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Brief communication (Original)

Comparison of intravenous tramadol and ketamine for prevention of catheter-related bladder discomfort after laparoscopic surgery: a randomized, placebo-controlled, double-blind study

Rattanaporn Burimsittichai[a], Phoonsak Limraksasin[a], Cameron Paul Hurst[b], Somrat Charuluxananan[a]
[a]*Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand*
[b]*Center of Excellence in Biostatistics, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand*

Background: *C*atheter-related bladder discomfort (CRBD) is a distressing symptom after anesthesia.
Objectives: *To compare the efficacy of tramadol and ketamine to prevent CRBD after laparoscopic surgery.*
Methods: After registration with the Thai Clinical Trial Registry (TCTR20140220001), we conducted a randomized controlled trial in 210 patients aged 18–70 years with American Society of Anesthesiologists physical status I or II undergoing elective laparoscopic surgery requiring bladder catheterization. These patients were randomly allocated into 1 of 3 groups: Group T received intravenous (i.v.) tramadol 1.5 mg/kg, Group K received i.v. ketamine 0.5 mg/kg, and Group P received i.v. saline as a placebo before catheterization. Patients received i.v. morphine for postoperative pain control. An anesthesiologist blinded to the randomization evaluated postoperative and CRBD pain severity using visual analog scales (VAS). The cumulative postoperative and CRBD pain was calculated by multiplying mean VAS scores by the hours of assessment.
Results: Groups T and K had significantly less cumulative CRBD pain compared with placebo (P = 0.04 and 0.001, respectively). Cumulative postoperative pain, total 24-h morphine consumption, and adverse effects were comparable between groups. Group T had a significantly lower incidence of shoulder pain (7/67, 10%) than Group K (21/70, 30%), and Group P (24/70, 34%) 24 h after surgery (P = 0.006 and 0.001, respectively).
Conclusions: Tramadol 1.5 mg/kg and ketamine 0.5 mg/kg administered i.v. before bladder catheterization are both effective in reducing the 24-h cumulative postoperative CRBD after laparoscopic surgery without significant adverse effects. Tramadol also decreases the incidence of postlaparoscopy shoulder pain.

Keywords: Catheter-related bladder discomfort, ketamine, laparoscopic surgery, laparoscopy, pain, prevention, tramadol

Patients recovering from general anesthesia with a urinary catheter in situ often complain of a burning sensation with an urge to void, or discomfort in the suprapubic region independent of and separate from pain caused by the trauma of surgery. These symptoms are described as catheter-related bladder discomfort (CRBD). A study of patients with indwelling bladder catheters reported that 75% of patients experienced discomfort from the catheter, and 25% of them rated it as extreme [1]. The prevalence of postoperative CRBD reportedly ranges from 47%–90% [2-4], and it is one of the most distressing complications encountered in the postanesthetic care unit (PACU).

The symptoms of CRBD mimic those of the overactive bladder (OAB) [2]. The underlying pathophysiological mechanisms for both are thought to involve involuntary contraction of detrusor muscles mediated by muscarinic stimulation [5, 6], upregulation of bladder afferent C-fibers [4, 7], and prostaglandins (PGs) synthesis by activation of cyclooxygenase-2 (COX-2) [8]. These pathways represent potential therapeutic targets for the prevention and treatment of CRBD. Most studies have been conducted in patients who have undergone urological surgery [2, 4, 8-15], but CRBD can occur in any patient with a urinary catheter. The outcomes of these studies have

Correspondence to: Somrat Charuluxananan, Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand. E-mail: somrat@md.chula.ac.th

been variable and inconsistent; consequently there is still no drug of choice for managing CRBD.

The pain after laparoscopy may have components of incisional pain, deep intra-abdominal (visceral) pain, and shoulder pain [16, 17]. Patients recovering from laparoscopic surgery with a urinary catheter in situ may complain that bladder catheter discomfort is worse than the surgical pain. Strategies that treat CRBD effectively would improve the quality of recovery for these patients.

