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지도교수 황 정 원

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부위원장 _____ (인)
위 원 _____ (인)

# Preventive effects of butylscopolamine for catheter-related bladder discomfort: a prospective, randomized, multicenter study

**by**

**Karam Nam**

**A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Master of Science in Medicine at Seoul National University College of Medicine**

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**Approved by Thesis Committee:**

**Professor _____Chairman**

**Professor _____Vice chairman**

**Professor _____**

# Abstract

**Introduction:** Postoperative catheter-related bladder discomfort (CRBD) is a severely distressing complication in patients to whom urinary catheter was inserted during surgery. The present randomized multicenter clinical trial aims to investigate effects of butylscopolamine on prevention of postoperative CRBD in patients undergoing various surgeries.

**Methods:** Adult male patients undergoing elective surgeries under general anesthesia and requiring intraoperative urinary catheterization were enrolled and randomly assigned to two groups. The butylscopolamine group (n = 49) received butylscopolamine 20 mg intravenously at extubation of an endotracheal tube, whereas no medication was given for prevention of CRBD in the control group (n = 50). The presence and severity of CRBD were assessed at 1, 2 and 6 h after surgery. Adverse effects of butylscopolamine were also examined.

**Results:** The overall incidence of CRBD was lower in butylscopolamine group than in control group (31% vs. 66%, $P$ = 0.001). The incidences of CRBD at 1, 2 and 6 h after surgery was also lower in butylscopolamine group ($P$ = 0.006, 0.040, and 0.048, respectively). In addition, the average severity

of CRBD during 6 hours after surgery was significantly lower in butylscopolamine group ($P$ = 0.002). Adverse effects were comparable between the two groups.

**Conclusion:** Intravenous administration of butylscopolamine at the end of surgery is effective in reducing the incidence and severity of postoperative CRBD without adverse effects.

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**Keywords:** Butylscopolamine, Complications, Urinary Catheterization

**Student Number:** 2012-21687

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# Introduction

Urinary catheterization is commonly performed intraoperatively to facilitate urination and assess urine output during the perioperative period. However, urinary catheterization can cause catheter-related bladder discomfort (CRBD), which is manifested by an urge to void, or severe suprapubic discomfort, in the post-anesthesia care unit (PACU) (1). Furthermore, CRBD is one of the most distressing complications in patients recovering from surgery and anesthesia (2).

Symptoms of CRBD result from disorganized bladder contraction mediated by muscarinic receptors. In addition, they are quite similar to those of overactive bladder, whose first-line treatment consists of antimuscarinic agents (3). In this perspective, several agents with antimuscarinic properties have been proposed as effective agents. Tolterodine, gabapentin, tramadol, ketamine and oxybutynin have preventive effects on CRBD (1, 4-8). Ketamine and butylscopolamine are effective in treatment of CRBD (9, 10). In these previous studies, the uses of the agents were confined to patients who underwent urologic surgeries. Moreover, some of them showed anticholinergic adverse effects. Tramadol and ketamine increased sedation (1, 8, 9), and tolterodine and oxybutynin showed dry mouth (5, 6). However, CRBD frequently occurs in patients undergoing not only urologic surgeries

but also other types of surgeries, thus more preventive drugs without adverse effects should be investigated to improve satisfaction and quality of life in every surgical patient with urinary catheters.

Butylscopolamine has been reported to be effective in treatment of CRBD in urologic surgery without adverse effects (10). Therefore, we postulated that butylscopolamine also has preventive effects on CRBD in patients with urinary catheters who undergo any kinds of surgery, not limited to urologic surgeries alone, and conducted a prospective, randomized, multicenter study.

# Materials and Methods

After approval from the Institutional Review Board of Seoul National University Hospital (H-1212-073-451) and that of Seoul National University Bundang Hospital (B-1209/169-012), the protocol of this study was registered to Clinical Research information Service (http://cris.nih.go.kr) (KCT0000662). Written informed consent was obtained from all patients who were recruited for the study.

Adult male patients with ASA physical status I or II, who were scheduled for elective surgeries in both centers from January to May 2013, were included in the study. Exclusion criteria included history of hypersensitivity to butylscopolamine, benign prostatic hyperplasia, overactive bladder, neurogenic bladder, and central nervous, cardiovascular, renal or psychiatric diseases.

Patients were randomly distributed into two groups, butylscopolamine group or control group, using a web-based randomization program (http://www.randomizer.org).

