

Effects of dezocine for the prevention of postoperative catheter-related bladder discomfort: a prospective randomized trial

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

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Purpose: To evaluate the effects of dezocine on the prevention of postoperative catheter-related bladder discomfort (CRBD).

Patients and methods: Ninety-six adult patients undergoing abdominal surgery with urinary catheterization under general anesthesia were randomized into dezocine and control (flurbiprofen) groups. The postoperative CRBD, pain score, sedation score and adverse effects were evaluated at 0, 1, 2 and 6 hrs after tracheal extubation.

Results: The primary outcome showed a lower incidence of CRBD at 1 hr post-extubation in the dezocine group (29.17%) than the control group (58.33%, $P<0.01$). The incidences at 0 and 2 hrs post-extubation and the overall incidence were also lower in the dezocine group than the control group (all $P<0.05$). The severity of CRBD at 0, 1, 2 and 6 hrs and the pain, sedation score and other adverse effects were comparable between the two groups ($P>0.05$); however, the overall severity of CRBD was decreased in the dezocine group compared with the control group ($P<0.05$).

Conclusion: Intraoperative dezocine reduces the incidence and severity of postoperative CRBD without clinically relevant adverse effects.

Keywords: dezocine, catheter-related bladder discomfort, general anesthesia, postoperation

Introduction

Catheter-related bladder discomfort (CRBD) is a clinical syndrome described as an urge to pass urine or as discomfort in the suprapubic region due to stimulation by the urinary catheter during recovery from general anesthesia.¹ The incidence of CRBD ranged from 47% to 95% during the postoperative period in patients with urinary catheterization.²⁻⁵ CRBD is extremely distressing to patients and usually accompanied by behavioral responses including strong vocal responses, flailing limbs and attempting to pull out the urinary catheter.² Moreover, CRBD increases postoperative pain and agitation.⁶⁻⁸ Therefore, attention and early intervention are needed for these patients.

Involuntary contractions of the bladder muscle triggered by muscarinic receptors are involved in the pathogenesis of CRBD, thus muscarinic antagonists including butylscopolamine, solifenacin, darifenacin, oxybutynin, glycopyrrolate, and tolterodine can improve CRBD symptoms.⁹⁻¹³ Moreover, drugs with other mechanisms, including anesthetics (ketamine, tramadol, dexmedetomidine and lidocaine-prilocaine cream), antiepileptics (gabapentin and pregabalin) and other drugs (amikacin, paracetamol and resiniferatoxin) have been reported to be effective in CRBD prevention.¹⁴⁻²³ In addition to pharmaceutical therapies, other approaches have

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been successfully used to improve CRBD, eg, caudal block and dorsal penile nerve block.²⁴

Dezocine is a mixed-opioid agonist/antagonist and often used for perioperative pain management.^{25–29} In clinical practice, we found that patients receiving dezocine for the treatment of postoperative pain appeared to suffer from less CRBD. However, the effect of dezocine on the prevention of CRBD has not been reported. Additionally, the spinal effect of dezocine through interactions with κ -receptors can produce a unique action in the treatment of visceral pain.^{26–29} Therefore, we hypothesized that dezocine is beneficial for CRBD and designed a prospective randomized trial to evaluate the effects of dezocine on the prevention of CRBD in patients undergoing abdominal surgery by investigating the incidence and severity of CRBD within 6 hrs after tracheal extubation.

Materials and methods

Patients

This study was conducted in accordance with the Declaration of Helsinki and reported in line with the Consolidated Standards of Reporting Trials (CONSORT) Guidelines. After receiving approval from the Institutional Ethics Committee for Clinical Research of Zhongda Hospital, Affiliated to Southeast University (approval no.: 2017ZDSYLL044-P01; August 18, 2017) and written informed consents from all patients, this prospective, randomized, and parallel design trial was performed. The protocol for this clinical trial was registered at ClinicalTrials.gov (registration no.: NCT03147066; May 10, 2017). Patients aged 18–65 years with American Society of Anesthesiologists (ASA) Physical Status I or II and scheduled for elective abdominal surgery with urinary catheterization for at least 6 hrs under general anesthesia were enrolled at the Zhongda Hospital and the Affiliated Hospital of Nanjing University of Traditional Chinese Medicine from September 2017 to October 2017. Exclusion criteria included bladder outflow obstruction, overactive bladder (frequency greater than three times per night or more than eight times per 24 h), drug use for benign prostatic hyperplasia, history of urethral surgery, multi-systemic diseases (cardiovascular, neuropsychiatric, hepatic, or renal dysfunction), chemical substance abuse, chronic pain or known allergy to medications used in the present trial.

