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Management of Catheter-Related Bladder Discomfort in Patients Who Underwent Elective Surgery

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Abstract

Objective: Despite the various treatment and prevention options for catheter-related bladder discomfort (CRBD), many uncertainties persist in clinical practice. To systematically review the literature on the management of CRBD in patients who underwent surgery.

Materials and Methods: Eligible, randomized controlled trials were identified from electronic databases (Cochrane Central Register of Controlled Trials, Medline, and EMBASE) without language restrictions. Selection criteria, methodological rigor, and risk of bias were evaluated by two independent reviewers using Cochrane Collaboration's tools.

Results: A total of 1441 patients from 14 articles published between 2005 and 2014 were included. Data heterogeneity precluded meta-analysis; therefore, data were synthesized narratively. Compared with nonurological surgery, CRBD is frequent and occurred immediately after urological surgery, especially after transurethral resection of the bladder tumor (TURBT). Data from included studies suggested that muscarinic antagonists, anesthetics, antiepileptics, and analgesics were associated with significant improvement in symptoms and reducing the incidence of CRBD, compared with placebo. Anticholinergic agents and antiepileptics (gabapentin and pregabalin) administered 1 hour before surgery reduced the incidence and severity of CRBD in the immediate postoperative period. Tramadol and ketamine are centrally acting opioid analgesics with antimuscarinic actions, which effectively prevent CRBD when administered intravenously. Paracetamol administered was also effective for the management of CRBD. Additionally, we perceived that TURBT is the surgical procedure that is the most refractory to treatment.

Conclusions: Muscarinic antagonists, anesthetics, antiepileptics, and paracetamol appear to achieve the greatest improvement in the clinical symptoms and a significant reduction in the incidence of CRBD compared with placebo. Although these studies observed a high incidence of intervention-related side effects, in general, patients tolerated these treatments well.

Introduction

Urinary catheterization during various surgeries, especially urinary interventions, frequently leads to catheter-related bladder discomfort (CRBD) in the immediate postoperative period. It is an important clinical entity, with an incidence ranging from 47% to 90%. CRBD is characterized by a burning sensation spreading from the suprapubic area to the penis and is associated with discomfort or the urge to void.[1–4] Symptoms of CRBD mimic those of an overactive bladder (OAB). In addition, CRBD is usually accompanied by behavioral responses, such as flailing limbs, strong vocal response, and attempting to pull out the urinary catheter. Therefore, targeting this discomfort early is necessary. These responses may result in the increased incidence of postoperative complications, including surgical incision dehiscence, bleeding, circulatory system instability, arrhythmia, and increased severity of coronary artery disease. Additionally, they can bring about exacerbated postoperative pain and prolonged hospital stay.

CRBD is caused by catheter-induced bladder irritation due to muscarinic receptor-mediated involuntary contractions of the bladder smooth muscle.[5] Therefore, agents with antimuscarinic properties, such as oxybutynin, tolterodine, and butylscopolamine,[3–7] are the mainstay treatment to reduce both the incidence and severity of CRBD. Additionally, tramadol, ketamine, paracetamol, pregabalin, and gabapentin administration were effective for the prevention and treatment

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of CRBD. Despite the existence of various treatment and prevention options for CRBD, many uncertainties persist in clinical practice. For instance, an effective treatment for CRBD without adverse effects is yet to be established, there is a lack of evidence in the medical literature regarding the efficacy and safety of drugs in treating urologic symptoms, and strategies for enhancing the quality of life in patients with CRBD are lacking. Therefore, a synthesis of the current evidence is needed.

To this end, we conducted a systematic review mapping all CRBD treatment or prevention regimens. To our knowledge, this study is the first systematic review of randomized controlled trials (RCTs) to assess the efficacy, safety, and tolerability of drug treatment in patients with CRBD. Hence, this article shall provide an outlook on future management for this medical problem.

Evidence Acquisition

A systematic literature search in the Medline, Embase, and Cochrane databases was performed to identify RCTs published until June 2014. Various algorithms, including the following terms: catheter-related bladder discomfort, catheter-related pain, catheter-related bladder irritation, and catheter-induced bladder discomfort, were used. Reference lists from included studies and previous reviews were also explored.

Identified studies were selected on the basis of their titles and abstracts by two independent authors. Full articles were retrieved if a decision could not be made based on the abstracts. Disagreement was resolved by consensus and by discussion with a third party. We defined study eligibility using the patient population, intervention/exposure, comparator, outcome, and study design (PICOS) approach. A record was considered relevant to this review if it assessed the following: patients with urinary bladder catheterization (P), complaint of CRBD (I), comparison with different interventions (C), and patient outcomes, including a reduced incidence and alleviation of the severity of CRBD and side effects (O). RCTs that were published in English and had sufficient data for extraction were selected (S).

CRBD severity was recorded as follows: none, no discomfort, even on asking; mild, reported by the patient only on questioning; moderate, reported by patient on their own; and severe, reported by the patient on their own along with behavioral responses.