Tramadol and ketamine are often used intravenously during anesthesia. Both have been reported to reduce the proportion of patients complaining of postoperative CRBD [10, 12]. In previous studies, tramadol was administered at the end of the surgery (percutaneous nephrolithotomy), while ketamine was given after the induction of anesthesia during open nephrectomy. Although both drugs reduced postoperative CRBD, the results might not be comparable owing to the differences in methodology. Ketamine is supposed to be more effective than tramadol, although it was given at the start of the operation. Therefore, we conducted a randomized, controlled trial to compare the efficacy of tramadol and ketamine for the prevention of postoperative CRBD after elective laparoscopic surgery with the hypothesis that ketamine is more effective than tramadol in reducing the severity of CRBD.

Methods

Conduct of the study was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand (certificate of approval No. 231/2014, IRB No. 078/57). All patients gave written, informed consent to participate. Each was well informed about the protocol, the characteristics of CRBD and how to use a 100 mm visual analog scale (VAS) during the preoperative visit. The study was registered with the Thai Clinical Trial Registry (TCTR20140220001) since February 2014 before enrollment began.

We recruited 210 consecutive adults aged 18–70 years and with American Society of Anesthesiologists physical status I or II who underwent elective laparoscopic surgery requiring urinary catheterization at King Chulalongkorn Memorial Hospital. Patients with a history of OAB, bladder outlet obstruction, benign prostatic hypertrophy, central nervous system disease, body mass index (BMI) >35 kg/m^2, psychiatric disease, chronic analgesic use or chemical substance misuse, patients who were likely to require postoperative intensive care or respiratory support, patients whose procedure was converted to an open technique and patients whose surgery took longer than 4 h were excluded.

Patients were randomized into three groups using a computer-generated random number table and each patient's group allocation was kept in a sealed envelope. Group T received intravenous tramadol 1.5 mg/kg (Tramal 50; Grünenthal, Aachen, Germany), Group K received i.v. ketamine 0.5 mg/kg (Calypsol; Gedeon Richter, Budapest, Hungary), and Group P received i.v. 0.9% saline solution as a placebo control. An independent attending anesthesiologist who was not involved in the study administered the study drugs before urinary catheterization.

None of the patients were given premedication. Standard monitoring was established, and anesthesia induced with i.v. propofol 2 mg/kg; cisatracurium 0.15 mg/kg was administered to facilitate tracheal intubation. Anesthesia was maintained with sevoflurane, and intermittent doses of fentanyl and cisatracurium were administered as necessary. Urinary catheterization was performed by the surgeon, using a 14 or 16 Fr Foley catheter (for women and men, respectively) lubricated with KY jelly, and the balloon was inflated with 10 ml distilled water. The catheter was secured with adhesive tape without traction. At the end of surgery, muscle relaxation was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg, the trachea was extubated and the patients were transferred to the PACU.

The attending anesthesiologist recorded patients' demographic and clinical characteristics including age, sex, weight, height, body mass index (BMI), type of surgery, underlying hypertension, the intraoperative administration of COX-2 inhibitor, duration of surgery, and intraoperative fentanyl administration. Patients were evaluated for CRBD and postoperative pain using a VAS 0, 1, 2, 6, and 24 h after arrival at PACU by an anesthesiologist who was blinded to the group assignment. Patients who had severe and intolerable CRBD (VAS ≥ 70 mm) were treated with hyoscine butylbromide 20 mg intravenously as rescue therapy. Postoperative pain was managed with morphine 2 mg intravenously incrementally every 15 min if the VAS exceeded 30 mm. Patients received morphine 4 mg intravenously as needed every 4 h at ward. The cumulative dose of morphine administered during the

first postoperative 24 h and complaints of shoulder pain were recorded. Adverse effects including sedation, postoperative nausea and vomiting (PONV), respiratory depression, hallucination, blurred vision, hypertension (defined as systolic blood pressure higher than 140 mmHg or diastolic blood pressure higher than 90 mmHg) and tachycardia (defined as heart rate more than 100 beats per minute) were also noted. The level of sedation and severity of PONV were both assessed using a four-point rating scale (for sedation: 1 = fully awake, 2 = somnolent, responsive to verbal command, 3 = somnolent, responsive to tactile stimulation, 4 = asleep, responsive to painful stimulation; and for PONV: 1 = no nausea or vomiting, 2 = queasy, 3 = severe nausea, 4 = vomiting) [18, 19]. Patients with PONV grade 3 or 4 were treated with ondansetron 8 mg intravenously.

