Original Study

Evaluation of the Efficacy of Solifenacin for Preventing Catheter-Related Bladder Discomfort After Transurethral Resection of Bladder Tumors in Patients With Non-Muscle Invasive Bladder Cancer: A Prospective, Randomized, Multicenter Study

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Abstract

We evaluated the incidence of catheter-related bladder discomfort (CRBD) and the efficacy of solifenacin in preventing CRBD after transurethral resection of a bladder tumor (TUR-BT) in 134 patients with non-muscle invasive bladder cancer. The incidence rate of CRBD at 1 and 2 hours after TUR-BT was 72.2% and 68.1%, respectively. Solifenacin failed to decrease the incidence and severity of CRBD.

Background: Catheter-related bladder discomfort (CRBD) secondary to an indwelling urinary catheter is worse after transurethral resection of a bladder tumor (TUR-BT). We evaluated the incidence of CRBD and the efficacy of solifenacin for preventing CRBD after TUR-BT in patients with non-muscle invasive bladder cancer. **Patients and Methods:** In the present prospective, randomized, multicenter trial, we enrolled 148 patients with non-muscle invasive bladder cancer who underwent elective TUR-BT under general anesthesia. The patients were randomized to group S (n = 72) or group C (n = 76). The primary outcome was evaluable for 134 patients, who were included in the final analysis. Group S received solifenacin (5 mg orally) on the day before, the day, and the day after TUR-BT. The control group (group C) received standard care. CRBD was assessed at 1 and 2 hours postoperatively. Pain was assessed for 3 days starting 6 hours after TUR-BT using the visual analog scale. **Results:** The incidence rates of CRBD in groups C and S were 72.2% and 64.5% at 1 hour and 68.1% and 53.2% at 2 hours, respectively. The incidence rates and severity of CRBD at 1 and 2 hours were not different between the 2 groups ($P > .05$ for both). The visual analog scale scores and the postoperative consumption of analgesics were not different between the 2 groups ($P > .05$ for both). None of the patients who received solifenacin experienced an adverse event. **Conclusion:** Pretreatment with solifenacin (5 mg) failed to decrease the incidence and severity of CRBD after TUR-BT.

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Introduction

Approximately 429,800 new cases and 165,100 deaths from bladder cancer were reported worldwide in 2012.[1] At the time that bladder cancer is diagnosed, approximately 70% of urothelial carcinoma cases will be classified as non-muscle invasive bladder cancer (NMIBC),[2] for which the standard primary treatment is transurethral resection of a bladder tumor (TUR-BT). After TUR-BT, a urethral catheter is inserted temporarily to monitor

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postoperative bleeding, prevent blood clots, and, potentially, remove floating cancer cells. However, irritative bladder symptoms are common and are burdensome to patients after transurethral resection (TUR). Moreover, the symptoms are often resistant to conventional opioid therapy.

An urge to void despite the good passage of urine and discomfort or pain in the suprapubic region are indications of catheter-related bladder discomfort (CRBD) secondary to an indwelling urinary catheter.[3] This discomfort can reduce the quality of life postoperatively and increase the incidence of postoperative pain and agitation.[4,5] Therefore, preventing or decreasing the severity of CRBD could be helpful for improving patients' quality of life and reducing the occurrence of postoperative agitation.

The mechanism of CRBD is not well-defined; however, it is similar to that of the symptoms of overactive bladder caused by involuntary bladder contractions, which are mediated by muscarinic receptors located in the urothelium and efferent nerves.[6] Antimuscarinic drugs such as tolterodine or oxybutynin have been reported to be effective treatment of CRBD. However, many studies have reported the results with only short-term indwelling urinary catheters.[3,4,7]

Solifenacin, a selective muscarinic 3 receptor, was reported to have greater selectivity for the bladder over the salivary glands and less potent antimuscarinic action than tolterodine.[8-10] Previous studies have confirmed the safety and efficacy of solifenacin compared with a placebo for overactive bladder.[11,12]

The primary objectives of the present study were to evaluate the incidence of CRBD after TUR-BT and determine whether solifenacin can decrease the incidence of postoperative CRBD. The secondary objectives were to assess the efficacy of solifenacin for managing postoperative pain after TUR-BT using the visual analog scale (VAS) and to evaluate the side effects that can occur with the use of these drugs.

