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Original Article

Efficacy and safety of Solifenacin combined with Mirabegron in treating overactive bladder in female patients following bladder instillation for bladder cancer

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Abstract: Objective: To investigate the efficacy and safety of Solifenacin combined with Mirabegron in treating overactive bladder (OAB) in female patients following bladder instillation for bladder cancer. Methods: A total of 62 female patients who developed OAB after undergoing transurethral resection of bladder tumor (TURBT) and subsequent intravesical chemotherapy with pirarubicin were enrolled from the Department of Urology at Guangzhou Twelfth People's Hospital. Patients were divided into two groups according to the method of treatment. The control group received Solifenacin, while the observation group received a combination of Solifenacin and Mirabegron. Pre- and post-treatment assessments included voiding frequency, Overactive Bladder Symptom Score (OABSS), urodynamic parameters, Incontinence Quality of Life (I-QOL) scores, and adverse reactions. Results: Both groups showed a significant reduction in 24-hour voiding frequency and average nocturia after treatment ($P<0.05$), with the observation group exhibiting a more pronounced decrease compared to the control group ($P<0.05$). Post-treatment evaluations revealed lower OABSS and maximum detrusor pressure during the storage phase in both groups, along with an increase in the initial sensation of bladder filling volume and maximum bladder capacity ($P<0.05$). The observation group demonstrated more significant improvements in OABSS and maximum detrusor pressure during the storage phase, as well as higher initial bladder sensation volume and maximum bladder capacity compared to the control group ($P<0.01$). Conclusion: The combination of Mirabegron and Solifenacin offers superior therapeutic effects in female patients with OAB following bladder instillation for bladder cancer, significantly improving patients' quality of life without adverse effects.

Keywords: Mirabegron, Solifenacin, female, overactive bladder, safety

Introduction

Bladder cancer is a common malignancy in urology, with over 470,000 new cases diagnosed worldwide each year. The incidence of bladder cancer increases with age, reaching 576.18 per 100,000 individuals in those over 45 years of age [1, 2]. This cancer is characterized by a high recurrence rate, along with the potential for metastasis and invasion into the muscle layer, posing a significant threat to life and health [3]. For patients with non-muscle-invasive bladder cancer, the standard treatment is transurethral resection of bladder tumor (TURBT); however, the post-surgical recurrence rate remains high, ranging from 60% to 70%, with approximately 20% of cases progressing to muscle-invasive disease [4, 5]. Given the elevated recurrence risk following surgery, postoperative intravesical chemotherapy is recommended as a prophylactic measure to reduce recurrence and improve clinical outcomes [6, 7].

Clinical studies have shown that patients undergoing intravesical chemotherapy after bladder cancer surgery are at an increased risk of developing overactive bladder (OAB) [8]. OAB is primarily characterized by symptoms of urinary frequency, urgency, and nocturia [9]. The prevalence of OAB among women ranges from 9% to 47%, with a marked increase in incidence in individuals over the age of 44 [10].

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Current clinical treatment options for OAB include lifestyle modifications and pelvic floor muscle training; however, many patients continue to experience persistent symptoms despite these interventions [11, 12]. Pharmacological treatments have been introduced to manage OAB, with anticholinergic agents being widely used in clinical practice. Solifenacin, a novel M3 receptor antagonist, is commonly prescribed to target M3 receptors in the bladder and urethra, thereby inhibiting bladder smooth muscle contraction and alleviating OAB symptoms [13, 14]. Additionally, recent studies have found that β3-adrenergic receptor agonists can relax the detrusor muscle and reduce bladder smooth muscle tension, providing an alternative therapeutic approach for OAB management [15]. Mirabegron, a β3 receptor agonist, has demonstrated significant efficacy in the clinical treatment of OAB. Previous studies comparing Mirabegron monotherapy for OAB have shown that its efficacy is comparable to that of anticholinergic agents and superior to placebo [16]. Another retrospective study further confirmed that Mirabegron is effective for OAB treatment, although for patients with severe OAB, combination therapy with other medications is often recommended [17]. Studies have shown that prostatic hyperplasia is a major cause of urinary obstruction, which can contribute to the development of OAB. Notably, patients with bladder cancer undergoing intravesical chemotherapy who also have prostatic hyperplasia exhibit a higher incidence of OAB, indicating that additional medications targeting prostatic hyperplasia may be necessary as part of combination therapy [18]. Based on these findings, this study aimed to evaluate the therapeutic efficacy and safety of Solifenacin in combination with Mirabegron for the treatment of severe OAB in female patients following bladder cancer surgery and intravesical instillation therapy.

