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CLINICAL PRACTICE

# Efficacy of butylscopolamine for the treatment of catheter-related bladder discomfort: a prospective, randomized, placebo-controlled, double-blind study

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## Editor's key points

- Catheterization for urological surgery can cause distressing bladder discomfort after operation; effective solutions are needed.
- This study investigates a peripherally acting anticholinergic agent in the prevention of catheter-related bladder discomfort (CRBD).
- Butylscopolamine reduced CRBD and rescue analgesia after urological surgery with minimal side-effects.
- Use of butlyscoploamine should be considered to reduce CRBD.

**Background.** Catheter-related bladder discomfort (CRBD) secondary to intraoperative catheterization of urinary bladder is one of the most distressing symptoms during recovery from anaesthesia. Butylscopolamine, a peripheral antimuscarinic agent, is effective for relieving the pain, which is because of smooth muscle contraction. The aim of this study was to assess the efficacy and safety profiles of butylscopolamine in treating CRBD after urological surgeries.

**Methods.** Adult male patients undergoing urological surgery requiring urinary bladder catheterization intraoperatively were enrolled. Induction and maintenance of anaesthesia were standardized. Patients were randomized into two groups after complaining of CRBD in the post-anaesthesia care unit. The control group ($n$=29) received normal saline and the butylscopolamine group ($n$=28) was administered butylscopolamine 20 mg i.v. The severity of CRBD, postoperative pain, and adverse effects were assessed at baseline, 20 min, 1, 2, and 6 h after administration of the study drug.

**Results.** The severity of CRBD observed in the butylscopolamine group was significantly lower than that of the control group at 1, 2, and 6 h after administration of the study drug [59 (12), 50 (16), 40 (21) in the control group *vs* 41 (22), 32 (25), 23 (18) in the butylscopolamine group, $P<0.01$]. Rescue analgesics were required less in the butylscopolamine group than in the control group ($P=0.001$). Adverse events were comparable between the two groups.

**Conclusion.** Butylscopolamine 20 mg administered i.v. after complaining CRBD during recovery reduced both the severity of CRBD and the need for rescue analgesics without adverse effects in patients undergoing urologic surgeries.

**Keywords:** complications; surgery, urological

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Patients with urinary bladder catheterization during various surgeries frequently complain of catheter-related bladder discomfort (CRBD) in the immediate postoperative period. CRBD is characterized by a burning sensation with an urge to void or discomfort in the supra-pubic region caused by catheter-related bladder irritation.[1] This condition is extremely distressing to the patient and reduces the quality of recovery by exacerbating postoperative pain.[2] However, to date, no effective treatment for CRBD without adverse effects has been established yet.

CRBD is caused by catheter-induced bladder irritation because of involuntary contractions of the bladder mediated by muscarinic receptors.[3] This mechanism is similar to that of overactive bladder (urinary frequency and with or without urge incontinence).[3] Therefore, agents with antimuscarinic properties including oxybutynin, tolterodine, ketamine, gabapentin, and tramadol have been investigated for the prevention and treatment of CRBD.[1 4–7] Oxybutynin, tolterodine, and gabapentin are oral agents with various anticholinergic side-effects that have been administered before operation to prevent CRBD.[1 4 5] I.V. tramadol and ketamine were effective for the prevention and treatment of CRBD, but these agents can cause sedation after operation.[6 7]

Butylscopolamine, an anticholinergic drug, has been administered to treat abdominal pain and has incidentally been effective against CRBD. In addition, butylscopolamine does not cross the

blood–brain barrier (BBB) because of the attachment of butylbromide, preventing central adverse effects such as blurred vision and facial flushing with the use of this peripheral anticholinergic.[8] Butylscopolamine has a high affinity for muscarinic receptors located on the smooth-muscle cells of the gastrointestinal (GI) tract[8] and its efficacy in treating CRBD has not yet been reported. This study, therefore, evaluated the efficacy and tolerability of butylscopolamine in the treatment of CRBD in male patients undergoing urinary bladder catheterization.