Routine monitoring of electrocardiography, pulse oximetry and blood pressure were started. General anesthesia was performed to all patients without premedication. Methods of anesthesia induction and maintenance were left to the assigned anesthesiologist's discretion, except administration of

antiemetics or analgesics. After induction of general anesthesia, urinary catheterization was done using 14 Fr Foley catheter, and the catheter was ballooned with 10 ml of normal saline. The catheter was fixed without traction, and was not clamped during the whole follow-up period. Intravenous patient-controlled analgesia (IV PCA) with fentanyl alone or fentanyl plus morphine was initiated in all patients at the end of surgery.

At extubation of an endotracheal tube, butylscopolamine 20 mg (Buscopan®, Boehringer Ingelheim Korea, Seoul, Korea) was administered intravenously in butylscopolamine group, and no medication was given in control group. All patients were transferred to the PACU after recovery of consciousness.

The primary outcome was the difference in the incidence of CRBD between the two groups. Secondary outcomes included severity of CRBD, incidences of adverse effects of butylscopolamine (dry mouth, facial flushing and blurred vision), postoperative nausea and vomiting (PONV), severity of postoperative pain, use of rescue antiemetic, and total amount of analgesics used. Patients were questioned about the presence and severity of CRBD 1, 2 and 6 h after surgery using a 100-point numeric rating scale (NRS) by blinded investigators. In this study, CRBD was defined as the presence of an urge to void or suprapubic discomfort with NRS $\geq$ 30. Postoperative pain and adverse effects of butylscopolamine were also assessed. Metoclopramide 10 mg and fentanyl 50 μg were given as rescue antiemetic and analgesic when patients

complained of PONV and postoperative pain NRS over 30, respectively. Total amount of fentanyl and morphine infused via IV PCA for 6 h of follow-up period was also recorded.

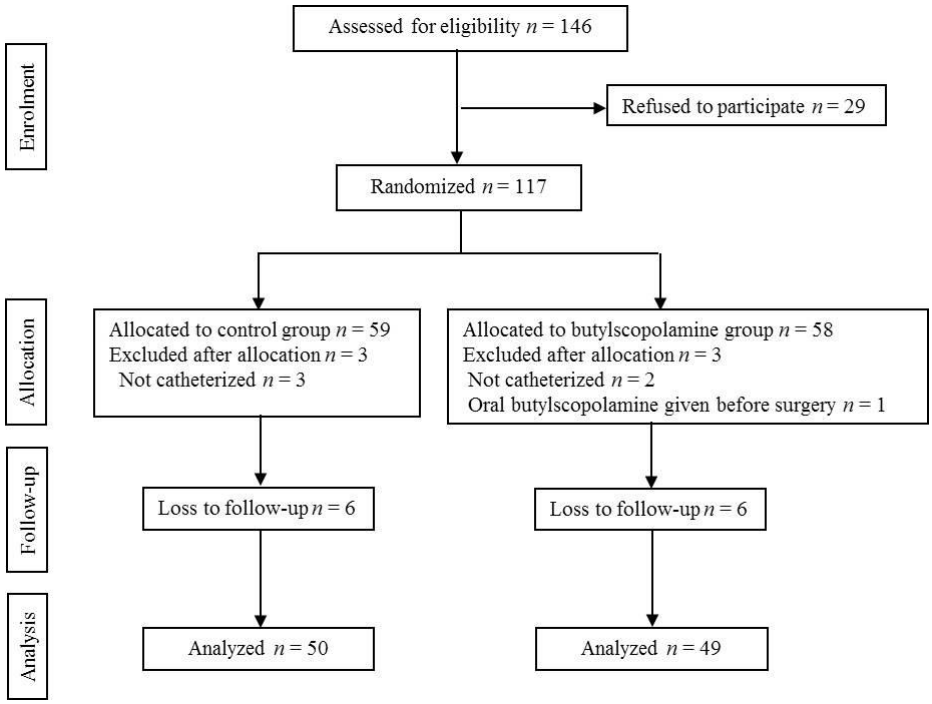
Based on the results of previous studies dealt with CRBD management (1, 6, 7, 10), the authors assumed that the incidence of CRBD was approximately 70% and it would be reduced to 40% by administration of butylscopolamine. Minimum of 49 patients were needed in each group with $\alpha = 0.05$ and power = 0.8.

Data were analyzed using SPSS program (version 18.0, SPSS Inc., Chicago, IL). After testing for normality, the groups were compared using Student's *t* or Mann-Whitney U test for continuous variables, such as patient demographics and group characteristics, except ASA class and composition of surgery, which were tested using $\chi 2$ test. The incidence of CRBD was analyzed with binary logistic regression, and severity of CRBD was tested using Mann-Whitney U test. Occurrence of PONV, use of rescue antiemetic, and adverse effects of butylscopolamine were analyzed using $\chi 2$ test or Fisher's exact test. Postoperative pain and total amount of analgesics were compared using Student's *t* or Mann-Whitney U test. *P*-value of $< 0.050$ was regarded as statistically significant.

