencies of dry mouth and constipation in group M were comparable to those in groups C and S.

We also looked examined the cardiovascular side effects. Surprisingly, at the 4 postoperative time points, the occurrences of common cardiovascular adverse effects (including SBP, DBP, and heart rate) of mirabegron were not statistically different between group M and the other 2 groups. Mueller et al[22] reported similar findings in a large randomized research. Their research compared the side effects of mirabegron alone, solifenacin alone, and mirabegron with solifenacin in older people. Patients treated with mirabegron alone (by 1.77 beats/min) or mirabegron plus solifenacin (by 1.27 beats/minute) had somewhat higher pulse rates than patients treated with solifenacin alone, but the differences were clinically insignificant. The authors theorized that the slight variation in heart rate was due to diminished agonist binding to β-adrenoceptors due to senescence-induced downregulation of β-adrenoceptors. As a result, the findings of this study further demonstrated that using mirabegron does not significantly increase cardiovascular adverse effects in senior people, indicating that it has a wide range of applications.

There are some drawbacks to this study. A single-blind trial, for starters, may inject bias into the outcomes. Second, this study's sample size was modest, and larger trials are needed to explore the efficacy of mirabegron and solifenacin in the treatment of CRBD following TURP. Third, the majority of the patients in this study had bladder outlet obstruction and may have already experienced severe OAB symptoms before to surgery. It would have been more trustworthy to draw conclusions if both the preoperative urodynamic results and the effects of these drugs had been considered.

5. Conclusion

Our findings suggest that Mirabegron, as an alternative to solifenacin for the prevention of CRBD after transurethral surgery, is not inferior to solifenacin in terms of efficacy and safety, making it a viable option for CRBD prevention.

Author contributions

All were involved in the validation of the final version of the manuscript.

Acquisition of data: Bohan Fan, Jianwu Shen.

Analysis and interpretation of data: Bohan Fan, Jianwu Shen.

Conceptualization and methodology: Bohan Fan, Jianwu Shen, Liyang Wu.

Development of methodology: Liyang Wu, Peng Zhang.

Funding Acquisition: Peng Zhang.

Writing, review and/or revision of the manuscript: Bohan Fan, Jianwu Shen, Peng Zhang.

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