Materials and methods

Clinical data

This study was approved by the Ethics Committee of Guangzhou Twelfth People's Hospital (No: 2024149). Between July 2016 and June 2019, a total of 62 female patients with bladder cancer who developed OAB following transurethral resection of bladder tumor (TURBT) and subsequent intravesical chemotherapy with pirarubicin were included from the Urology Department at Guangzhou Twelfth People's Hospital. Patients were divided into two groups according to the method of treatment: the control group (n=31) received Solifenacin, while the observation group (n=31) received a combination of Solifenacin and Mirabegron.

Sample size calculation

The study employed a parallel 1:1 design, with participants randomly assigned to either the control group or the observation group. Based on similar studies, the OABSS score in the control group (μ1) was 2.73, while in the observation group (μ2), it was 3.73. Considering a 10% dropout rate, and assuming a significance level (a) of 0.05 and a power (1-β) of 80%, the required sample size was estimated. The following formula was used to calculate the sample size:

$$n1 = n2 = \frac{2(Z_{1-a/2} + Z_{1-\beta})^2 \times \sigma^2}{(\mu 1 - \mu 2)^2}$$

Where, μ1=2.73, μ2=3.73, σ=1, a=0.05, β=0.2. Substituting these values into the equation, the minimum required sample size was calculated to be 24 (12 patients per group). To enhance the reliability of the results, all patients who met the inclusion criteria during the study period were enrolled, resulting in a total of 62 participants.

Inclusion criteria

(1) Diagnosis of non-muscle-invasive bladder cancer according to the 8th edition of the 2016 AJCC guidelines [19]; (2) Pathological diagnosis of urothelial carcinoma; (3) Tumor staging of T0 or T1 as per the 8th edition of the 2016 AJCC guidelines [19]; (4) Diagnosis of severe OAB based on the 2014 edition of the Chinese Guidelines for the Diagnosis and Treatment of Urological Diseases [20]; (5) Female; (6) Age >18 years.

Exclusion criteria

(1) Pre-existing OAB (OABSS≥3) prior to surgery and intravesical instillation therapy [20]; (2) Inability to tolerate intravesical chemotherapy; (3) Known allergies to Solifenacin or Mirabegron.

Treatment methods

Comprehensive treatment measures

Patient concerns were addressed proactively, with psychological support provided throughout the treatment process. Clear and timely communication with patients was prioritized, focusing on treatment approaches for lower urinary tract symptoms, expected timelines for symptom relief, and other relevant factors. By enhancing patient understanding, these measures aimed to reduce anxiety, alleviate the treatment burden, and promote active collaboration between patients and healthcare providers during the treatment process.

Pharmacological treatment

The control group received oral Solifenacin succinate [5 mg, Astellas Pharma (China) Co., Ltd., National Drug Approval No. J20140096], administered once daily. The observation group received a combination of Solifenacin succinate [5 mg, Astellas Pharma (China) Co., Ltd., National Drug Approval No. J20140096], once daily, and Mirabegron [25 mg, Astellas Pharma (China) Co., Ltd., Imported Drug Registration Certificate No. H20171305], once daily. Both treatment regimens were administered for a duration of 12 weeks.

Observation indicators

Primary observation indicators

Voiding diary: All included patients recorded a voiding diary before and after treatment. The pre- and post-treatment urinary parameters compared between the two groups included 24-hour voiding frequency, number of incontinence episodes, and average nocturia frequency.

Overactive Bladder Symptom Score (OABSS) [20]: The OABSS was assessed based on four aspects: daytime frequency, nocturia, urgency, and incontinence. The scores were classified as follows: mild (3-6), moderate (7-11), and severe (≥12). Higher scores indicated more severe symptoms.

Urodynamic examination: Urodynamic assessments were performed before and after treatment using a urodynamic analyzer (Shanghai Hanfei Medical Instrument Co., Ltd., China; Model: Ndly11). Key measurements included initial bladder sensation capacity, maximum bladder capacity, and maximum detrusor pressure during the storage phase. The specific method is as follows: urine flow rate and volume were measured first. Subsequently, the patient was then placed in the lithotomy position, and a urethral manometer catheter was inserted through the urethra to drain any residual urine from the bladder. A rectal manometer catheter was then inserted approximately 10 cm into the rectum. Both catheters were connected to an urodynamic analyzer. Normal saline was gradually infused into the bladder while continuously monitoring intravesical and rectal pressures. When the patient reported a strong urge to urinate, the infusion was paused, and the patient was instructed to void naturally.