## Methods

This prospective, randomized, double-blind, and placebo-controlled study was performed after approval from the Institutional Review Board of Seoul National University Bundang Hospital (No. B-1201-070-002). During the preoperative visit, informed consents were provided by all patients and patients were educated about the CRBD (characterized as a burning sensation with an urge to void or discomfort in the supra-pubic area) and numerical rating scale (NRS). The protocol of this clinical trial was registered in the Clinical Research information Service (KCT 0000380). From February to November 2012, male patients (18–70 yr) with an ASA physical status I and II, who were to undergo elective urologic surgery for the upper urinary tract or robotic retropubic radical prostatectomy, were included. The patients required intraoperative catheterization of the urinary bladder and complained of CRBD after operation. Patients with a history of bladder outflow obstruction, prostate hyperplasia, overactive bladder (frequency: more than three times during the night or more than eight times in 24 h), neurogenic bladder, end-stage renal disease (serum creatinine $>1.6$ mg $dl^{-1}$), morbid obesity, disturbances of the central nervous system (CNS), chronic analgesic abuse, and hepatic or psychiatric disease were excluded from the study.

All patients were premedicated with i.v. midazolam 0.03 mg $kg^{-1}$ before induction of anaesthesia. Standard monitoring consisted of ECG, non-invasive arterial pressure, and pulse oximetry. Anaesthesia was induced with propofol 2 mg $kg^{-1}$ and remifentanil 3 ng $ml^{-1}$ using a target controlled infusion pump. Tracheal intubation was facilitated by rocuronium bromide 0.6 mg $kg^{-1}$. Anaesthesia was maintained using remifentanil 3–4 ng $ml^{-1}$ and sevoflurane 2–2.5 vol % in oxygen with medical air ($F_{IO_2}$ 0.5). Patients were mechanically ventilated to maintain the end-tidal $CO_2$ between 4.5 and 5 kPa. Intermittent dosages of rocuronium (0.15 mg $kg^{-1}$) were administered, as necessary. Normothermia (36–37°C) was maintained with a forced warm air device. The bladder was catheterized using a 16 or 18 Fr Foley's catheter and the balloon was inflated with 15 ml of distilled water during the operation. The urinary catheter was fixed with an adhesive tape without any traction and was allowed to drain freely into a bag. After the surgery, muscle relaxation was antagonized with neostigmine 0.05 mg $kg^{-1}$ and glycopyrrolate 0.01 mg $kg^{-1}$. Patients undergoing robotic retropubic radical prostatectomy received patient-controlled analgesia (PCA) with fentanyl for postoperative pain management and i.v. ramosetron 0.3 mg for the prophylaxis of postoperative nausea and vomiting (PONV). The PCA was programmed with a continuous infusion of 15 μg $h^{-1}$ and a bolus dose of 15 μg with a 15 min lockout interval. Patients were transferred to the post-anaesthesia care unit (PACU) after operation.

After reporting CRBD, patients were randomized into two groups using sealed envelopes by an anaesthesiologist responsible for the randomization. The control group received the same volume (1 ml) of normal saline whereas the butylscopolamine group received butylscopolamine 20 mg (Buscopan®, Boehringer Ingelheim Korea, Seoul, South Korea) i.v. All medications were prepared by an anaesthetic nurse blinded to the study and administered in identical 2 ml syringes.

The primary outcome was defined as the reduction in the severity of CRBD. Secondary outcomes were the requirement of rescue analgesic, heart rates (HRs), mean arterial pressure (MAP), and adverse effects including PONV, sedation, dry mouth, facial flushing, and blurred vision. All these outcomes except HR and MAP were assessed at baseline (when the patient complained of CRBD), 20 min, and 1, 2, and 6 h after administration of the study drug by blinded assessors. During each evaluation, patients were asked to specify whether the pain was related to CRBD or to the surgical wound. HR and MAP were recorded at 5, 10, and 20 min and 1 h after administration of the study drugs. The incidences of tachycardia (HR$\geq$100 bpm) and hypertension (systolic/diastolic arterial pressure $\geq$140/90 mm Hg) during the study period were also recorded.

Severity of CRBD was recorded using an NRS ranging from 0 (no discomfort) to 100 (most severe discomfort). The rescue analgesic (fentanyl 50 μg) was administered when the post-operative pain NRS (0=no pain, 100=most severe pain) was $>$30 despite the PCA and the amount of rescue analgesics needed during the study period was recorded. The incidence of PONV and the need for rescue antiemetics were also assessed. Other adverse effects including dry mouth, facial flushing, and blurred vision were also observed. Sedation was evaluated using a modified observer's assessment of alertness/sedation score[9] at baseline, 20 min and 1 h after administration of the study drug.

The calculation of the sample size was based on preliminary results. The severity of CRBD (NRS) of 10 patients was 75 (25) at the time of reporting CRBD. Assuming that the severity of CRBD reduced from 75 to 55 (decrease of 20) after therapy with butylscopolamine, 26 patients in each group were required for results to be statistically significant (with $\alpha$=0.05 and power=0.80). To allow for a 10% dropout rate, 29 patients per group were included.