# Results

Total 146 patients were screened from January to May 2013, and 29 patients who refused to participate in the study were excluded, 18 patients were dropped out for various reasons after recruitment. The remaining 99 patients were finally investigated (Figure 1).

**Figure 1.** CONSORT diagram for the trial.



Both groups were similar with regard to patient demographics and group characteristics (Table 1).

**Table 1.** Patient demographics and group characteristics.

| | Butylscopolamine (n = 49) | Control (n = 50) | *P*-value |
|---|---|---|---|
| Age (yr) | 58 (10) | 60 (9) | 0.342* |
| Weight (kg) | 69 (11) | 67 (9) | 0.330* |
| Height (cm) | 168 (5) | 168 (6) | 0.828* |
| ASA class (I/II) | 23/26 | 23/27 | 0.925† |
| Composition of surgery | | | 0.858† |
| Stomach | 14 (29) | 17 (34) | |
| Hepatobiliary | 9 (18) | 8 (16) | |
| Colorectal | 20 (41) | 21 (42) | |
| Others | 6 (12) | 4 (8) | |
| Duration of surgery (min) | 154 (89) | 160 (95) | 0.834‡ |
| Duration of anesthesia (min) | 198 (95) | 203 (101) | 0.953‡ |

Data are expressed as mean (SD), except for composition of surgery that is expressed as number of cases (%). ASA, American Society of Anesthesiologists. *$t$ test, †$\chi 2$ test, ‡Mann-Whitney U test.

The overall incidence of CRBD was significantly lower in butylscopolamine group than in control group (15 of 49, 31% vs. 33 of 50,

66%) (95% C.I. 0.098 to 0.528, $P$ = 0.001). The incidences of CRBD at each time point were also significantly lower in butylscopolamine group (Figure 2, Table 2).