Materials and Methods

Study Setting

The present study was a prospective, randomized, single-blind, placebo-controlled, multicenter study (Clinical Research Information Service identifier, KCT0000498) conducted in Korea. The study was performed from April 2012 through May 2015 at 4 training hospitals in accordance with the ethical principles of the Declaration of Helsinki. The ethics committee at each study site (institutional review board approval no. NCCCTS-44-560) approved the protocol. All the patients provided written informed consent.

Eligible patients aged 19 to 84 years who presented with a bladder mass were screened. The exclusion criteria were any recent or current long-term use ($>$ 3 months in $<$ 1 year) of analgesic or antimuscarinic drugs; any history of cerebral or spinal disease, chronic kidney disease with a creatinine clearance $<$ 30 mL/min, or hepatic failure with a Child-Pugh score of class B or more; any history of voiding problems either with residual urine $>$ 200 mL or maximal flow rate $\leq$ 5 mL/sec; incomplete resection of the tumor after TUR; and any pathologic confirmation of muscle invasive bladder cancer.

Randomization

A previous study reported that approximately 55% of patients complained of CRBD after insertion of an indwelling urethral catheter.[3] Assuming that this incidence would decrease to 30% after treatment, we calculated that a sample size of 60 patients would be needed in each group to achieve 80% power with a 2-sided type 1 error rate of 5%. Considering a 10% withdrawal rate, 74 patients were included in each group. We enrolled 148 patients with NMIBC who underwent elective TUR-BT under general anesthesia. Eligible patients were randomly assigned to either the solifenacin (group S; n = 72) or control (group C; n = 76) group, at a 1:1 ratio. Mixed, permuted, block randomization within the strata (sex and institution) was used. After confirming the eligibility criteria, randomization was performed using the sealed envelope method. Among the randomized patients, the primary endpoint was evaluable for 134 patients, and these patients were included in the final analysis (group S, n = 62; and group C, n = 72).

Treatment and Assessment

All operations were performed with the patient under general anesthesia. In group S, patients received solifenacin (5 mg orally) the day before, the day of, and the day after surgery. In group C, patients received standard care. All the patients were catheterized with a Foley catheter (usually 18Fr), and the balloon was inflated with 10 mL of distilled water after TUR-BT. CRBD was assessed at 1 and 2 hours postoperatively in the recovery room and general ward, respectively. Postoperative immediate mitomycin C instillation was not performed in the present study. Induction was performed with or without maintenance intravesical bacillus Calmette-Guérin or chemotherapy after pathologic confirmation instead of immediate intravesical chemotherapy. The severity of CRBD was graded using a simple 4-step severity scale: no pain, mild pain (determined only by interviewing the patient), moderate pain (a spontaneous complaint by the patient), and severe discomfort (determined by the patient's agitation, loud complaints, and attempts to remove the Foley catheter). Pain was assessed for 3 days, starting 6 hours after TUR-BT using the VAS. Standardized postoperative analgesia was administered according to the policy of each institution. The dose of analgesics used at each institution was converted to the dose of tramadol/acetaminophen combination tablets (Ultracet; Ortho-McNeil Pharmaceutical, Inc) using the table for the drug dosage calculation of opioids.[13] The Foley catheter was removed on the third postoperative day after confirming that no further active bleeding or risk of clot retention was present, and the uroflowmetry and postvoid residual volumes were assessed.