Sample size calculation and statistical analysis

The sample size was calculated using the findings of a pilot study by means of a two-tailed test with a type I error of 0.05, study power of 90%, and an assumed 10% dropout rate. The number of participants required in each group was 70, giving a total number of participants of 210 including the placebo group.

Patients' demographic data and baseline characteristics were analyzed using analysis of variance for continuous data and a chi-square or Fisher exact test for categorical data. CRBD and postoperative pain severity were assessed using linear mixed model. The 24-h cumulative pain of CRBD and postoperative pain were assessed by the area under the curve of VAS scores versus time. This was calculated by multiplying mean VAS scores by

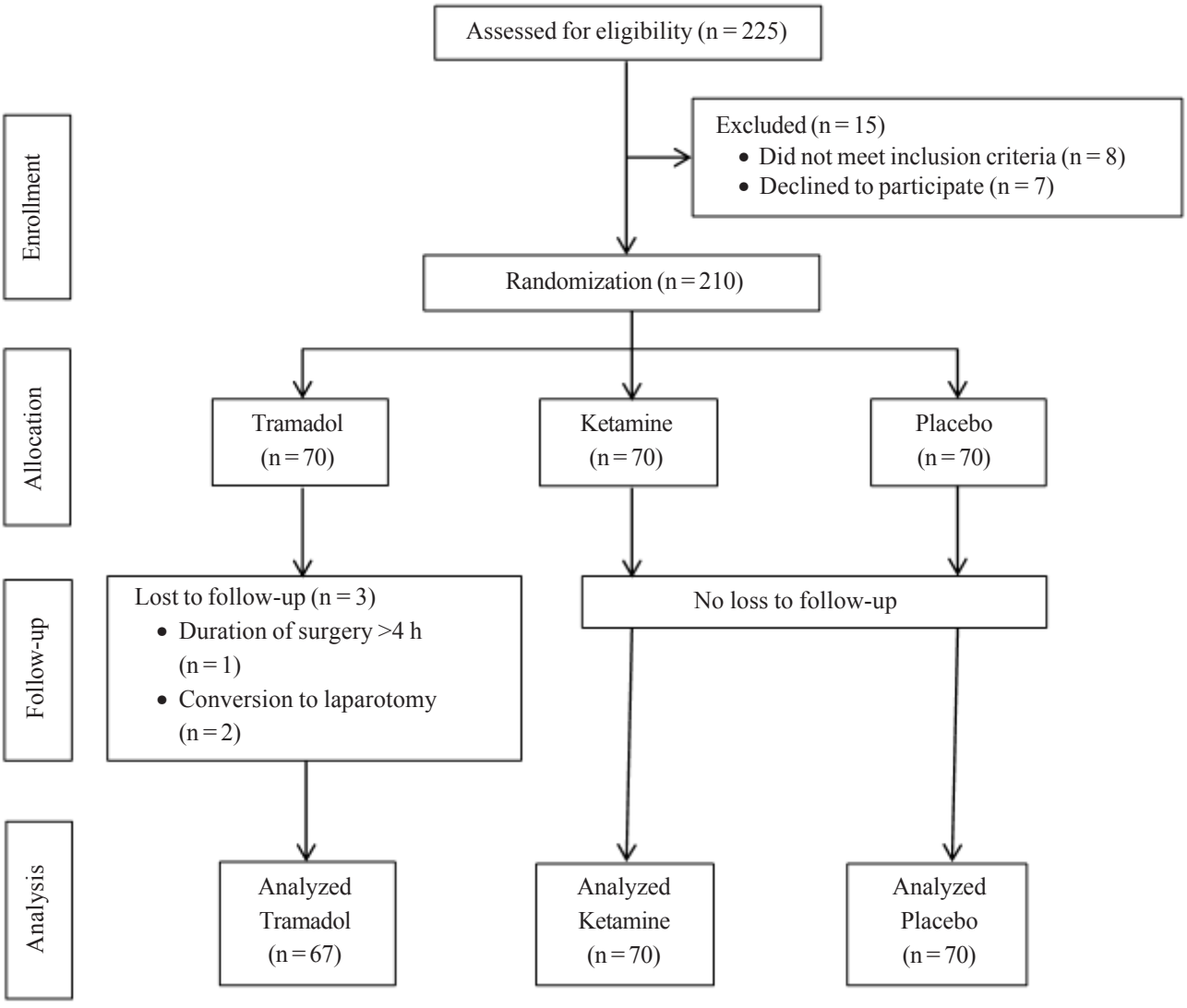

Figure 1. CONSORT diagram of the study

the hours of assessment and then was analyzed using analysis of variance. The 24-h morphine consumption, sedation and PONV data were analyzed by Kruskal-Wallis test. The incidence of blurred vision, respiratory depression, hallucinations, postoperative hypertension and tachycardia and shoulder pain was analyzed by a chi-square or Fisher exact test. Data were analyzed using R software version 3.2.2. The level of significance was $P < 0.05$.

Results

A total of 210 patients undergoing elective laparoscopic surgery requiring urinary catheterization participated in the study from April 2014 to February 2015. Three patients in Group T were excluded: two in whom the procedure was converted to a laparotomy and one in whom the duration of surgery exceeded 4 h (**Figure 1**).

The groups were comparable in terms of age, sex, weight, height, BMI, type of surgery, duration of surgery, intraoperative fentanyl administration, the proportion with arterial hypertension and the proportion of patients administered a COX-2 inhibitor (**Table 1**).