SPSS ver. 15.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. The severity of CRBD (NRS), HR and MAP over time between the groups were analysed by repeated-measures analysis of variance (ANOVA) and then *t*-test was used to compare values at each time point. Analyses of categorical variables (rescue analgesics, incidence of PONV, dry mouth, facial flushing, and blurred vision) were performed by $\chi^2$ or Fisher's exact-tests. Data were analysed according to the intention-to-treat principle. $P<0.05$ was considered to indicate significance.

## Results

Eighty-two patients were recruited between February and November 2012 and 24 patients were excluded from the study after enrolment because they did not report CRBD during recovery (Fig. 1). One patient in the butylscopolamine group was excluded after randomization because of desaturation at PACU. Therefore, the data of the remaining 57 patients (29 in the control group and 28 in the butylscopolamine group) were analysed. Data on patients, surgeries, and anaesthesia are presented in Table 1.

There was a significant difference over time between the two groups in the severity of CRBD ($P=0.001$). Patients in the butylscopolamine group reported significantly less CRBD after administration of study drugs than did those in the control group at 1, 2, and 6 h after administration of study drugs (Table 2). In addition, CRBD was completely relieved in five patients in the butylscopolamine group whereas all patients in the control group complained of CRBD at 6 h ($P=0.023$).

There was a significant change in HR between the control and butylscopolamine groups over time ($P=0.02$) whereas no difference was observed in MAP. HR in the butylscopolamine group was higher than those of the control group at 5, 10, and 20 min and 1 h after administration of the study drugs (Fig. 2). However, there were no differences in the incidences of tachycardia (1 patient in each group) or hypertension (10 patients in the control group and 7 patients in the butylscopolamine group) between the two groups.

Significant differences were observed in the requirement for rescue analgesics (i.v. fentanyl 50 μg) between the two groups after drug administration ($P<0.01$, Table 3). Twenty-seven patients in the control group and 26 in the butylscopolamine group complained of dry mouth and no significant differences were observed between the control and butylscopolamine groups (Table 3). Other adverse events, including facial flushing and blurred vision were not reported and two patients (one in each group) showed PONV (Table 3). Sedation scores were comparable between the two groups (Table 3).