Statistical Analysis

The incidence of CRBD at 1 and 2 hours after TUR-BT was analyzed between the 2 groups using the χ^2 test, and the severity of discomfort (mild, moderate, and severe) was analyzed using Fisher's exact test. An efficacy analysis was performed on the full analysis set, which included all randomized patients, except for those who had not met the study inclusion or exclusion criteria and were not evaluated for the primary outcome. The pain grade was evaluated using the VAS, and the VAS scores were compared between the 2 groups using the Mann-Whitney U test. The incidence of side effects was analyzed using Fisher's exact test. Differences in the baseline characteristics between the 2 groups were analyzed using the χ^2 test, Fisher's exact test, and the Mann-Whitney U test, as appropriate. Logistic regression analysis was performed to estimate the odds ratio and corresponding 95% confidence interval.

A P value $< .05$ was considered statistically significant. All statistical analyses were performed with R statistical software, version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 156 patients were screened for inclusion in the study (Figure 1). Eight patients were excluded (n = 2) or refused to participate (n = 6). In group S, 6 patients were not allocated to the active group because TUR-BT was not performed, and 4 were excluded from all analysis sets because of incomplete resection or muscle invasive bladder cancer. In group C, 1 patient was not allocated to the active group because TUR-BT was not performed, and 3 were excluded from all analysis sets because of incomplete resection or muscle invasive bladder cancer. Thus, 134 patients (62 in group S and 72 in group C) who completed the study were evaluated in all analysis sets.

The patient demographic data and characteristics, including voiding symptoms (International Prostate Symptom Score, uroflowmetry findings, and postvoid residual volume), pathologic findings (T stage, tumor size, and tumor multiplicity), and diameter of the Foley catheter, were not significantly different statistically between the 2 groups ($P > .05$; Table 1). The incidence rate of CRBD after TUR-BT in patients with NMIBC was 72.2% and 68.1% at 1 and 2 hours, respectively. The incidence rates of CRBD at 1 and 2 hours were not different between the 2 groups (group C, 72.2% and 64.5% at 1 hour, $P = .34$; group S, 68.1% and 53.2% at 2 hours, $P = .08$; Table 2). Moreover, the severity of CRBD was not different between the 2 groups (Table 2).

The VAS scores were not different at 6 hours or 1, 2, and 3 days postoperatively between the 2 groups ($P = .082$, $P = .350$, $P = .163$, and $P = .287$, respectively). The postoperative consumption of analgesics was not different between the 2 groups ($P = .286$). None of the patients who received solifenacin experienced a dry mouth or voiding difficulty after the Foley catheter was removed (Table 3).

No predictive factors were found for moderate or severe CRBD, except for the diameter of the Foley catheter ($P = .019$ and $P = .011$, respectively) on univariate analysis. However, in most cases, an 18Fr Foley catheter was used (86.6%; Table 4).

Discussion

CRBD due to an indwelling urinary catheter is a common and distressing postoperative symptom. Unlike postoperative pain, CRBD can be resistant to conventional analgesic therapy such as opioids, because a different underlying mechanism is involved. A previous study demonstrated that the incidence of CRBD varied widely, ranging from 47% to 90%, depending on the operation type, method of anesthesia, sex, and diameter of the Foley catheter.[3,14-16]

It has been reported that TUR-BT is associated with a greater risk of CRBD compared with percutaneous nephrolithotomy and nonurologic surgery.[17] The reason for this difference is the discomfort from the catheter and discomfort from resection of the bladder wall (resection-related bladder discomfort). In the present study, we defined CRBD as catheter- or resection-related bladder discomfort, because all patients underwent resection and had a catheter. Previous studies' results for CRBD after TUR-BT differed from those in our study. The incidence rate of CRBD after TUR-BT was reported to range from 90% to 93.1% at 6 hours in previous studies.[16,18] However, our study showed that the incidence