The results from linear mixed model with effect modification considered demonstrated that patients in Group T had a significantly lower CRBD severity score than Group P at 6 and 24 h (–7.43 and –6.06, respectively, both $P < 0.05$) and patients in Group K also had a significantly lower CRBD severity score than Group P at 6 and 24 h (–8.83 and –7.93, respectively, both $P < 0.05$) (**Figure 2**).

The 24-h cumulative pain of CRBD was significantly different between 3 groups (scale (VAS), in all of the 3 groups over a 24 h postoperative period ($P = 0.001$). The patients in Groups T and K had a significantly lower cumulative pain of CRBD than those in Group P with P of 0.04 and 0.001, respectively.

The cumulative VAS scores for surgical pain was not statistically significant different between groups ($P = 0.25$).

The overall incidence of shoulder pain in the study was 30%. The proportion of patients in Group T reporting shoulder pain 24 h after surgery was significantly lower than Groups K and P ($P = 0.006$ and 0.001, respectively; **Table 2**).

Table 1. Patients' demographic data and baseline characteristics

Variables	Tramadol (T) (n = 67)	Ketamine (K) (n = 70)	Placebo (P) (n = 70)
Age (years)	44 (12.7)	47 (12.8)	46.8 (11.2)
Sex			
Male	12 (18%)	14 (20%)	14 (20%)
Female	55 (82%)	56 (80%)	56 (80%)
Weight (kg)	61.2 (11.7)	60.7 (10.6)	59.5 (13.3)
Height (cm)	159 (7.2)	160 (6.6)	160.3 (7.9)
BMI (kg/m^2)	24.2 (3.9)	23.8 (4.0)	23.1 (4.5)
Type of surgery			
Laparoscopic upper abdominal surgery	5 (8%)	8 (11%)	2 (3%)
Laparoscopic lower abdominal surgery	11 (16%)	9 (13%)	9 (13%)
Laparoscopic uterine surgery	20 (30%)	17 (24%)	25 (36%)
Laparoscopic ovarian surgery	18 (27%)	22 (31%)	14 (20%)
Laparoscopic nephrectomy/ adrenalectomy	13 (19%)	14 (20%)	20 (29%)
Underlying hypertension	11 (16%)	13 (19%)	19 (27%)
Administration of COX-2 inhibitor	18 (27%)	9 (13%)	15 (21%)
Duration of surgery (min)	130 (52.6)	117 (49.4)	113.8 (55.1)
Intraoperative fentanyl administration (mg/h)	45 (35.1)	53 (30.8)	55.0 (37.9)