Randomization

The patients were randomly allocated into one of the two groups (dezocine or control group) with the help of

a computer-generated random number table. The assignments were concealed in opaque envelopes and opened by two anesthesiologists who administered the study drugs in the two hospitals. All outcomes were assessed by the other two anesthesiologists who were blinded to the group assignments.

Study intervention

During the preoperative visit, patients were told about the symptoms of CRBD. No preoperative medicine was used. After establishing intravenous access in the operating room, monitors for electrocardiogram, peripheral oxygen saturation, blood pressure and temperature were applied to all patients. Following preoxygenation with 100% oxygen, anesthesia was induced with midazolam 0.04 mg/kg, sufentanil 0.3 μ g/kg and propofol 1.5–2.5 mg/kg. Endotracheal intubation was facilitated by rocuronium 0.6 mg/kg. Ventilation was mechanically controlled to maintain the end tidal carbon dioxide tension at 35–40 mmHg. Then, urinary catheterization was performed with a 14 or 16 Fr Foley catheter, and its balloon was inflated with 10 ml saline. The catheter was lubricated with paraffin oil before insertion and was fixed to the leg with adhesive tape without traction after successful insertion. Patients with complicated catheter insertion requiring more than 3 repeated attempts were dropped from the present trial. Anesthesia was maintained using 2%–3% sevoflurane in a mixture of 50% oxygen and 50% air, with intermittent intravenous injection of sufentanil and cis-atracurium as needed. Patients received intravenous dezocine 0.1 mg/kg (dezocine group, n=48) or flurbiprofen axetil 1 mg/kg (control group, n=48) 20–30 mins before the end of surgery according to the assignment. After the end of surgery, ondansetron 8 mg was used as a prophylaxis for postoperative nausea and vomiting, and patients were transferred to the post anesthesia care unit. When patients regained adequate spontaneous ventilation and responded to commands, the tracheal tube was extubated. Then, patients received patient-controlled analgesia with sufentanil (0.0125 μ g/kg bolus with a 15 min lock-out and 0.04 μ g/kg/h background infusion for laparotomy and 0.02 μ g/kg/h for laparoscopy 2 days)

Outcomes

The primary outcome was the incidence of CRBD at 1 hr after tracheal extubation. The secondary outcome measures included the incidence and severity of CRBD, numeric rating scale (NRS), Ramsay sedation score, and adverse effects (postoperative nausea and vomiting, dizziness, respiratory

depression, oversedation and hypotension/hypertension) at 0, 1, 2 and 6 hrs after extubation. The overall incidence and overall severity from 0 to 6 hrs after extubation were also calculated. The overall incidence was defined as the ratio of patients who experienced CRBD at any time point to total patients and the overall severity was analyzed according to the highest level of CRBD severity that patients experienced within 6 hrs after extubation. The severity of CRBD was recorded as: mild (reported by the patient only on questioning), moderate (reported by the patient on their own but without any behavioral response) and severe (reported by the patient on their own along with behavioral responses, including flailing limbs, vocal responses and attempts to pull out catheter).⁹⁻²³ When severe CRBD occurred, a rescue therapy of 1 mg/kg intravenous tramadol was administered. Postoperative pain was assessed using a verbal NRS (0 represents “no pain” and 10 represents “the worst pain possible”). Fentanyl 50 µg was supplemented as a rescue therapy in cases with an NRS ≥ 4 , and cases were removed from the present trial to avoid the confounding analgesic effect of fentanyl on the development of CRBD. The Ramsay sedation score was evaluated at the same time points and recorded as follows: 1 (anxious, agitated or restless); 2 (cooperative, oriented and tranquil); 3 (responds to commands, asleep); 4 (brisk response to light glabellar tap or loud noise); 5 (sluggish response to light glabellar taps or loud noise) or 6 (no response). The incidences of postoperative nausea and vomiting, dizziness, respiratory depression (respiratory rate < 8 breaths per minute, or $SpO_2 < 90\%$), oversedation (Ramsay score ≥ 5), hypotension (systolic blood pressure < 90 mmHg or 30% lower than the pretreatment value) and hypertension (systolic blood pressure > 180 mmHg or 30% higher than the pretreatment value) were also recorded.