Figure 1 Flow Chart of Patient Enrollment and Randomization

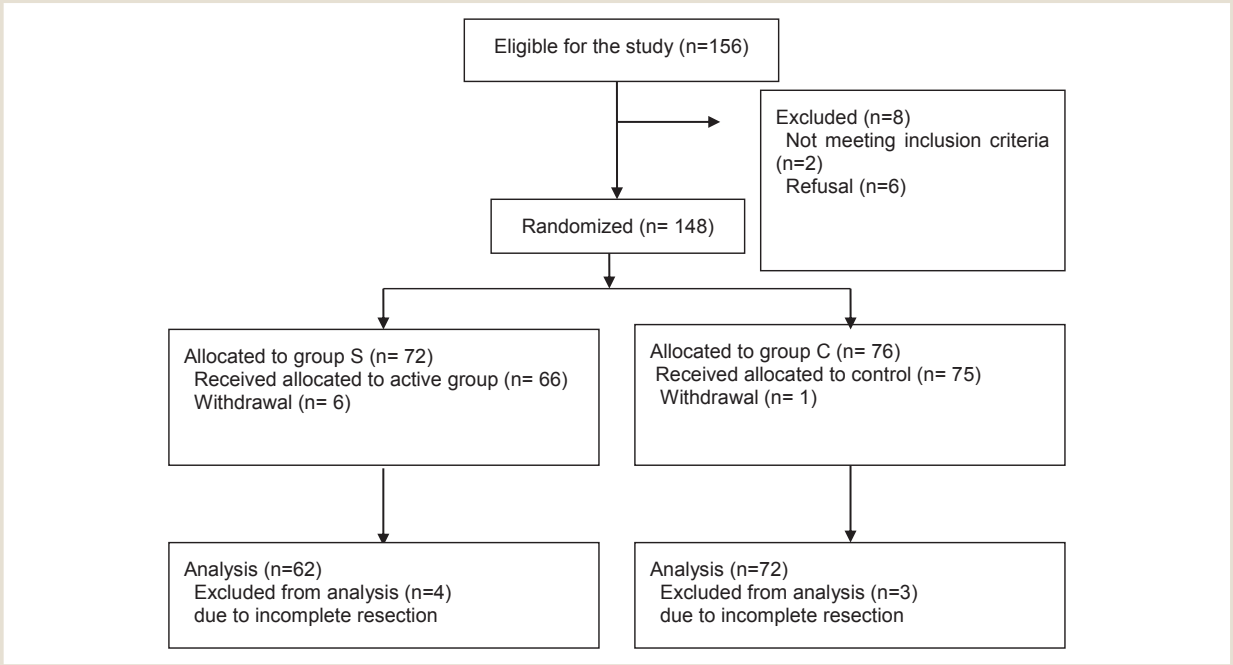

Table 1 Characteristics of Study Population

Variable	Control Group (n = 72)	Solifenacin Group (n = 62)	*P* Value[a]
Age (years)	68 (26-85)	66 (43-84)	.550
Sex (n)			.701
Male	61 (85)	51 (82)	
Female	11 (15)	11 (18)	
IPSS	9 (0-31)	10.5 (0-31)	.956
Qmax (mL/sec)	13.3 (5.4-39.3)	15.3 (6.4-49.4)	.533
Voided volume (mL)	150.8 (10.5-573.3)	145 (23.3-608)	.891
PVR (mL)	13 (0-134)	10 (0-140)	.900
T stage (%)			.304[b]
No tumor	0 (0)	1 (1.6)	
PUNLMP	2 (2.8)	1 (1.6)	
Ta	43 (59.7)	41 (66.1)	
Tis	0 (0)	1 (1.6)	
T1	27 (37.5)	18 (29.0)	
Tumor size (cm)			.725
<3	50 (69.4)	45 (72.6)	
≥3	22 (30.6)	17 (27.4)	
Tumor multiplicity			.297
Single	40 (55.6)	29 (46.8)	
Multiple	32 (44.4)	33 (53.2)	
Foley catheter diameter (Fr)			.954[b]
16	1 (1.4)	1 (1.6)	
18	63 (87.5)	53 (85.5)	
20	6 (8.3)	7 (11.3)	
24	2 (2.8)	1 (1.6)	
Dichotomized (18 vs. 16, 20, 24)	9 (12.5)	9 (14.5)	.733