Secondary observation indicators

Incontinence quality of life (I-QOL) score before and after treatment [21]: The I-QOL score was used to assess the impact of OAB on the patient's quality of life. The I-QOL questionnaire consists of 22 items, which are categorized into three domains: ① Psychological impact; ② Restrictive behavior; ③ Social activity limitations. Each item is rated on a 5-point scale, with higher scores indicating better quality of life. The total I-QOL score is derived from the sum of the scores across all three domains.

Incidence of adverse reactions during treatment: Adverse reactions during treatment were recorded, including dry eyes, dry mouth, constipation, nausea, vomiting, and urinary retention.

Statistical analysis

SPSS 17.0 statistical software was used for data analysis. Categorical data were expressed as frequencies and percentages [n (%)]. Continuous variables with a normal distribution were presented as mean ± standard deviation ($\bar{X}$ ± SD). A t-test was used for normally distributed and homoscedastic data. Paired-sample t-tests were applied for within-group pre- and post-treatment comparisons, and independent-sample t-tests (expressed as t) were used for between-group comparisons. For non-normally distributed or heteroscedastic data, the rank-

Table 1. Comparison of general data between the two groups

	Observation group (n=31)	Control group (n=31)	t/χ^2	P
Age (years)	52.7±9.1	51.6±8.4	0.495	0.623
Body mass index (kg/m^2)	24.39±1.97	24.25±2.03	0.276	0.784
Duration of disease (months)	42.1±11.2	40.7±10.4	0.510	0.612
Pathological stage			0.648	0.421
T0	19	22		
T1	12	9		
Tumor Size (cm)	1.3±0.5	1.5±0.6	1.426	0.159
Combined underlying disease (n, %)				
Hypertension	15	13	0.261	0.610
Type 2 diabetes	9	7	0.337	0.562
Coronary heart disease	6	7	0.097	0.755
Cerebrovascular disease	7	8	0.088	0.767

Table 2. Comparison of urination status before and after treatment between the two groups

Parameter	Observation group (n=31)		Statistics	Control group (n=31)		Statistics
	Before treatment	After treatment	t/P	Before treatment	After treatment	t/P
24-hour voiding frequency	15.3±2.5	10.8±1.7	8.287/<0.001	14.9±2.6	12.1±1.9	4.841/<0.001
Incontinence episodes	0.8±0.3	0.6±0.5	1.910/0.061	0.7±0.5	0.5±0.5*	1.575/0.121
Average nocturia frequency	3.9±0.9	2.6±0.5	7.030/<0.001	4.1±0.8	3.1±0.6*	5.568/<0.001

Note: Compared with the observation group after treatment, *P<0.05.

sum test (expressed as Z) was applied. Categorical data were analyzed using Pearson's chi-square test (expressed as χ^2). A *P*-value <0.05 was considered statistically significant.

Results

Comparison of general data

There were no statistically significant differences in the general data between the two groups (P>0.05), as shown in **Table 1**.

Comparison of urinary parameters before and after treatment

Before treatment, no statistically significant differences were observed between the two groups in terms of 24-hour voiding frequency, number of incontinence episodes, or average nocturia frequency (P>0.05). After treatment, both groups showed a significant reduction in 24-hour voiding frequency and average nocturia frequency compared to pre-treatment values (P<0.05). The observation group demonstrated a significantly lower 24-hour voiding frequency and average nocturia frequency than the control group post-treatment (P<0.01), as shown in **Table 2**.

Comparison of OABSS scores before and after treatment

There were no significant differences in OABSS scores or severity between the two groups before treatment (P>0.05). Post-treatment, both groups showed a significant decrease in OABSS scores compared to pre-treatment values (P<0.001). The observation group exhibited greater improvement in both OABSS scores, and severity compared to the control group (P<0.01), as illustrated in **Figure 1**.

Comparison of urodynamic parameters before and after treatment

Before treatment, no significant differences were observed between the two groups in initial bladder sensation capacity, maximum bladder capacity, or maximum detrusor pressure during the storage phase (P>0.05). After treatment, both groups showed a significant in-