Statistical analyses

The sample size was calculated by PASS 15.0 (NCSS, Utah, USA). According to previous studies, approximately 70% of patients complained of CRBD postoperatively.^{3,30} Assuming that dezocine reduces the incidence of CRBD by 30%, 38 patients are needed in each group to detect statistical significance with $\alpha = 0.05$ and $\beta = 0.10$. Considering a 20% dropout rate, 48 patients were included per group in the present trial. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Patient characteristics were compared by independent samples *t*-test for continuous variables and chi-squared test/Mann-Whitney U test for categorical variables. The incidence of CRBD, postoperative nausea and vomiting, dizziness and the number of

patients receiving tramadol or fentanyl treatment were compared by the chi-squared test or Fisher’s exact test. The severity of CRBD was compared by the Mann-Whitney U test. The NRS and Ramsay scores were analyzed by repeated measures analysis of variance, followed by Tukey’s test for post hoc comparisons. $P < 0.05$ was considered statistically significant. Data are expressed as the mean (SD) or the number (proportion) as appropriate.

Results

A total of 121 patients were screened from September to October 2017 for inclusion in the present trial (Figure 1). Twenty-five patients were excluded [exclusion criteria (n=15), refusal (n=7) and cancellation of surgery (n=3)]. Thus, 96 patients (n=48 in the dezocine and control groups, respectively) were enrolled and all patients completed the present trial. There were no significant differences in the demographic data between the two groups (Table 1).

The primary outcome showed a lower incidence of CRBD at 1 hr post-extubation in the dezocine group (29.17%) than the control group (58.33%) ($P < 0.01$). The secondary outcome showed that the incidence of CRBD was lower in the dezocine group than in the control group at 0 [(20.83%) vs (58.33%); $P = 0.000$], and 2 hrs [(31.25%) vs (52.08%); $P = 0.038$] but not 6 hrs [(20.83%) vs (33.33%); $P = 0.168$] after tracheal extubation. However, the severity of CRBD was comparable at 0, 1, 2 and 6 hrs after extubation between the two groups ($P > 0.05$). The overall incidence of CRBD was lower in the dezocine group than in the control group [(41.67%) vs (66.67%); $P = 0.014$]. The overall severity of CRBD was lower in the dezocine group compared with the control group ($P = 0.048$) (Table 2). The numbers of patients treated with tramadol for CRBD were 1 (2.08%) and 3 (6.25%) in the dezocine and control groups, respectively ($P = 0.617$).

No patient needed rescue analgesia with fentanyl for postoperative pain relief. The NRS at 0, 1, 2 and 6 hrs after extubation were comparable between the two groups ($P > 0.05$). The Ramsay sedation scores at 0, 1, 2 and 6 hrs after extubation were comparable between the two groups ($P > 0.05$). (Table 3)

No significant difference was observed in the overall incidence of postoperative nausea and vomiting and dizziness between the dezocine and control groups within 6 hrs after extubation ($P > 0.05$). No patient experienced respiratory depression, oversedation or hypotension/hypertension in the present trial. (Table 4)