The results of the database searches were compiled in ENDNOTE. Data from all selected studies were extracted and tabulated by one author and corroborated by a second. Any discrepancy was resolved through consensus by all authors. Missing information was sought by contacting the corresponding authors of the studies. The information retrieved included the following: (1) authors names and publication year; (2) details of the study design (number of patients randomized, the method of randomization, and the length of observation); (3) the characteristics of the recruited patients (including gender, age, and type of surgery); (4) details of the interventions used (drug doses and schedules); and (5) data relating to primary and secondary outcomes and *p*-values.

The data analysis was performed using the Cochrane software Review Manager version 5.1. Comparable data from each study were combined in a meta-analysis where possible. Dichotomous data were presented as relative risk (RR) and continuous outcomes as MD, both with 95% confidence intervals (CIs). The random effects model was used when the trials yielded heterogeneous ($p < 0.1$) results. Otherwise, the fixed effects model was used. Significance was set at $p < 0.05$.

Evidence Synthesis

Search results

Of the 101 potentially relevant publications identified and screened for retrieval, 87 were excluded because they did not meet the inclusion criteria. Consequently, 14 RCTs (with a total of 1441 patients) were eligible for analysis,[1,3–15] 12 for urologic surgeries, and 1 for spine surgery. Manual searches did not result in additional studies on CRBD. All of these included studies compared outcomes between active treatment(s) and placebo (Table 1). These treatments included muscarinic antagonists,[1,5–8,15] anesthetics,[9–11] antiepileptics,[3,4,14] and analgesics.[12,13]

Description of effective treatments

Anticholinergic agents and antiepileptics administered 1 hour before surgery reduced the incidence and severity of CRBD. Tramadol and ketamine are centrally acting opioid analgesics with antimuscarinic actions, which effectively prevent CRBD when administered intravenous (i.v.). Additionally, i.v. paracetamol administration was effective for the prevention and treatment of CRBD. Although the abovementioned agents were accompanied by side effects, nearly all of them were mild and transient and the treatments were well tolerated by patients.

Effect of muscarinic antagonists on CRBD solifenacin. Zhang et al.[5] focused on the evaluation of solifenacin in the management of CRBD. One hundred six patients with nonmuscle-invasive bladder cancer undergoing transurethral resection of bladder tumor (TURBT) with subsequent intravesical chemotherapy were treated with either solifenacin or placebo. The schedules were as follows: solifenacin 5 mg 6 hour before surgery and 5 mg/day following surgery for 2 weeks. The incidence and severity of CRBD were significantly reduced in the solifenacin treatment group compared with the placebo group at 6, 12, 24, 48, and 72 hours after surgery ($p < 0.05$). The incidence of CRBD at 6 hours after TURBT decreased from 93.1% (placebo group) to 67.2% (solifenacin group; $p = 0.001$). In addition, a significant difference was observed in OAB symptom scores between the two groups (5.67 *vs* 7.86; $p < 0.001$). Symptoms of CRBD in solifenacin group were also significantly less severe than those in the placebo group ($p < 0.05$). Therefore, the authors stated that solifenacin can be beneficial for the management of CRBD. However, the study does not distinguish between the symptoms of chemical cystitis and CRBD.

Butylscopolamine: Butylscopolamine (20 mg) administered i.v. postoperatively was compared with placebo in an RCT, including 57 male patients with CRBD following urologic surgery.[6] The results showed that the severity of CRBD observed in the butylscopolamine group was significantly lower compared with the placebo group at 1, 2, and 6 hours after

Table 1. Characteristics of Included Studies and the Main Outcomes of Included Studies