**Figure 2.** Bar chart outlining the incidence of catheter-related bladder discomfort (CRBD).

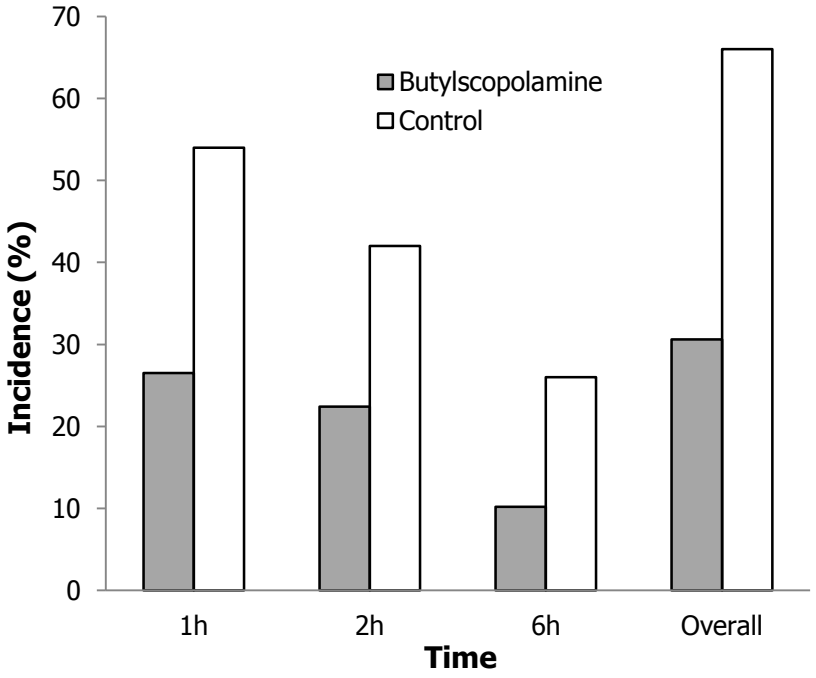



**Table 2.** Incidence of catheter-related bladder discomfort (CRBD).

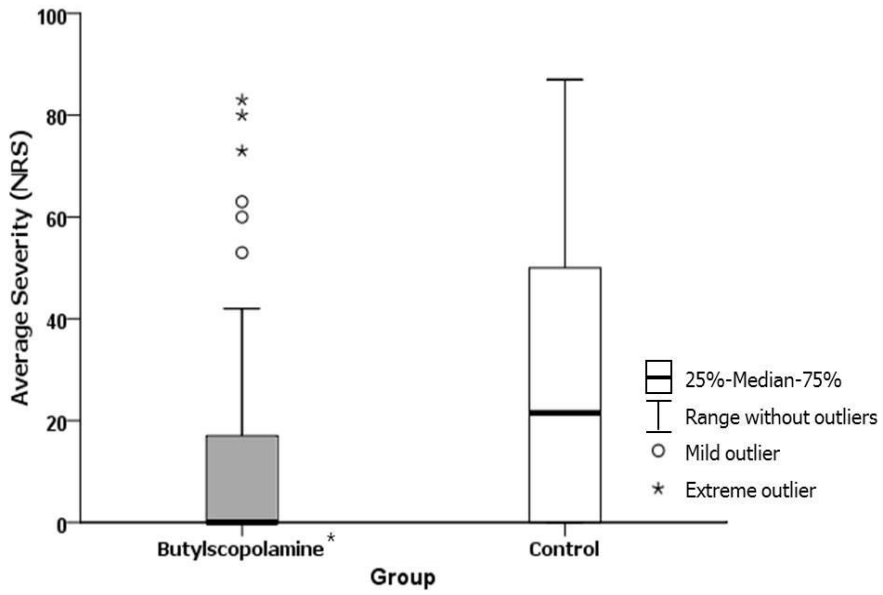
| | Butylscopolamine (n = 49) | Control (n = 50) | Odds Ratio* | 95% C.I.* | | *P*-value* |
|---|---|---|---|---|---|---|
| | | | | Lower | Upper | |
| Overall | 15 (31%) | 33 (66%) | 0.227 | 0.098 | 0.528 | 0.001 |

| | | | | | | |
|---|---|---|---|---|---|---|
| at 1 h | 13 (27%) | 27 (54%) | 0.308 | 0.132 | 0.715 | 0.006 |
| at 2 h | 11 (22%) | 21 (42%) | 0.400 | 0.167 | 0.959 | 0.040 |
| at 6 h | 5 (10%) | 13 (26%) | 0.323 | 0.106 | 0.991 | 0.048 |

Data are expressed as number of cases (%), except for odds ratio and 95% confidence interval. *Binary logistic regression.

In addition, the average severity of CRBD during 6 hours after surgery was significantly lower in butylscopolamine group than in control group (median [interquartile range] ; 0 [0-17] vs. 22 [0-47], $P$ = 0.002). A boxplot for severity of CRBD is depicted in *Figure 3*.

**Figure 3.** Box plot for severity of catheter-related bladder discomfort (CRBD).



Adverse effects were comparable between the two groups. Incidences of anticholinergic symptoms such as dry mouth, facial flushing, and blurred vision were similar. Incidence of PONV and use of rescue antiemetic were also similar. Severity of postoperative pain was not different between the two groups (Table 3).

**Table 3.** Incidences of adverse effects of butylscopolamine, Incidence of PONV and use of rescue antiemetic, and severity of postoperative pain.

| | Butylscopolamine (n = 49) | Control (n = 50) | *P*-value |
|---|---|---|---|
| Dry mouth | 42 (86) | 47 (94) | 0.200* |
| Facial flushing | 4 (8) | 5 (10) | 1.000* |
| Blurred vision | 6 (12) | 5 (10) | 0.722† |
| PONV | 2 (4) | 7 (14) | 0.160* |
| Rescue antiemetic | 1 (2) | 4 (8) | 0.362* |
| Postoperative pain | | | |
| NRS points at 1 h | 66 ( 27) | 64 ( 25) | 0.641‡ |
| NRS points at 2 h | 53 (26) | 59 (27) | 0.284‡ |
| NRS points at 6 h | 41 (26) | 48 (26) | 0.155§ |

Data are presented as number of cases (%), except for postoperative pain scores expressed as mean (SD). *Fisher's exact test, †$\chi 2$ test, ‡Mann-Whitney U test, §*t* test.

Mean total amount of fentanyl was 228 μg in butylscopolamine group and 226 μg in control group, which showed no statistical difference ($P$ = 0.952). Difference of total amount of morphine was also insignificant ($P$ = 0.718).

# Discussion

Catheter-related bladder discomfort is a very common and distressing complication observed in patients who undergo intraoperative urinary catheterization. However, it is frequently neglected and left untreated in the PACU. Previous studies reported up to 90% incidence of postoperative CRBD (7). Nonetheless, CRBD is often resistant to conventional analgesics including opioids. The present study demonstrates that the administration of butylscopolamine at the end of surgery effectively reduces the incidence and severity of postoperative CRBD without severe adverse effects.