Data are presented as mean (standard deviation) and frequency (percentage).
BMI, body mass index; COX-2, cyclooxygenase-2

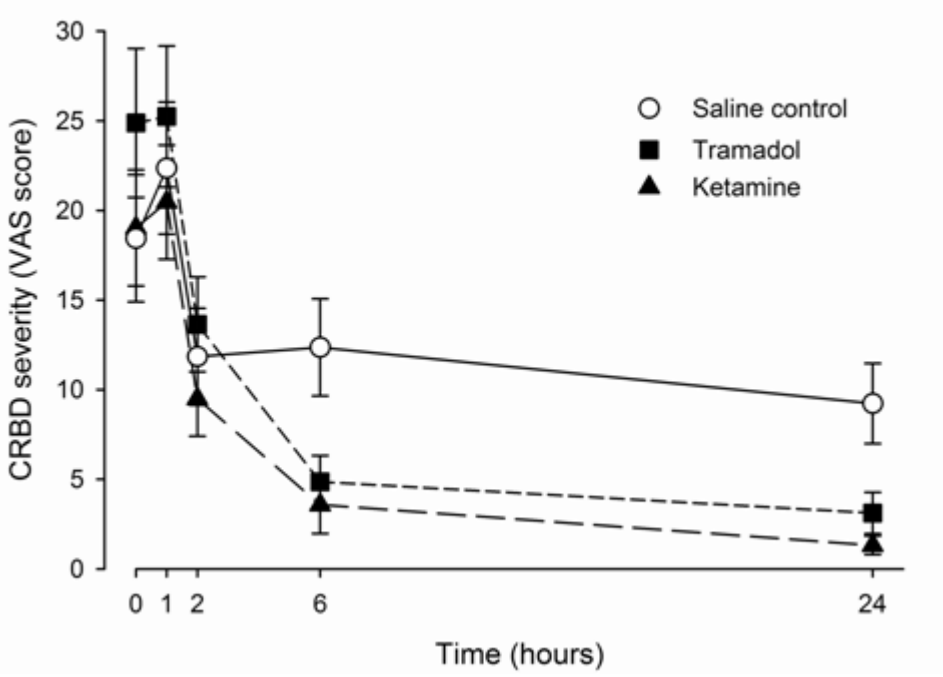

Figure 2. Catheter-related bladder discomfort (CRBD) severity, assessed by using visual analog scale. Error bars are standard error of the mean.

Table 2. Incidence of postoperative shoulder pain

Time	Tramadol (n = 67)	Ketamine (n = 70)	Placebo (n = 70)	*P*
Overall incidence	12 (18%)	26 (37%)	24 (34%)	0.03[a]
0 h	1 (2%)	3 (4%)	1 (1%)	0.62
1 h	3 (5%)	9 (13%)	3 (4%)	0.1
2 h	2 (3%)	8 (11%)	2 (3%)	0.06
6 h	4 (6%)	12 (17%)	5 (7%)	0.06
24 h	7 (10%)[b]	21 (30%)	24 (34%)	0.003[a]

Data are presented as the number of patients in each group reporting shoulder pain (percentage)
[a]Statistical significance between the three groups (chi-square test)
[b]Statistical significance compared with ketamine ($P = 0.006$) and placebo ($P = 0.001$)

Mean 24-h morphine consumption was 6.4 mg (± 5.2 mg standard deviation) in Group T, 5.8 mg (± 3.9 mg) in Group K, and 7.4 mg (± 5.4 mg) in Group P. There was no statistically significant difference between the groups. There were also no significant differences in sedation level, severity of PONV, postoperative hypertension and tachycardia or reports of blurred vision between the groups. There was no incidence of respiratory depression during the study, and none of the patients reported hallucinations (**Table 3**).

Discussion

We found that a single intraoperative i.v. dose of either tramadol or ketamine had a significant beneficial therapeutic effect on the severity of CRBD 6 and 24 h after laparoscopic surgery without significantly increasing the incidence of adverse effects compared with placebo.