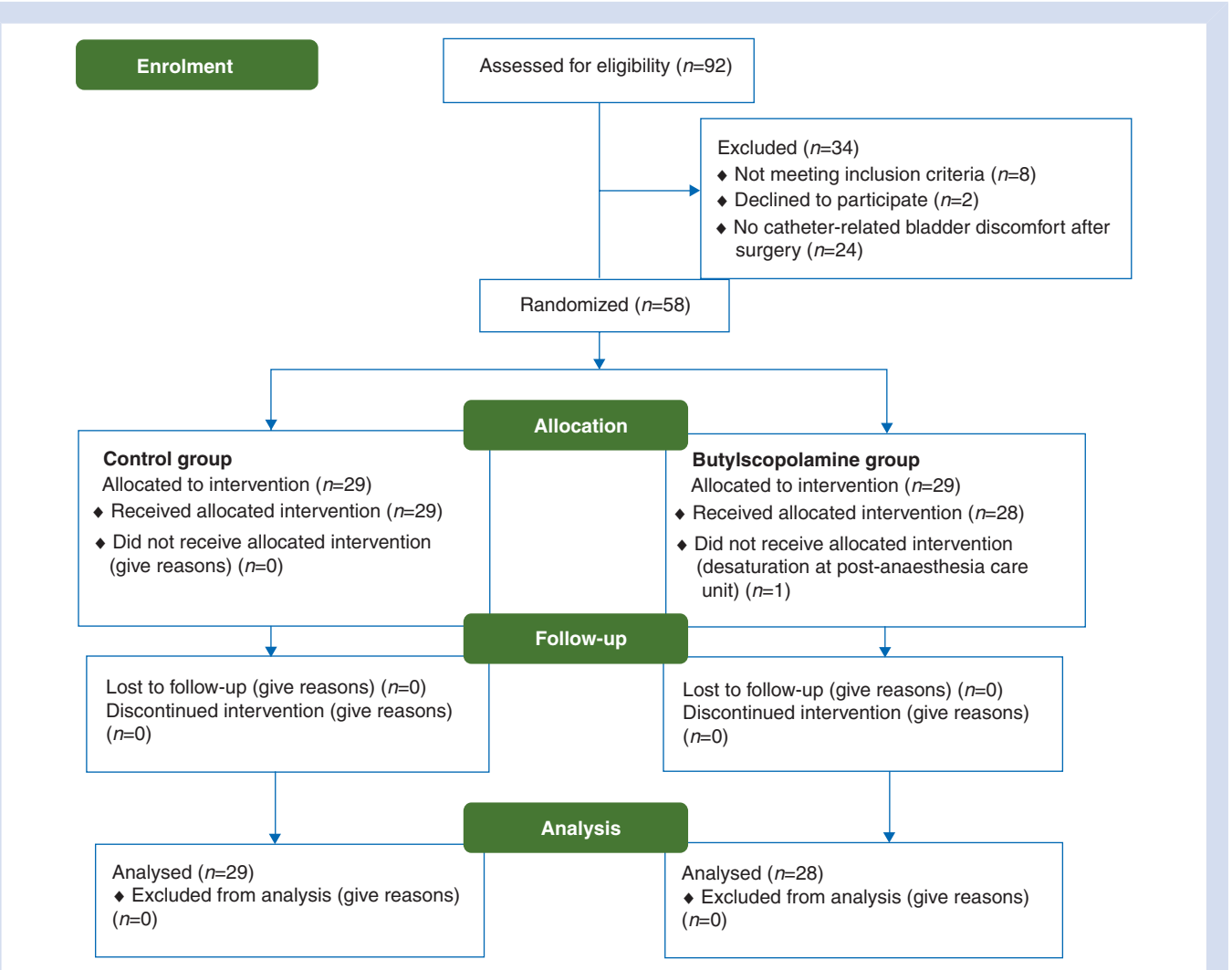


**Fig 1** A CONSORT diagram.

**Table 1** Characteristics of patients, anaesthesia and surgery. Values are given as mean (SD) or number of patients (%) except age [mean (range)]

| Characteristic | Control group ($n=29$) | Butylscopolamine group ($n=28$) |
|---|---|---|
| Age (yr) | 61 (24–69) | 61 (22–70) |
| Weight (kg) | 70 (11) | 67 (10) |
| Height (cm) | 169 (7) | 168 (6) |
| ASA class (I/II) | 17 (59)/12 (41) | 10 (38)/18 (69) |
| Name of operations [*n*, (%)] | | |
| Urethrolithotomy | 1 (3) | 0 (0) |
| Nephrolithotomy | 3 (10) | 6 (21) |
| Radical retropubic prostatectomy | 25 (86) | 22 (79) |
| Duration of operation (min) | 190 (76) | 178 (66) |
| Duration of anaesthesia (min) | 238 (82) | 224 (70) |
| Diameter of urinary catheter (16 Fr/18 Fr) | 5 (17)/24 (83) | 4 (14)/24 (86) |
| Intraoperative remifentanil ($\mu g\ kg^{-1}\ min^{-1}$) | 0.16 (0.03) | 0.14 (0.05) |

**Table 2** Severity of CRBD after administration of normal saline (control group) or butylscopolamine 20 mg (butylscopolamine group). Values are given as mean (SD) or number of patients (%). NRS, numerical rating scale (0=no pain, 100=the worst possible discomfort)

| | Control group ($n=29$) | Butylscopolamine group ($n=28$) | *P*-value |
|---|---|---|---|
| CRBD (NRS) | | | |
| Baseline | 83 (12) | 86 (14) | 0.43 |
| 20 min after study drug | 70 (14) | 62 (21) | 0.11 |
| 1 h after study drug | 59 (12) | 41 (22) | <0.01 |
| 2 h after study drug | 50 (16) | 32 (25) | <0.01 |
| 6 h after study drug | 40 (21) | 23 (18) | <0.01 |