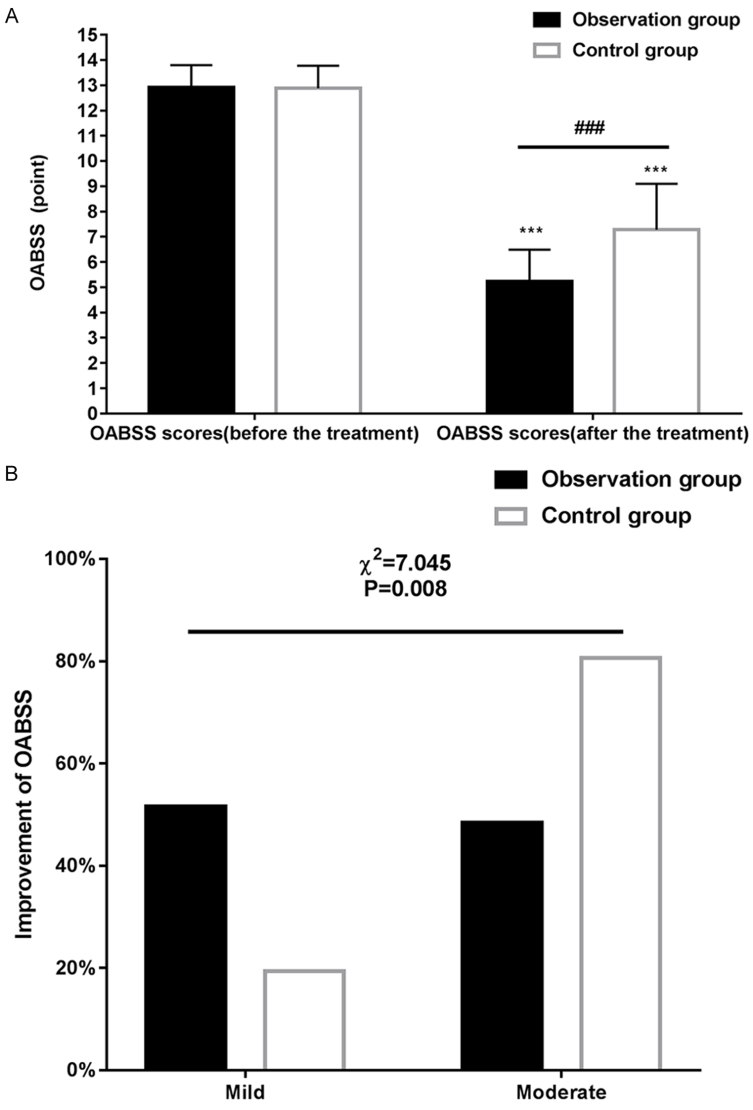

Figure 1. Comparison of OABSS scores before and after treatment between the two groups. A. Comparison of OABSS scores between the two groups before and after treatment; B. Comparison of the improvement in OABSS scores between the two groups after treatment. Note: Compared with the same group before treatment, ***P<0.001; Compared between the two groups before treatment, ###P<0.001. OABSS: Overactive Bladder Symptom Score.

crease in initial bladder sensation capacity and maximum bladder capacity, along with a significant decrease in maximum detrusor pressure during the storage phase compared to pre-treatment values (P<0.05). The observation group demonstrated a more pronounced increase in initial bladder sensation capacity and maximum bladder capacity, as well as a greater reduction in maximum detrusor pressure during the storage phase compared to the control group (P<0.001), as shown in **Table 3**.

Comparison of I-QOL scores before and after treatment

No significant differences in I-QOL scores were found between the two groups before treatment (P>0.05). After treatment, I-QOL scores increased significantly in both groups compared to pre-treatment values (P<0.05), with the observation group showing a significantly higher I-QOL score than the control group (P< 0.001), as shown in **Table 4**.

Comparison of adverse reaction rates after treatment

The incidence of adverse reactions was higher in the observation group compared to the control group; however, this difference was not statistically significant (P>0.05), as shown in **Table 5**.

Discussion

Intravesical chemotherapy has become an increasingly common therapeutic approach for bladder cancer and other urological conditions in recent years. While this treatment has proven highly effective in controlling tumor growth and alleviating related symptoms, it is also associated with a range of side effects. Among these, OAB is a frequently encountered and distressing symptom following intravesical chemotherapy. OAB is a pathological condition characterized by symptoms such as urinary frequency, urgency, and nocturia. The primary manifestation is a frequent and urgent need to urinate, which disrupts daily routines and may lead to feelings of embarrassment and discomfort in social settings.

Previous studies have indicated that the prevalence of OAB in Chinese women increases with age and, when combined with the impact of pri-

Table 3. Comparison of urodynamic parameters before and after treatment between the two groups

Parameter	Observation group (n=31)		Statistics	Control group (n=31)		Statistics
	Before treatment	After treatment	t/P	Before treatment	After treatment	t/P
Initial bladder sensation capacity (mL)	93.25±19.39	176.92±27.62	13.804/<0.001	90.78±20.01	147.23±25.92*	9.598/<0.001
Maximum bladder capacity (mL)	176.21±17.92	241.32±24.67	11.889/<0.001	179.82±18.22	211.92±23.76*	5.969/<0.001
Maximum detrusor pressure during storage phase (cmH_2O)	56.92±5.82	41.38±3.25	12.980/<0.001	57.22±6.03	45.98±4.65***	8.227/<0.001

Note: Compared with the control group after treatment, *P<0.05, ***P<0.001.