Previous studies have demonstrated the efficacy of tramadol and ketamine in attenuating CRBD in the early postoperative period, likely owing to their antimuscarinic actions [20, 21]. Agarwal administered

Table 3. Adverse effects

Adverse effect	Tramadol n = 67	Ketamine n = 70	Placebo n = 70	*P*
Sedation level				0.29
1	28 (42%)	22 (31%)	27 (39%)	
2	39 (58%)	45 (64%)	42 (60%)	
3	0	3 (4%)	1 (1%)	
4	0	0	0	
PONV				0.06
Queasy	10 (15%)	8 (11%)	15 (21%)	
Severe nausea	6 (9.%)	18 (26%)	10 (14%)	
Vomiting	16 (24%)	11 (16%)	3 (4%)	
Blurred vision	1 (2%)	1 (1%)	0	0.77
Respiratory depression	0	0	0	N/A
Hallucination	0	0	0	N/A
Postoperative hypertension	22 (33%)	23 (33%)	28 (40%)	0.60
Postoperative tachycardia	5 (8%)	3 (4%)	0	0.07

Data are presented as the number of patients in each group (percentage)
Sedation level: 1, fully awake; 2, somnolent, responsive to verbal command; 3, somnolent, responsive to tactile stimulation; 4, asleep, responsive to painful stimulation.

intravenous tramadol 30 min before extubation aiming to achieve a therapeutic effect in the early recovery period [10]. Shariat Moharari and colleagues undertook their study in a cohort of patients who had undergone open nephrectomy [12]. It has been reported that open abdominal surgery itself contributes to the likelihood of a patient experiencing moderate to severe CRBD compared with those who have undergone a laparoscopic procedure. In the present study, tramadol and ketamine, administered before the urinary catheterization, were effective in reducing CRBD severity at 6 and 24 h after elective laparoscopic surgery compared with control. However, both significantly reduced the 24-h cumulative pain of CRBD.

Cumulative postoperative pain and 24-h morphine consumption were comparable between the groups, but the incidence of shoulder pain was significantly lower in Group T. It has been proposed that a multimodal strategy be adopted to manage shoulder pain after laparoscopy [22, 23]. We found that a single dose of tramadol alleviated shoulder pain after laparoscopy, which is usually minor on the first day but becomes significant on the following day [16].

Sedation scores were broadly comparable between the groups, and no patient was so deeply sedated that he or she could only be roused by a painful stimulus. The severity of PONV in Group T was higher than Group K, but the sample size may not have been sufficiently large to detect a statistically significant difference. One patient in Group T and one in Group K reported blurred vision immediately after surgery, which resolved within 1 h in both cases. Blurred vision may have arisen as a result of the action of tramadol on the opioid receptor, ketamine-induced nystagmus, or the residual effects of anesthesia. Although postoperative arterial hypertension was common, it was generally mild and some patients had a preexisting diagnosis of hypertension before surgery. Hypertension may have been caused by CRBD, or pain caused by surgery. None of the patients developed respiratory depression or complained of hallucinations, allowing us to conclude that both drugs were relatively safe.

Our study has several limitations. First, CRBD is a subjective symptom that is difficult to evaluate. We chose to use a VAS, which has been validated for the assessment of pain in adults. Second, the majority of patients in the study were women. This arose by chance, and the proportions of men and women in each group were not significantly different. Third, the symptoms of deep visceral pain caused by laparoscopy may overlap with the symptoms of CRBD. We addressed this by fully informing the participants of the characteristics of CRBD at recruitment. Finally, although CRBD is reportedly resistant to conventional

opioid therapy, the administration of opioids for peri- and postoperative pain may have masked the symptoms of CRBD or mimicked the side effects of the study drugs. Although the total amount of fentanyl and morphine administered in the study did not differ between the groups, further studies will be needed with fixed doses of opioid analgesics or nonopioid analgesic strategies to elucidate the effect of tramadol and ketamine on CRBD, without the potential influence of opioids on outcome measures.

Conclusion

The i.v. administration of tramadol 1.5 mg/kg or ketamine 0.5 mg/kg before urinary catheterization reduced the severity of CRBD at 6 and 24 h after elective laparoscopic surgery and 24-h cumulative pain of CRBD without increasing the incidence of adverse effects. Tramadol also appeared to reduce the proportion of patients reporting postlaparoscopy shoulder pain.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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