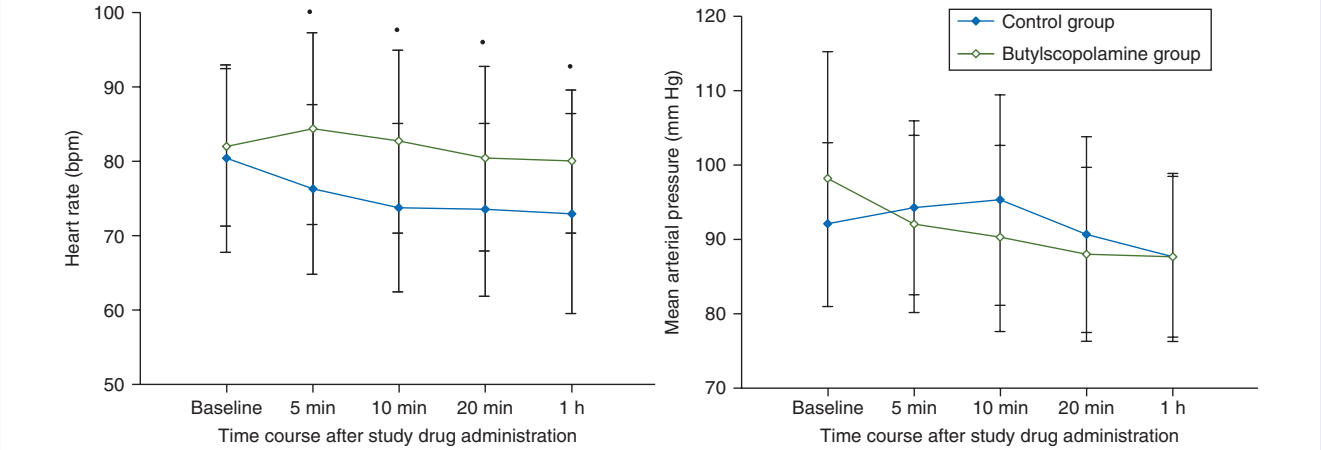


**Fig 2** Changes in HR and MAP after administration of the study drug. Repeated measures ANOVA shows a statistically significant difference in HRs over time between the two groups. HRs of butylscopolamine group were higher than those of the control group at 5, 10, 20 min and 1 h after administration of the study drugs. *$P<0.05$.

## Discussion

CRBD is a common complication in the PACU and the incidence of CRBD at 1 h after operation is reported to be 55–63% in male patients.[1] Significant predictors of CRBD are male gender and use of a urinary catheter ≥18 Fr.[10] These findings are explained by anatomical differences (the length of the urethra), but the

**Table 3** The use of rescue analgesics after administration of the study drugs and adverse events. Values are presented as the number of patients (%). MOAA/S score, modified observer's assessment of alertness/sedation score: 5, respond readily to name spoken in normal tone; 4, lethargic response to name spoken in normal tone; 3, responds only after mild prodding or shaking

| | Control group ($n=29$) | Butylscopolamine group ($n=28$) | *P*-value |
|---|---|---|---|
| The use of rescue analgesics | | | <0.01 |
| None | 7 (24) | 15 (54) | |
| Once | 14 (48) | 13 (46) | |
| Twice | 8 (28) | 0 (0) | |
| PONV | 1 (3) | 1 (4) | >0.99 |
| Rescue antiemetics | 1 (3) | 1 (4) | >0.99 |
| Dry mouth | 27 (93) | 26 (93) | >0.99 |
| Blurred vision | 0 | 0 | N/A |
| Facial flushing | 0 | 0 | N/A |
| MOAA/S score | | | |
| Baseline 5/4/3 | 8 (28)/20 (69)/1 (3) | 6 (21)/22 (79)/0 (0) | 0.51 |
| 20 min after study drug 5/4 | 27 (93)/2 (7) | 27 (96)/1 (4) | 0.98 |
| 1 h after study drugs 5/4 | 28 (97)/1 (3) | 28 (100)/0 (0) | >0.99 |

relationship between the size of the bladder catheter and the severity of CRBD has not been investigated.[10] In this study, 16 or 18 Fr bladder catheters were used during urologic surgery and 71% of the patients (58 of 82 patients) complained of CRBD after operation. Most patients complained of a feeling of needing to void and suffered from a burning sensation at the urethra. Therefore, it is desirable to prevent or treat CRBD in male patients who undergo intraoperative bladder catheterization.

Prevention and treatment of CRBD using various agents with anticholinergic property have been investigated.[1 2 4–7] Anticholinergic agents (such as tolterodine and oxybutynin) and gabapentin administered 1 h before surgery reduced the incidence and severity of CRBD.[1 2 4 5 8] However, these are oral agents and can cause adverse effects including dry mouth.[1 2 5] Tramadol is a centrally acting opioid analgesic with antimuscarinic actions, which effectively prevent CRBD when administered i.v.[7] Additionally, i.v. ketamine administration was effective for the prevention and treatment of CRBD.[6 11] However, administration of tramadol and ketamine was associated with a higher incidence of sedation compared with the control group.[6 7 11]