Table 4. Comparison of I-QOL scores before and after treatment between the two groups

Parameter	Observation group (n=31)		Statistics	Control group (n=31)		Statistics
	Before treatment	After treatment	t/P	Before treatment	After treatment	t/P
I-QOL score	50.22±4.89	64.23±7.01###	9.126/<0.001	51.29±5.43	57.35±5.85	4.227/<0.001

Note: Compared with the control group after treatment, ###P<0.001. I-QOL: Incontinence Quality of Life score.

Table 5. Comparison of the incidence of adverse reactions after treatment between the two groups

Adverse reaction	Observation group (n=31)	Control group (n=31)	χ^2	P
Dry eyes and mouth	3 (9.68%)	1 (3.23%)	0.267	0.605
Constipation	2 (6.45%)	1 (3.23%)	-	1.000
Nausea and vomiting	2 (6.45%)	1 (3.23%)	-	1.000
Urinary retention	1 (3.23%)	0 (0.00%)	-	1.000
Total	8 (25.81%)	3 (9.68%)	2.763	0.096

mary bladder cancer, significantly impairs patients' quality of life [22]. The clinical treatment of OAB mainly targets symptoms that occur during the storage phase of the bladder cycle, which are closely related to detrusor muscle function. Effective regulation of detrusor muscle activity has thus become a key focus in clinical research. The bladder contains both M2 and M3 muscarinic receptors. While the number of M2 receptors exceeds that of M3 receptors, their regulatory effect is much weaker. In clinical practice, pharmacological interventions primarily target and selectively block the function of M3 receptors due to their stronger impact on detrusor muscle contraction [23].

The results of this study demonstrate that the clinical symptoms in both groups of patients significantly improved after treatment with Solifenacin. This improvement is primarily attributed to the following factors: Solifenacin effectively reduces bladder excitability, alleviating symptoms such as urinary urgency and frequency. It decreases detrusor muscle tension, enhances the tone of the bladder and urethral sphincter, and increases both bladder capacity and the initial sensation of bladder filling. These effects lead to a reduction in residual urine volume and improved urodynamic outcomes, which align with previous research findings [24]. In this study, the combination of Mirabegron and Solifenacin was administered within dosage ranges that do not typically cause adverse reactions. Meanwhile, the combination therapy resulted in a significant reduction in both 24-hour voiding frequency and average nocturia, along with marked improvements in OAB symptom scores and urodynamic parameters. The underlying mechanisms may involve the following: the primary β-adrenergic receptor subtype expressed in the bladder is the β3 receptor. β3 receptors on the detrusor muscle bind to norepinephrine released from sympathetic nerve endings, leading to detrusor muscle relaxation. As a β3 receptor agonist, Mirabegron plays a crucial role in treating OAB by stimulating these receptors. Mirabegron increases intracellular cyclic adenosine monophosphate (cAMP) levels, which activates the release of Ca^{2+} and promotes the release of nitric oxide (NO) from urothelial cells. This process results in detrusor muscle relaxation, reducing the frequency of contractions during the bladder's storage phase without impacting contraction amplitude during voiding. Consequently, Mirabegron enhances detrusor relaxation, improves bladder stability, and more effectively alleviates symptoms during urine storage, such as nocturia and urinary incontinence. Additionally, Mirabegron helps relax pathological detrusor contractions by mediating the release of inhibitory factors from the urothelium, suppressing detrusor contractions, and increasing bladder capacity. These effects lead to significant relief from urinary urgency, improvement in urodynamic parameters, and a reduced risk of adverse events, such as urinary tract infections, renal injury, and leakage. Similar findings have been reported in previous studies [25-27].

In conclusion, the combined clinical use of Mirabegron and Solifenacin in female patients with OAB following bladder instillation for bladder cancer demonstrates significantly greater efficacy compared to Solifenacin monotherapy. This combination can improve patients' quality of life without adverse side effects, suggesting its potential for broader clinical application. However, this study is limited by its single-center design, homogeneous patient population, and small sample size. Future research should consider increasing the sample size and employing a multi-center approach to further validate these findings and enhance the generalizability of the results.

Disclosure of conflict of interest

None.

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