Study	Design	Participants	Interventions	Incidence of CRBD[a]	Severity of CRBD[a]	Other outcome[a]	Adverse effects[a]
Muscarinic antagonists							
Zhang et al.[5]	Randomized, prospective single-blind	116 patients with nonmuscle-invasive bladder cancer undergoing TURBT	G1: solifenacin 5 mg, 6 h before surgery and after surgery 5 mg/day for 2 weeks, po ($n=58$) G2: placebo ($n=58$)	6 h: 67.2% *vs* 93.1% 12 h: 62.1% *vs* 82.8% 24 h: 56.9% *vs* 79.3% 48 h: 48.3% *vs* 62.1% 72 h: 32.8% *vs* 48.3% ($p<0.05$)	The severity of CRBD (mild, moderate, severe) was significantly reduced in group 1 compared with group 2 ($p=0.008$)	Overactive bladder symptom scores: 5.67 *vs* 7.86 ($p<.001$)	Dry mouth: 10.3% *vs* 6.9% ($p=0.743$) Constipation:8.6% *vs* 3.4% ($p=0.438$) Headache:1.7% *vs* 0 ($p=1.0$) Dizziness:1.7% *vs* 0 ($p=1.0$)
Ryu et al.[6]	Randomized, prospective double-blind	57 male patients with CRBD after elective urologic surgery for the upper urinary tract or robotic retropubic radical prostatectomy	G1: butylscopolamine 20 mg/iv ($n=28$) G2: normal saline 1 mL/iv ($n=29$)	—	1 h: 59 (12) *vs* 41 (22) 2 h: 50 (16) *vs* 32 (25) 6 h: 40 (21) *vs* 23 (18) ($p=0.01$)[b]	Rescue analgesics (<0.01) None: 24% *vs* 54% Once: 48% *vs* 46% Twice: 28% *vs* 0	Dry mouth: 93% *vs* 93% ($p>0.99$) PONV: one in each group
Nam et al.[15]	Randomized, prospective double-blind	99 patients undergoing nonurologic surgeries	G1: butylscopolamine 20 mg/iv ($n=49$) G2: placebo ($n=50$)	Overall: 31% *vs* 66% 1 h: 27% *vs* 54% 2 h: 22% *vs* 42% 6 h: 10% *vs* 26% ($p<0.05$)	First 6 h postoperatively was less in the butylscopolamine group than the control group (median [interquartile range], 0 [0–17] *vs* 22 [0–47], respectively; $p=0.002$)	Rescue analgesics: 2% *vs* 8% ($p=0.362$)	Dry mouth: 86% *vs* 94% ($p=0.20$) PONV: 4% *vs* 14% ($p=0.16$)
Tauzin-Fin et al.[7]	Randomized, prospective double-blind	46 men undergoing radical retropubic prostatectomy	G1: oxybutynin 5 mg/po, every 8 h during the 24 h after surgery ($n=23$) G2: placebo, po ($n=23$)	17% *vs* 65% ($p<0.01$)		Cumulative tramadol consumption (mg) [mean (SD)]: 146 (48) *vs* 322.9 (124.3) ($p<0.01$) Patient satisfaction score[c]: 8 (7–9) *vs* 5 (4–5) ($p<0.001$)	No patient in group oxybutynin reported a dry mouth
Agarwal et al.[8]	Randomized, prospective double-blind	234 patients undergoing elective PCNL surgery for renal and upper ureteral stone	G1: oxybutynin 5 mg/po ($n=78$) G2: tolterodine 2 mg/po ($n=78$) G3: placebo, po ($n=78$)	35% *vs* 33% *vs* 58% ($p<0.05$)	Significant reduction was observed after oxybutynin and tolterodine therapy compared with control ($p<0.05$)	There were no differences in fentanyl consumption between the groups	Dry mouth ($p<0.05$) 0 h:51.3% *vs* 46.2% *vs* 19.2% 1 h: 59% *vs* 55.1% *vs* 24.4%

(*continued*)

TABLE 1. (CONTINUED)

Study	*Design*	*Participants*	*Interventions*	*Incidence of CRBD*[a]	*Severity of CRBD*[a]	*Other outcome*[a]	*Adverse effects*[a]
Agarwal et al.[1]	Randomized, prospective double-blind	215 patients undergoing elective endoscopic or open urologic surgery for the kidney and ureter	G1: tolterodine 2 mg/po, 1 h before induction of anesthesia ($n=50$) G2: placebo, po ($n=165$)	0 h: 17% *vs* 82% 1 h: 18% *vs* 91% 2 h: 15% *vs* 83% 6 h: 10% *vs* 60% ($p<0.05$)	—	—	Dry mouth 0 h: 54% *vs* 22% ($p<0.05$) 1 h: 66% *vs* 47% ($p<0.05$) There were no differences at 2 and 6 h
Anesthetics							
Shariat et al.[9]	Randomized, prospective double-blind	114 patients undergoing an elective nephrectomy	G1: ketamine 0.5 mg/kg/iv after induction of anesthesia, but before urinary catheterization ($n=57$) G2: normal saline 2 mL/iv ($n=57$)	At 0 and 1 h in recovery: 38.6% (22/57), 22.8% (13/57) *vs* 68.4% (39/57), 57.9% (33/57), respectively ($p<0.001$)	At 2 and 6 h, the incidence and severity were not significantly different between the two groups ($p>0.05$)	—	Sedation: at 0 h:12% *vs* 0 ($p<0.05$) A decreased incidence of PONV was observed at 2- and 6-h visits in the intervention group
Safavi et al.[10]	Randomized, prospective double-blind	120 patients undergoing urological surgery who complained of CRBD in the recovery room	G1: ketamine 150 μg/kg/iv ($n=30$) G2: ketamine 200 μg/kg/iv ($n=30$) G3: ketamine 250 μg/kg/iv ($n=30$) G4: normal saline, 2 mL/iv ($n=30$)	—	Significantly less in G2 and 3 compared with G1 and 4 till 24 h after operation ($p<0.05$) There was no significant difference between G2 and 3 ($p>0.05$)	Rescue analgesic consumption: significantly less in G2 and 3 compared with G1 and 4 ($p<0.05$). No significant difference was noted between G2 and 3 ($p>0.05$)	Sedation: lower in 15 min and 30 min in recovery in G2 and 3 compared with G4 and 1 ($p<0.05$) There was no significant difference between G2 and 3 ($p>0.05$)
Agarwal et al.[11]	Randomized, prospective double-blind	54 patients undergoing elective PCNL for renal and upper ureteral stone and who spontaneously complained of CRBD, after operation	G1: ketamine 250 μg/kg/iv ($n=27$) G2: normal saline, 2 mL/iv ($n=27$)	2 h: 20% *vs* 92% 6 h: 19% *vs* 84% ($p<0.05$)	Moderate ($p<0.05$) 1 h: 4% *vs* 64%	—	Sedation ($p<0.05$) 1 h: 64% *vs* 4% 2 h: 92% *vs* 0
Agarwal et al.[12]	Randomized, prospective double-blind	54 patients undergoing elective PCNL for renal and upper ureteral stone	G1: tramadol 1.5 mg/kg/iv ($n=27$) G2: normal saline, 2 mL/iv ($n=27$)	0 h: 28% *vs* 60% 1 h: 32% *vs* 64% 2 h: 28% *vs* 56% 6 h: 20% *vs* 48% ($p<0.05$)	—	Postoperative fentanyl requirement (mg/kg): 210 (34.6) *vs* 176 (SD 26.5) ($p<0.05$)	Sedation: 60% (15/25) *vs* 16% (4/25) ($p<0.05$) Vomiting: 40% (10/25) *vs* 12% (3/25) ($p<0.05$) Nausea: 56% (14/25) *vs* 20% (5/25) ($p<0.05$)