Data presented as median (range) or n (%).
Abbreviations: IPSS = International Prostate Symptom Score; PUNLMP = papillary urothelial neoplasm of low malignant potential; PVR = postvoid residual (volume); Qmax = maximum urinary flow rate.
[a]χ^2 test or Mann-Whitney *U* test, as appropriate.
[b]Fisher's exact test.

rates of CRBD after TUR-BT in patients with NMIBC were 72.2% and 68.1% at 1 and 2 hours postoperatively, respectively. The lower incidence rate of CRBD in our study can be explained by several factors. Binhas et al[14] reported that a bladder Foley catheter diameter of ≥ 18Fr and male sex are independent predictors of severe or moderate CRBD.[14] Therefore, we controlled for the diameter of the Foley catheter by routinely using an 18Fr Foley catheter (86.6%).

The immediate postoperative intravesical instillation of a chemotherapeutic agent such as mitomycin or epirubicin can affect the incidence of CRBD.[18] Therefore, we enrolled only patients with NMIBC who did not require immediate intravesical instillation of a chemotherapeutic agent. In our study, immediate intravesical instillation of a chemotherapeutic agent was never used.

A previous study demonstrated that the use of antimuscarinic agents, including tolterodine and oxybutynin; anesthetics; antiepileptic agents, including gabapentin and pregabalin; and analgesics

Table 2 Effect of Solifenacin on CRBD After Transurethral Resection

Variable	Control Group (n = 72)	Solifenacin Group (n = 62)	*P* Value
CRBD at 1 h			.140[a]
Mild	29 (40.3)	28 (45.2)	
Moderate	19 (26.4)	12 (19.4)	
Severe	4 (5.6)	0 (0)	
Total	52 (72.2)	40 (64.5)	.338[b]
CRBD at 2 h			.582[a]
Mild	34 (47.2)	26 (41.9)	
Moderate	13 (18.1)	7 (11.3)	
Severe	2 (2.8)	0 (0)	
Total	49 (68.1)	33 (53.2)	.079[b]

Data presented as n (%).
Abbreviation: CRBD = catheter-related bladder discomfort.
[a]Fisher's exact test.
[b]χ^2 test.

such as tramadol and paracetamol was associated with significant improvement in symptoms and a decrease in the incidence of CRBD compared with placebo.[15] These drugs block the muscarinic receptors on bladder muscle fibers and modulate the excitability of the sacral reflex center. Muscarinic receptors play an important role in several main cholinergically mediated functions, including the contraction of urinary bladder smooth muscle and the stimulation of salivary secretion. Antimuscarinic actions, in particular, of the subtype 3 blockers, affect postoperative management. Solifenacin succinate, a tertiary amine with anticholinergic properties, is a competitive muscarinic receptor 3 antagonist. Solifenacin is used for the symptomatic treatment of overactive bladder. In our study, solifenacin failed to decrease the incidence of CRBD at 1 and 2 hours postoperatively. These results differ from those of other studies that used antimuscarinic agents to prevent CRBD.[18] A few possible reasons exist for why different findings were obtained. First, our study had a lower incidence of CRBD after TUR-BT than that

Table 3 Visual Analog Scale and Side Effects After Transurethral Resection

Variable	Control Group (n = 72)	Solifenacin Group (n = 62)	*P* Value[a]
Median VAS score (range)			
At 6 h	2 (0-8)	2 (0-8)	.082
At 1 day	2 (0-8)	1 (0-5)	.350
At 2 days	1 (0-8)	1 (0-3)	.163
At 3 days	1 (0-7)	0 (0-3)	.287
Ultracet consumption (n)			
Median postoperative tablets	1 (0-9)	0 (0-8)	.392
Patients	38 (52.8)	27 (43.5)	.286
Adverse events	0 (0)	0 (0)	

Data presented as median (range) or n (%).
Abbreviation: VAS = visual analog scale.
[a]Fisher's exact test and Mann-Whitney *U* test, as appropriate.