Symptoms of CRBD, as in overactive bladder, come from disorganized detrusor muscle contraction evoked by the stimulation of muscarinic receptors located in the bladder (11). So far, several agents such as tolterodine, oxybutynin, ketamine, tramadol and gabapentin, have been proposed for the management of postoperative CRBD in previous studies. Antimuscarinic actions of these drugs are considered to be responsible for reducing the incidence and severity of CRBD (1, 2, 4, 6-9). However, adverse anticholinergic effects such as dry mouth and sedation can occur, and these studies were confined to patients who underwent urologic surgeries, such as transurethral resection of the bladder, nephrectomy, nephrolithotomy or prostatectomy. Therefore, limitations exist in application to patients who

undergo other types of surgery.

Butylscopolamine, known as hyoscine N-butylbromide, is an old spasmolytic drug that has been widely prescribed for acute abdominal cramping pain (12). Its pharmacologic action mainly comes from antagonism of muscarinic receptors in the gastrointestinal tract (13). The onset time of butylscopolamine is known to be within 10 min, maximal effect occurs in 15 min, and duration of action is about 40 min (14).

Preventive effect of butylscopolamine on the incidence of postoperative CRBD lasted for 6 hours of follow-up period, and the patients given butylscopolamine complained of milder symptoms of CRBD in the present study. Considering relatively short duration of butylscopolamine, the preventive effect of the drug on postoperative CRBD seems to be durable than expected. Further study with longer follow-up period is needed to find out whether there is rebound increase in the incidence and severity of CRBD. Moreover, only single dose of butylscopolamine 20 mg was examined, and dose-response relationship of butylscopolamine for prevention of CRBD was not evaluated in our study. Further studies using multiple or larger doses of butylscopolamine are warranted to test whether postoperative CRBD can be prevented for a longer duration.

Butylscopolamine is known to have few minor adverse effects related to its anticholinergic property, so it is generally regarded as a safe drug (12). In this study, incidences of anticholinergic adverse effects, such as dry mouth,

flushing and blurred vision, were not increased after butylscopolamine injection. Most of the patients in both groups complained of dry mouth, but this seems to be a result of perioperative dehydration rather than anticholinergic adverse effect. Sedation was not evaluated in the study, but butylscopolamine does not pass the blood-brain barrier (12), so sedation is theoretically not expected to occur after administration of butylscopolamine.

Postoperative pain and requirement of analgesics were not decreased by butylscopolamine injection, which is contrary to previous studies (1, 4, 10). However, these studies were carried out in urologic surgeries alone, thus symptoms of CRBD could be confused with urogenital surgical pain. In fact, there is no evidence that anticholinergic drugs including butylscopolamine can alleviate surgical pain resulting from direct tissue injury by surgery. Further studies are suggested in this area as well.

In conclusion, intravenous administration of butylscopolamine 20 mg reduces the incidence and severity of postoperative CRBD without adverse effects. Therefore, we suggest that intravenous administration of butylscopolamine is a safe and effective modality for prevention of CRBD in various kinds of surgeries.

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# 초 록

**서론:** 도뇨관 삽입 후 발생하는 방광 불편감 (Catheter-related bladder discomfort, CRBD)은 수술 및 마취에서 회복 중인 환자에게 발생하는 심각한 합병증 중 하나이다. 이번 연구에서 항콜린 약물인 butylscopolamine의 전처치가 CRBD의 예방에 미치는 영향을 알아보고자 한다.

**방법:** 수술 중 요로 도자술이 필요한 수술을 받는 성인 남자 환자를 대상으로 두 군으로 무작위 배정하였다. butylscopolamine 군(n = 49)의 환자들은 기관내튜브 발관 시 butylscopolamine 20mg을 정주하였으며, 대조군(n = 50)의 환자들에게는 아무 약물을 투여하지 않았다. 수술 1, 2, 6시간 후, CRBD의 발생 및 중증도를 평가하였으며, butylscopolamine의 부작용도 함께 평가하였다.

**결과:** 전체 CRBD의 발생률이 butylscopolamine 군에서 유의하게 낮았다 ($P$ = 0.001). 수술 후 1, 2, 6시간째의 CRBD 발생률도 butylscopolamine 군에서 유의하게 낮았다 ($P$ = 0.006, $P$ =

0.040, $P$ = 0.048). 또한, butylscopolamine 군에서 수술 후 6시간 동안의 평균 CRBD 중증도가 대조군에 비해 유의하게 낮았다 ($P$ = 0.002). 두 군 간 부작용의 발생에는 차이가 없었다.

**결론:** Butylscopolamine 20 mg 정주로 수술 후 CRBD의 발생률 및 중증도를 효과적으로 줄일 수 있다.

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**주요어:** 요로 도자술, 합병증, Butylscopolamine

**학 번:** 2012-21687