(*continued*)

Table 1. (Continued)

Study	*Design*	*Participants*	*Interventions*	*Incidence of CRBD*[a]	*Severity of CRBD*[a]	*Other outcome*[a]	*Adverse effects*[a]
Analgesics							
Ergenoglu et al.[13]	Randomized, prospective double-blind	64 patients undergoing elective PCNL	G1: paracetamol 15 mg/kg/iv ($n=32$) G2: normal saline, 1.5 mL/kg/iv ($n=32$)	Postoperative ($p<0.05$) 0 h: 68.75% *vs* 87.5% 1 h: 62.5% *vs* 84.4% 2 h:59.4% *vs* 78.1% 4 h: 37.5% *vs* 78.1% 6 h: 28.2% *vs* 68.75%	Moderate ($p<0.05$) 1 h: 21.9% *vs* 43.8% 2 h: 9.4% *vs* 43.8% 4 h: 3.1% *vs* 56.3% 6 h: 0 *vs* 37.5%	Total consumption of meperidine: 52.72 [63.73] mg *vs* 75.81 [58.16] mg ($p<0.05$); Patient satisfaction scores: 4.53 (0.51) *vs* 3.84 (0.95) ($p=0.002$)	No patients required rescue analgesia
Antiepileptics							
Bala et al.[4]	Randomized, prospective double-blind	100 patients undergoing TURBT	G1: gabapentin 1200 mg/po ($n=34$) G2: gabapentin 600 mg/po ($n=33$) G3: placebo, po ($n=33$)	Postoperative ($p<0.05$) 1 h: 0 *vs* 9% *vs* 66% 2 h: 26% *vs* 42% *vs* 90% 4 h: 18% *vs* 66% *vs* 87% 6 h: 9% *vs* 63% *vs* 87% 12 h: 0 *vs* 57% *vs* 87% 24 h: 0 *vs* 15% *vs* 84%	1 h: Mild: 9% *vs* 0 *vs* 43.8% 2 h: Moderate: 0 *vs* 0 *vs* 43.8% 4 h: Mild: 61.8% (G1) *vs* 18.2% (G2), moderate: 3% *vs* 0 *vs* 39.4% 6, 12, 24 h: moderate: 3% *vs* 0 *vs* 45.5%	The number needed to treat was 6 and 2 in G1 and G2, respectively	Blood pressure were comparable among groups Hypotension or bradycardia: None Dizziness: 1 *vs* 2 *vs* 0 (number)
Agarwal et al.[3]	Randomized, prospective double-blind	108 patients undergoing elective PCNL for renal and upper ureteral stone	G1: gabapentin 600 mg/po ($n=54$) G2: placebo, po ($n=54$)	The absolute risk reduction in G2 observed was 30% 0 h: 50% *vs* 80% 1 h: 61% *vs* 80% 2 h: 55% *vs* 76% 6 h: 37% *vs* 61%	Mild: 0 h: 78% *vs* 21%, 6 h: 80% *vs* 39% Moderate: 1 h: 61% *vs* 30%, 6 h: 20% *vs* 57% Severe: 0 h: 0 *vs* 42%, 1 h: 0 *vs* 40%, 2 h: 3% *vs* 25%	Number-needed-to-treat was 4 in G2. Requiring fentanyl (Number) ($p<0.05$): 0 h: 0 *vs* 7, 1 h: 3 *vs* 12, 2 h: 2 *vs* 10, 6 h: 1 *vs* 8	There were no differences in postoperative sedation, PONV, feeling of light-headedness, or headache between the groups ($p<0.05$)
Srivastava et al.[14]	Randomized, prospective double-blind	60 patients undergoing elective spine surgery	G1: pregabalin 150 mg/po ($n=30$) G2: placebo, po ($n=30$)	0 h: 36.7% *vs* 70% 1 h: 36.7% *vs* 66.7% 2 h: 30% *vs* 60% 6 h: 16.7% *vs* 50% ($p<0.05$)	Mild: 0 h: 23.3% *vs* 13.3%, 6 h: 13.3% *vs* 30% Moderate: 0 h: 13.3% *vs* 16.7%, 6 h: 3% *vs* 13% Severe: 0 h: 0 *vs* 40%, 2 h: 0 *vs* 20%, 6 h: 0% *vs* 6.7%	Fentanyl requirements (ug): 211.83[43.54] *vs* 355.33[51.44] ($p<0.05$)[b]	Sedation score: 2.63 [0.67] *vs* 2.10 [0.61] ($p=0.002$); no significant differences in other side-effects between the two groups