We administered butylscopolamine 20 mg i.v., which has been used to treat abdominal cramping pain.[10] Butylscopolamine is an anticholinergic drug indicated for the treatment of GI spasm.[10] The onset of i.v. butylscopolamine is ~10 min with a peak effect at 20–60 min and an elimination half-life ranging from 1 to 5 h.[10] As butylscopolamine is a quaternary ammonium derivative, it does not pass the BBB and rarely shows anticholinergic effects such as dry mouth, facial flushing, and blurred vision.[8] Transdermal scopolamine, another anticholinergic, effectively prevented bladder contractions after open prostatectomy,[12] but has been associated with a decreased salivary flow rate and mouth dryness.[13]

Urgency to urinate and increased frequency of urination are symptoms of CRBD, which are similar to those of an overactive bladder. CRBD and overactive bladder result from involuntary contractions of the bladder detrusor muscle mediated by muscarinic receptors and, therefore, antimuscarinic therapy that suppresses involuntary bladder contractions has been used to treat overactive bladder.[14] Tolterodine and gabapentin are used to treat this condition.[15–17] Butylscopolamine has a high affinity for muscarinic receptors located on the smooth-muscle cells of the GI tract and relaxes the smooth muscle. The mechanism by which butylscopolamine relieves CRBD may be explained by its antimuscarinic and spasmolytic properties and also a relaxant effect on the bladder. M2 and M3 muscarinic receptors are responsible for detrusor contraction of the bladder,[18–20] and butylscopolamine is known to have a high affinity for human M2 and M3 muscarinic receptors expressed in Chinese hamster ovary cells.[8]

Fewer rescue analgesics were required in the butylscopolamine groups than in the control group although butylscopolamine is a peripheral antimuscarinic agent without analgesic effects. In previous investigations of tramadol and gabapentin to prevent CRBD, postoperative pain and the requirement of rescue analgesics were reduced by the analgesic and anticholinergic properties of these agents.[4 7]

There was no difference in the incidence of adverse effects between the butylscopolamine and control groups. Only two patients (one per group) showed postoperative nausea, probably because of prophylactic antiemetic agents administered at the end of surgery. Most patients in both groups complained of dry mouth at the PACU, which was attributable to preoperative fasting rather than anticholinergic side-effects. Other adverse effects such as facial flushing and blurred vision were not reported. As butylscopolamine rarely penetrates the BBB and enters the CNS, it did not induce anticholinergic effects.[8] A previous study with butylscopolamine also demonstrated that the incidence of adverse events was both low and similar to that of the placebo group.[21]

Several limitations of the current study should be considered. I.V. butylscopolamine was clinically effective for the

treatment of CRBD as an antimuscarinic agent, but an inhibitory action of butylscopolamine on the activity of the detrusor muscle has not been reported in animal or human studies. Further experiments in these areas are warranted. Secondly, a single dose of 20 mg butylscopolamine, which has been used for abdominal cramping pain, was used in this study. We did not evaluate the dose–response effect of butylscopolamine for the treatment of CRBD. Thirdly, in patients with severe CRBD despite administration of the study drug, rescue treatment of CRBD was not performed, as standard treatment of CRBD without side-effect has not been established yet. Fourthly, different sizes of urinary catheter were used in this study without standardization. The urologist decided the size of the urinary catheter during the operation depending on the possibility of catheter obstruction because of haematuria and there was no significant difference in the size of the urinary catheters between the control and butylscopolamine groups. Fifthly, various urologic surgeries with different degrees of CRBD and postoperative pain were included. Patients undergoing radical retropubic prostatectomy may complain of minor postoperative pain, but a higher incidence of CRBD whereas patients undergoing other urologic surgeries such as nephrolithotomies may suffer from more severe surgical pain than CRBD. This may cause confusion in the interpretation of the results though no significant difference regarding the type of surgery was observed between the two groups.

In this study, the severity of CRBD was significantly decreased after administration of butylscopolamine 20 mg i.v. without adverse effects. Therefore, butylscopolamine seems to be an effective treatment for CRBD during the postoperative period.

## Authors' contributions

J.H.R.: study design, data collection, data analysis, and writing up the first draft of the paper; J.W.H.: study design and data collection; J.W.L.: data collection and data analysis; J.H.S.: data analysis; H.P.P.: study design; A.Y.O.: patient recruitment and data collection; Y.T.J.: patient recruitment and data collection; S.H.D.: patient recruitment and study design.

## Declaration of interest

None declared.

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