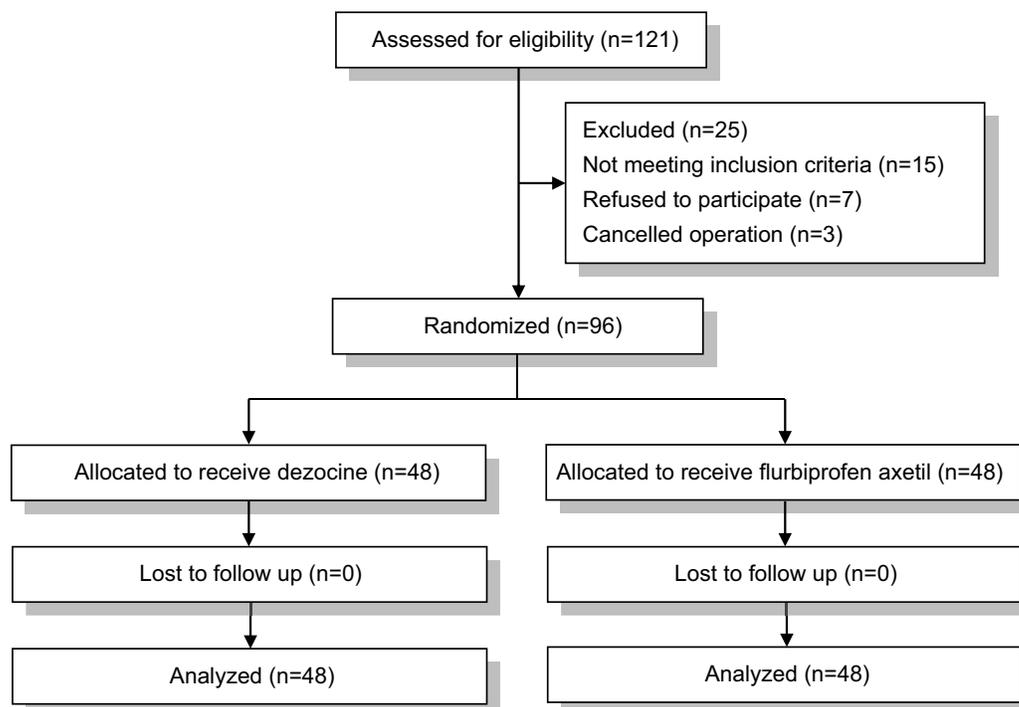


Figure 1 Flowchart of study progress.

Discussion

The present trial demonstrated that dezocine administration before the end of the surgery reduced the incidence and severity of postoperative CRBD without inducing severe drug-related adverse effects.

CRBD, a high incidence complication during the postoperative period, deserves more attention from anesthesiologists and surgeons. Although many pharmacologic therapies have been applied in the prevention or treatment of CRBD, the adverse effects of the majority of drugs have limited their clinical application.^{9–23}

Dezocine, an opioid medication, was approved by the Food and Drug Administration for perioperative pain management after its development in the 1970s but was discontinued with the closure of its parent company.²⁶ Recently, dezocine has been commonly used in China. Dezocine interacts with three major opioid receptors, ie, μ , κ and δ , and the unique molecular pharmacological profile of dezocine as a partial μ receptor agonist reduces its adverse reactions in comparison with other pure opioids. Dezocine has been proven to be effective in relieving moderate to severe surgical pain,^{27–29} which was also shown in the present trial. CRBD is usually resistant to conventional opioids, however, the activation of κ receptors by dezocine may contribute to the improvement of CRBD through inhibiting nociceptive

stimulation from spasms of the vesical neck and urethral mucosal injury. In addition, dezocine did not increase the overall incidence of postoperative nausea and vomiting, dizziness, respiratory depression, oversedation or hypotension/hypertension.

Previous studies investigated the incidence and severity of CRBD at 0, 1, 2, 6 and 24 hrs postoperatively.^{3,10,17,31} In this trial, since the elimination half-life of dezocine ranges from 1.2 to 7.4 hrs and the catheters were removed in most patients within 24 hrs postoperatively, we selected the time points of 0, 1, 2 and 6 hrs after tracheal extubation. All patients were resting in bed for at least 6 hrs after tracheal extubation in the present study. Dezocine reduced the incidence of CRBD at 0, 1 and 2 hrs but not 6 hrs after tracheal extubation. The overall severity of CRBD was attenuated by dezocine but not the severity at 0, 1, 2 and 6 hr assessments, probably due to the small sample size calculated based on differences in incidence rather than in severity.