[a]Interventions *vs* placebo.

[b]Values are given as mean (SD) or number of patients (%).

[c]Patient satisfaction score is given as values that are expressed as median (interquartile range).

CBRD, catheter-related bladder discomfort; G=group; OABSS=Overactive bladder symptom scores; PCNL=percutaneous nephrolithotomy; PONV=postoperative nausea and vomiting; TURBT=transurethral resection of bladder tumors.

administration ($p = 0.001$). Rescue analgesics were required less often in the butylscopolamine group than in the placebo group ($p = 0.001$) and untoward effects were comparable between the two groups. The data (Table 1) suggest that butylscopolamine reduced the incidence of CRBD and the need for rescue analgesia with minimal side effects following urologic surgery. For other types of operations, a recent study by Nam et al.[15] assessed the presence and severity of CRBD at 1, 2, and 6 hours postoperatively of 99 patients with/without butylscopolamine. The results showed that the overall incidence of CRBD was less in the butylscopolamine group compared with the control group (31% *vs* 66%, respectively; $p = 0.001$). The incidence of CRBD at 1, 2, and 6 hours postoperatively was also significantly less in the butylscopolamine group. In addition, the average severity of CRBD for 6 hours postoperatively was significantly less in the butylscopolamine group than in the control group ($p = 0.002$). Adverse effects were comparable between the two groups. Therefore, i.v. administration of butylscopolamine at the end of an operation decreases the incidence and severity of early postoperative CRBD without adverse effects.

Oxybutynin: Two RCTs have assessed the efficacy of oxybutynin in the management of CRBD. However, pooling of these data and meta-analysis was considered inappropriate due to considerable clinical heterogeneity. Tauzin-Fin et al.[7] determined that sublingual oxybutynin (5 mg, every 8 h) was effective for decreasing postoperative bladder catheter-related pain in 46 patients undergoing radical prostatectomy. During the 24-hour study period, cumulative tramadol administration was 65% lower in the oxybutynin group compared with the control group. As such, the pain scores as per the visual analogue scale were significantly lower in the oxybutynin group. Furthermore, no oxybutynin-related adverse effects were observed. In a study by Agarwal et al.,[8] 78 patients requiring urinary bladder catheterization after percutaneous nephrolithotomy (PCNL) surgery received oral oxybutynin (5 mg, 1 hour before surgery) to prevent CRBD. The results showed that the incidence of CRBD in the control group was higher (58%) compared with oxybutynin group (35%). A significant reduction in the severity of CRBD was also observed with oxybutynin therapy compared with placebo. These data suggest that pretreatment with oxybutynin reduces the incidence and severity of CRBD for patients undergoing catheterization following PCNL surgery.

Tolterodine: We selected two RCTs that assessed the effect of tolterodine on the outcomes of patients with CRBD, the study and patient characteristics of which are presented in Table 1. Agarwal et al.[8] found that pretreatment with oral tolterodine (2 mg, 1 hour before surgery) is effective in reducing the incidence of CRBD by 25%, whereas oxybutynin showed a similar reduction of 23%. In the control group, the severity of CRBD at 1 hour after surgery was significantly higher compared with the tolterodine group. An additional study evaluated the efficacy of tolterodine in preventing CRBD in 215 patients undergoing urologic surgery requiring bladder catheterization.[1] Patients receiving tolterodine showed a significant reduction in the overall incidence of CRBD. Specifically, the absolute risk reduction with tolterodine was 19%, the RR reduction was 35%, and the number needed to treat was five. In conclusion, oral tolterodine (2 mg) administered 1 hour before surgery significantly reduced the incidence and severity of CRBD in patients undergoing urologic surgery requiring bladder catheterization.

Effect of anesthetics on CRBD. We selected four studies that evaluated the efficacy and safety of anesthetics in the management of CRBD. Study and patient characteristics are presented in Table 1.