Table 4 Univariate Analysis for Predictive Factors of CRBD

Variable	CRBD at 1 h (n = 92)			CRBD at 2 h (n = 82)		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age	0.979	0.94-1.02	.275	0.967	0.93-1	.083
Sex (male vs. female)	1.657	0.63-4.22	.293	1.389	0.54-3.5	.485
IPSS	1.02	0.97-1.07	.41	1.006	0.96-1.05	.782
QOL	1.052	0.83-1.34	.675	1.039	0.83-1.3	.736
Qmax	1.011	0.96-1.07	.665	1.016	0.97-1.07	.507
pT stage (T1 vs. Ta)	0.624	0.28-1.38	.24	1.046	0.49-2.26	.908
Foley catheter (16, 20, 24 vs. 18Fr)	0.295	0.1-0.81	.019	0.257	0.08-0.71	.011
Group (S vs. C)	0.699	0.336-1.455	.339	0.534	0.26-1.08	.080

Abbreviations: C = control; CI = confidence interval; CRBD = catheter-related bladder discomfort; IPSS = International Prostate Symptom Score; Qmax = maximum urinary flow rate; OR = odds ratio; QOL = quality of life; S = solifenacin; VAS = visual analog scale.

reported by other studies. In our study, the incidence rates of CRBD were 72.2% and 68.1% at 1 and 2 hours postoperatively, respectively, similar to the incidence of CRBD treated with gabapentin or solifenacin in other studies.[16,18] Moreover, TUR-BT destroys the normal barrier mechanism of the bladder wall; thus, a larger Foley catheter is needed, which is more refractory to medical treatment. Anticholinergic drugs can have some effect on bladder spasms but would probably have less effect on the burning of the inside of the bladder with resection and fulguration. One dose of solifenacin (5 mg) the day before surgery might have been a suboptimal dose to control CRBD in this difficult condition. Second, CRBD was checked at 1 and 2 hours after TUR-BT. This probably did not provide adequate time for recovery to identify the obvious changes. However, we enrolled patients who underwent TUR-BT under general anesthesia to exclude the effects of spinal anesthesia. Third, one of the main mechanisms of CRBD after TUR-BT might be mechanical urethral stretching due to a large Foley catheter, which is supported by the finding that CRBD was rare in patients who had undergone suprapubic cystostomy.[19] Although the mechanism of CRBD is not well-defined, we assumed that the possible main causes of CRBD are bladder spasm and mechanical urethral stretching. It was reported that certain surgeries, including bladder surgery (a common cause of bladder spasms in both children and adults), prostatectomy, and other lower abdominal surgeries can cause bladder spasms. Furthermore, mechanical stretching of the urethra by the urethral catheter, which is a foreign body, can trigger bladder spasms or cause irritation of the bladder or prostate. A previous study showed that the diameter of the bladder catheter is associated with the incidence of CRBD.[14] This mechanism might not be controlled by medications, especially anticholinergic drugs.

The present study had some potential limitations. First, the study was not a double-blind trial, which could have caused bias in the results. Second, we did not use the detrusor activity index in the present study, which is a good diagnostic model that has a high accuracy in evaluating overactive bladder. Third, we used a 5-mg dose of solifenacin daily for 3 days after surgery; however, this might have been a suboptimal dose for controlling postoperative CRBD.

Conclusion

The incidence rates of CRBD at 1 and 2 hours after TUR-BT in patients with NMIBC were 72.2% and 68.1%, respectively. Treatment with solifenacin (5 mg) did not decrease the incidence and severity of CRBD after TUR-BT in patients with NMIBC. Therefore, further study is needed to assess the mechanism of CRBD to control it.

Clinical Practice Points

- Catheter-related bladder discomfort secondary to an indwelling urinary catheter is worse after TUR-BT.
- Catheter-related bladder discomfort at 1 and 2 hours after TUR-BT was very common.
- Pretreatment with a low, single dose of solifenacin (5 mg) failed to decrease the incidence and severity of catheter-related bladder discomfort secondary to an indwelling urinary catheter after TUR-BT.

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Disclosure

The authors declare that they have no competing interests.

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