Previous studies showed that sevoflurane, as a maintenance agent of general anesthesia, reduced the incidence of CRBD during the first 24 hrs postoperatively in patients undergoing transurethral resection of bladder tumors when compared with desflurane (76% vs 93%)³⁰ and propofol (66% vs 93%).³ Dexmedetomidine administration during surgery decreased the incidence of

Table I Characteristics of study population

	Dezocine (n=48)	Control (n=48)	P-value
Age (years)	53.19 (11.99)	52.56 (11.67)	0.796
Sex (male/female)	36/12	34/14	0.646
Weight (kg)	69.73 (11.72)	67.81 (12.20)	0.434
Height (cm)	168.88 (6.92)	166.93 (6.86)	0.171
BMI (kg m ⁻²)	24.42 (3.74)	24.20 (3.22)	0.757
ASA physical status (I/II)	28/20	25/23	0.538
Duration of surgery (min)	99.17 (56.57)	108 (71.11)	0.225
Duration of anesthesia (min)	122.02 (60.55)	137.40 (75.29)	0.273
Time to tracheal extubation (min)	30.10 (14.20)	33.54 (14.77)	0.248
Urinary catheter size			0.186
14 Fr	12 (25.00)	18 (37.50)	
16 Fr	36 (75.00)	30 (62.50)	
Type of operation			0.332
Stomach	6 (12.50)	10 (20.83)	
Colorectal	8 (16.67)	9 (18.75)	
Gallbladder	18 (37.50)	15 (31.25)	
Hernia	16 (33.33)	14 (29.17)	
Operative approach			0.283
Laparotomy	14 (29.17)	19 (39.58)	
Laparoscopic	34 (70.83)	29 (60.42)	
Intraoperative fluid volume			
Lactated ringer's solution	1166.67 (429.41)	1083.33 (465.09)	0.36
6% hydroxyethyl starch	319.79 (218.98)	355.83 (204.53)	0.41
Intraoperative urine volume	312.92 (183.01)	354.17 (195.91)	0.29
Intraoperative sufentanil requirement (µg)	53.13 (17.71)	56.51 (16.01)	0.33
Postoperative sufentanil requirement within 6 hrs (µg)	11.13 (4.92)	12.10 (5.48)	0.36

Note: Data are presented as the mean (SD) or the number (%) of patients.

CRBD in patients undergoing TURBT (57% vs 85%)¹⁷ or elective open abdominal surgery (20% vs 68%)³¹ when compared with the control group at 1 hr postoperatively. Reductions in the CRBD incidence ranging from 23% to 50% following anticholinergic and antiepileptic administration have been reported in previous studies.^{5,10,19} In the present trial, the reduction in CRBD incidence at 1 hr after extubation was 29.16% in the dezocine group compared with the control group. These results suggested that the application of anticholinergics, sevoflurane (rather than desflurane or propofol), or dezocine (rather than flurbiprofen) during the anesthesia procedure may be beneficial for preventing postoperative CRBD. Multiple drugs, such as sevoflurane and midazolam, which may help with CRBD were used in both groups in the present trial; therefore, the effects of these drugs on CRBD could not be accounted for in the study design. The use of the PCA was matched in the

two groups and there was no significant difference in the overall sufentanil dose postoperatively.

Saline served as a control for the prevention of CRBD in previous studies and may increase patients' pain experience.^{14,15,17} Flurbiprofen axetil, a nonsteroid anti-inflammatory drug, was used for postoperative multimodal analgesia and as a control in the present trial. Although Ergenoglu et al.²³ reported that paracetamol, a COX-2 inhibitor, alleviated the occurrence and symptoms of CRBD, flurbiprofen axetil seemed to be ineffective for CRBD; the incidence of CRBD in the flurbiprofen axetil control group (58.33% in all patients and 67.65% in male patients) were similar to the saline controls in previous studies (58% in all patients¹⁰ and 68% in male patients³¹).