Ketamine: Of the four studies of patients with CRBD, three compared the efficacy and safety of ketamine with placebo. Several studies have demonstrated the efficacy of ketamine for CRBD treatment.[9–11] The first clinical study on ketamine was published by Agarwal et al. in 2006.[11] Following this study, clinical studies using more homogeneous study populations were performed.[9,10] Agarwal et al.[11] demonstrated that i.v. ketamine (250 μg/kg) is an effective treatment for reducing the incidence and severity of CRBD without any untoward effects or fentanyl requirement was similar to the control group in operative time and intraoperative. Shariat et al.[9] found that preemptive administration of i.v. ketamine (0.5 mg/kg) can reduce the incidence and severity of CRBD in the early postoperative period (at 0 and 1 h). However, no significant differences were observed between the two groups at the 2- and 6-hour evaluations. Safavi et al.[10] evaluated the efficacy of different doses of ketamine in comparison with placebo for the treatment of CRBD during the postoperative period. The results indicated that i.v. ketamine (200 μg/kg) had similar efficacy to i.v. ketamine (250 μg/kg) in reducing the severity of CRBD without the occurrence of significant side effects.

Effect of antiepileptics on CRBD. Two studies[3,4] have specially focused on gabapentin for the prevention of postoperative CRBD. In both these studies, oral gabapentin was administered 1 hour before surgery. Agarwal et al.[3] reported that oral gabapentin (600 mg) administered in patients undergoing PCNL reduced the incidence and severity of CRBD, the number of patients requiring fentanyl, and total postoperative fentanyl administration. In this study, the incidence of CRBD was 80% in the control group and 50% in the gabapentin group. The study of Bala et al.[4] reported a decrease in the incidence of CRBD following TURBT from 90% (placebo group) to 66% in the 600 mg gabapentin group, which was further decreased to 26% in the 1200 mg group. Furthermore, none of the patients in the 1200 mg group complained of bladder discomfort after 6 hours. The CRBD severity was also less in the gabapentin group patients compared with the control group and none of the patients experienced severe discomfort. It is noteworthy that patients receiving a higher dose of gabapentin (1200 mg) had a significantly lower incidence of CRBD compared with the other groups (600 mg gabapentin and placebo).

Recently, pregablin, another antiepileptic, also was evaluated for its efficacy on the prevention of postoperative CRBD in patients undergoing spine operations.[14] Sixty patients undergoing elective spine surgery and requiring urinary bladder catheterization were included in this study. The patients in pregabalin group received 150 mg of pregabalin orally 1 hour before induction of anesthesia and the patients in the control group received placebo. The incidence of CRBD was significantly less in the pregabalin group

compared with the control group at all time intervals ($p < 0.05$). The severity of CRBD was reduced in the pregabalin group compared with the control group at all time intervals except 6 hours. The postoperative consumption of fentanyl was significantly less in pregabalin group, while the sedation score was significantly higher in the pregabalin group compared with the control group (Table 1). The authors concluded that oral pregabalin (150 mg) administered 1 hour before induction of anesthesia significantly reduced the incidence and severity of CRBD along with a reduction in postoperative fentanyl consumption, but at the cost of increased sedation.

Effect of analgesics on CRBD. Tramadol: An Indian study[12] has evaluated tramadol for the prevention of CRBD. They reported that both the incidence and severity of CRBD was reduced in the tramadol group at 0, 1, 2, and 6 hours following surgery compared with the control group. Furthermore, total postoperative fentanyl requirement was reduced in the tramadol group compared with the control group (176 *vs* 210 μg/kg, $p < 0.05$). Therefore, the authors concluded that i.v. tramadol (1.5 mg/kg) administered 30 minutes before extubation decreased the incidence (50%) and severity of CRBD and postoperative fentanyl requirement (20%). Unfortunately, they did not evaluate the dose–response titration or the effect of tramadol in treating CRBD.

Paracetamol: Ergenoglu et al.[13] found that a single intraoperative dose of i.v. paracetamol (15 mg/kg) decreased the severity of CRBD and total meperidine administration. The paracetamol group had significantly lower CRBD scores at 1, 2, 4, and 6 hours postoperatively compared with the placebo group ($p < 0.05$). Total meperidine consumption was significantly higher in the placebo group (75.81 mg *vs* 52.72 mg; $p = 0.018$), and no patients receiving paracetamol required rescue analgesia with tenoxicam. The main limitation of this study was the possibility of misperception between CRBD and surgical pain symptoms.

Effect of the type of surgery on CRBD

Two RCTs[4,5] evaluated the efficacy of solifenacin and gabapentin for prevention of CRBD after TURBT. Four RCTs[3,11–13] evaluated the efficacy of interventions for prevention of CRBD after PCNL. Besides the two types of urological operations, nonurological surgery was also included in present study.[14,15] The incidences of CRBD in the control group at 1, 2, 6, 12, and 24 hours after TURBT were 66.7% (22 of 33 cases), 90.9% (30 of 33 cases), 91.2% (83 of 91 cases), 84.6% (77 of 91 cases), and 81.3% (74 of 91cases), respectively. The incidences of CRBD in the control group at 1, 2, 6, and 12 hours after PCNL were 69.3% (131 of 189 cases), 62.4% (118 of 189 cases), 50.3% (95 of 189 cases), and 31.25% (10 of 32 cases), respectively. Similarly, the incidences of CRBD at 1, 2, and 6 hours after nonurological surgery were 58.75% (47 of 80 cases), 48.75% (39 of 80 cases), and 35% (28 of 80 cases), respectively. On the basis of the above analysis, there seems to be a higher risk of CRBD after TURBT without any interventions early postoperatively in comparison with PCNL and nonurological surgery. Compared with nonurological surgery, PCNL has higher incidence of CRBD.

The absolute risk reductions in the experimental group compared with the control group at 6 hours after surgery were 28% to 59% for TURBT (pooled RR: 0.55, 95% CI: 0.31, 0.99, $p = 0.04$),[4,5] 39% to 59% for PNCL (pooled RR: 0.51, 95% CI: 0.37, 0.70, $p < 0.001$),[3,12,13] and 66% to 67% for nonurological surgery (pooled RR: 0.26, 95% CI: 0.11, 0.59, $p = 0.001$). Obviously, the effectiveness of the intervention at 6 hours after TURBT was lesser than nonurological surgery.

Side effects

Side effects, such as dry mouth, facial flushing, and blurred vision, may occur with muscarinic antagonist administration, while sedation may occur with ketamine, gabapentin, and paracetamol. It is worth noting that patient and surgeon satisfaction is instrumental in the selection of agents used for the management of CRBD.

Solifenacin was well tolerated with the most common adverse event being dry mouth (10.3%), most cases of which were mild.[5] Agarwal et al.[1] reported that 54% of patients receiving tolterodine complained of dry mouth at 0 hour compared with only 22% in the control group ($p < 0.05$). At 1 hour, the incidence increased to 66% *vs* 47% ($p < 0.05$), and there were no differences in dry mouth incidence at other times. Therefore, these results suggest that tolterodine can be safely given to patients preoperatively to minimize CRBD. As such, in 2006, the same group[8] reported that the incidence of dry mouth was significantly higher in the tolterodine and oxybutynin groups compared with the control. Moreover, although 93% of patients receiving butylscopolamine complained of dry mouth, no significant differences were observed compared with the control group.[6]

Shariat et al.[9] reported that the incidence of sedation during the 0 hour visit in recovery was significantly higher in the ketamine group compared with the control group (12% *vs* 0%). There was a higher incidence of postoperative nausea and vomiting (PONV) in the control group at the 2 and 6 hour visits. Hallucinations were experienced by one of the patients in the ketamine group just after entering the recovery room, but it resolved without any need for intervention at the 1 hour visit. Agarwal et al.[11] stated that a higher incidence of mild sedation was observed in the ketamine group at 1 and 2 hours following operation. No differences in sedation (moderate or severe) or PONV between the ketamine and control groups were observed. None of the patients in either group had respiratory depression, hallucinations, or unpleasant dreams. One patient in the ketamine group reported diplopia 1 hour after ketamine administration, which resolved within the next hour. Furthermore, Safavi et al.[10] reported no significant difference in the incidence of side effects between groups receiving different ketamine doses.

In the tramadol group,[12] three patients developed respiratory depression (oxygen saturation < 90%), requiring oxygen supplementation using a face mask in the postoperative period compared with none in the control group. Although they observed a high incidence of PONV and sedation with tramadol, none of the patients were deeply sedated.

Gabapentin is usually well tolerated in doses as much as 1200 mg.[4] The most common side effects are somnolence, dizziness, ataxia, and fatigue. Agarwal et al.[3] reported that

there were no differences in postoperative sedation, PONV, feeling of light-headedness, or headache between the gabapentin and control groups. Likewise, there were no significant differences in side effects between the pregabalin group and placebo group.[14] In addition, paracetamol had sedative properties.[13] However, the patients treated with paracetamol were less agitated and anxious in their early recovery. As such, none of the patients exhibited hypotension, hypertension, or arrhythmia.

Discussion

We performed a systematic review of treatments and preventions for CRBD in patients who underwent urologic surgery. Muscarinic antagonists, anesthetics, antiepileptics, and analgesics appear to achieve the greatest improvement in clinical symptoms and significantly reduce the incidence of CRBD compared with placebo. Although these studies observed a high incidence of intervention-related side effects, patients tolerated these treatments well.

Catheterization during surgery, especially in males, and use of a urinary catheter ≥18F Foley frequently cause discomfort in patients during recovery, which is due to CRBD.[2] This study showed that the overwhelming majority of patients who required an indwelling catheter, especially those who received TURBT, developed moderate or severe CRBD during the immediate postoperative period. Compared with urological surgery, patients who underwent any other types of operations have a lower incidence of CRBD. These results are consistent with previous studies.[16,17] The observational study by Li et al. in 2014[16] identified that the type of surgery might be the predictive factor of moderate and severe CRBD after urological surgery. Study by Maro et al.[17] evaluated the correlation between the type of surgical procedure and the existence of CRBD in 100 patients who need bladder catheter. Surgical procedure concerned prostate, bladder, endourology, upper urinary tract, and lower urinary tract, and 40% of patients presented CRBD. Bladder resection and endourology were the main surgical procedures that induced CRBD. CRBD can lead to patient dissatisfaction in the postoperative period and increased incidence of postoperative complications. Therefore, if we reduce this discomfort, then the related side effects will also decrease.