The study was initially registered at clinicaltrials.gov with a placebo control arm (NCT03147066), which was changed to flurbiprofen control. This change was made because of a suggestion from the Institutional Ethics

Table 2 Incidence and severity of postoperative catheter-related bladder discomfort

	Dezocine (n=48)	Control (n=48)	P-value
Postextubation 0 h Incidence	10 (20.83)	28 (58.33)	0.000
Severity			
Mild	6 (12.50)	14 (29.17)	0.682
Moderate	3 (6.25)	12 (25.00)	
Severe	1 (2.08)	2 (4.17)	
Postextubation 1 hrs Incidence	14 (29.17)	28 (58.33)	0.004
Severity			
Mild	13 (27.08)	19 (39.58)	0.189
Moderate	1 (2.08)	8 (16.67)	
Severe	0 (0)	1 (2.08)	
Postextubation 2 hrs Incidence	15 (31.25)	25 (52.08)	0.038
Severity			
Mild	12 (25.00)	17 (35.42)	0.416
Moderate	3 (6.25)	8 (16.67)	
Severe	0 (0)	0 (0)	
Postextubation 6 hrs Incidence	10 (20.83)	16 (33.33)	0.168
Severity			
Mild	10 (20.83)	16 (33.33)	1.000
Moderate	0 (0)	0 (0)	
Severe	0 (0)	0 (0)	
Overall Incidence	20 (41.67)	32 (66.67)	0.014
Severity			
Mild	14 (29.17)	13 (27.08)	0.048
Moderate	5 (10.42)	16 (33.33)	
Severe	1 (2.08)	3 (6.25)	

Notes: Data are presented as the number (%) of patients. CRBD, catheter-related bladder discomfort.

Committee for ruling out the analgesic effect of dezocine on the occurrence of CRBD. A few limitations of the present trial should be considered. First, we did not completely rule out confounding factors such as the sedative effect of dezocine on the incidence of CRBD. Although the Ramsay sedation score was comparable between the two groups, we could not exclude the possibility that the sedative effect of dezocine did not mask symptoms of CRBD. Second, we could not blind the two anesthesiologists who administered the drugs because of the different drug appearances. Thus, the other two anesthesiologists blinded to the study drugs performed the outcome measurements. Third, it remains

uncertain whether flurbiprofen axetil is of benefit for CRBD because no saline controls were included in the present trial. Fourth, although no significant difference between groups was observed in the intraoperative fluid volume and urine volume, the effects of the postoperative volume of fluid and urine on CRBD should not be completely neglected in the present trial.

Conclusion

Dezocine administration before the end of surgery attenuated the incidence and severity of CRBD without inducing severe adverse effects for patients undergoing

Table 3 Postoperative pain and sedation scores

Time (hrs)	0		1		2		6	
	Dezocine	Control	Dezocine	Control	Dezocine	Control	Dezocine	Control
NRS (0–10)	0.85 (0.62–1.09)	0.96 (0.69–1.22)	1.06 (0.84–1.28)	1.06 (0.78–1.35)	0.85 (0.63–1.08)	0.85 (0.62–1.09)	0.85 (0.62–1.09)	0.83 (0.62–1.04)
Ramsay score (1–6)	2.04 (1.94–2.14)	1.98 (1.91–2.05)	1.98 (1.93–2.02)	1.96 (1.90–2.02)	2.02 (1.95–2.10)	1.94 (1.87–2.01)	1.94 (1.87–2.01)	1.96 (1.90–2.02)

Note: Data are presented as the mean (95% confidence interval for mean).

Table 4 Overall incidence of adverse effects

	Dezocine (n=48)	Control (n=48)	P-value
Nausea/vomiting	8 (16.67)	3 (6.25)	0.109
Dizziness	3 (6.25)	1 (2.08)	0.617
Respiratory depression	0(0)	0(0)	
Oversedation	0(0)	0(0)	
Hypotension/Hypertension	0(0)	0(0)	

Note: Data are presented as absolute frequency (%). No additional data are available.

elective abdominal surgery with general anesthesia. These results suggest the application of dezocine as an analgesic for postoperative pain in patients at high risk of CRBD.

Disclosure

The authors report no conflicts of interest in this work.

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