A better understanding of CRBD and its pathophysiology may lead to better management and decreased morbidity. The bladder receives cholinergic innervation from the pelvic nerves and adrenergic innervation from the hypogastric nerves. It has a heterogeneous population of type 2 and 3 muscarinic receptors (M2 and M3), which are located in the urothelium and on efferent nerves. Although M2 receptors predominate in the bladder and modulate detrusor urinae contraction, the subtype M3 receptors are primarily responsible for bladder contraction.[18,19] Catheterization can stimulate the afferent nerves of the bladder leading to acetylcholine release, which can bring about muscarinic receptor-mediated involuntary contractions of the detrusor urinae. Based on the philosophy, various treatments such as muscarinic antagonists have been implemented with differing degrees of success for CRBD management. On the other hand, detrusor muscle contraction and activity of inflammatory mediators due to catheterization can prompt prostaglandin (PG) synthesis, which may play an important role in the occurrence of CRBD.[20] Therefore, paracetamol, a PG synthesis and COX-2 inhibitor, may alleviate the occurrence and symptoms of CRBD.[13] In addition, calcitonin gene-related peptide (CGRP) nerve fibers, which regulate the immune system, were located in bladder smooth muscle and more densely distributed in the neck compared with the dome.[21] Recently, CGRP has shown to be associated with inflammation and venular relaxation.[21,22] Thus, we hypothesize that CGRP may play a role in CRBD. Unfortunately, few literatures have reported on this issue.

When these aforementioned drugs are used, we must adequately consider their unique pharmacological properties, as it is helpful in treatment selection. For example, butylscopolamine does not cross the blood–brain barrier; thus, there are no central adverse effects associated with it (e.g., blurred vision and facial flushing).[23] Oxybutynin has a 10-fold higher affinity for M3 than M2 receptors, which can bring about a direct relaxing effect on the detrusor muscle.[24] However, this property is responsible for the high incidence of dry mouth because salivary glands have high levels of M3 receptors. In addition, tramadol is a synthetic opioid analgesic that inhibits detrusor muscle contraction through the inhibition of M1 and M3 receptors.[25] Epidural tramadol increases the bladder capacity and delays the filling sensation, thus decreasing the need for catheterization in the postoperative period.

Moreover, deciding which of these medications to use also requires consideration of their side effects. Anticholinergic agents (e.g., solifenacin, tolterodine, and oxybutynin) and gabapentin are oral agents and can cause adverse effects, including dry mouth. Administration of tramadol and ketamine was associated with a higher incidence of sedation. Another thing worth noting is that chronic ketamine use is associated with severe urinary tract dysfunction, but this does not exist in the management of CRBD after various surgeries. We know that every agent causes some side effects, the studies in which they were implemented revealed patient satisfaction scores that were higher in the treatment groups compared with control groups, thus supporting the importance of treating CRBD. As mentioned, future studies are needed that more adequately assess and compare the agents' management of CRBD. Furthermore, their dose–response titration and effects in treating, rather than preventing, CRBD should also be evaluated.

Patients tolerated these aforementioned treatments well, but there was a high incidence of intervention-related side effects. To overcome this problem, a recent study by Weinberg et al.[26] tried to use a dorsal penile nerve block to prevent CRBD after radical prostatectomy. Their data revealed that dorsal penile nerve block failed to reduce the incidence and severity of postoperative CRBD. Currently, periprostatic nerve block provides better pain control in transrectal ultrasound-guided prostate biopsy. In addition, periurethral infiltration with local anesthetic before operation can also reduce immediate postoperative pain.[27,28] However, these approaches have not been introduced in the management of CRBD. Further studies in this area are warranted.

Although our criteria stressed the selection of studies with limited heterogeneity in their cohorts, we note that there is substantial heterogeneity across the set of included studies for each intervention, which prohibited a meta-analysis. Such

heterogeneity was evident not only in patient baseline characteristics but also in the different treatment regimens and outcome indicators. In addition, our study has several limitations. First, most studies were unclear in randomization sequence generation; hence, selection bias or confounding may be present. Second, most studies' lack of standardized intraoperative and postoperative pain management can induce some bias, which can affect CRBD evaluation. Finally, publication bias must always be considered in systematic reviews.

Conclusion

Based on the published data, muscarinic antagonists, anesthetics, antiepileptics, and analgesics appear to achieve the greatest improvement in the clinical symptoms and a significant reduction in the incidence of CRBD compared with placebo. Although these studies observed a high incidence of intervention-related side effects, in general, patients tolerated these treatments well.

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Disclosure Statement

The authors declare that they have no conflicts of interest.

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Abbreviations Used

CI = confidence interval
CGRP = calcitonin gene-related peptide
CRBD = catheter-related bladder discomfort
MD = mean difference
OAB = overactive bladder
PCNL = percutaneous nephrolithotomy
PONV = postoperative nausea and vomiting
RCT = randomized controlled trial
RR = risk ratio
TURBT = transurethral resection of bladder tumor