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# Comparison of Different Strategies for Prevention of Catheter-Related Bladder Discomfort: A Randomized Controlled Trial

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## Abstract

**Aim:** Catheter-related bladder discomfort (CRBD) is characterized by pain and a burning sensation in the suprapubic region caused by stimulation of type 3 muscarinic (M3) receptors. The aim of this study was to compare the effects of tramadol and dexmedetomidine on CRBD, which have inhibitory effects on the M3 receptor.

**Methods:** A total of 135 male patients with ASA I-II, aged between 18 and 70 years and scheduled to undergo elective retrograde intrarenal surgery between March and July 2020, were included in the study. Patients were randomized into three groups: tramadol (group T), dexmedetomidine (group D), and control (group C). Patients were evaluated for the incidence and severity of CRBD and postoperative pain at the postoperative 0$^{th}$ ($t_0$), 1$^{st}$ ($t_1$), 3$^{rd}$ ($t_2$), and 6$^{th}$ ($t_3$) hours.

**Results:** The incidence and severity of CRBD were lower in group D at $t_1$ than in the other groups ($p<0.05$). The incidence and severity of CRBD were similar between groups T and D, and they were significantly lower than those in group C at $t_2$ and $t_3$ ($p<0.01$). Postoperative pain levels were significantly lower in groups T and D than in group C at $t_0$ and $t_1$ ($p<0.01$). Postoperative recovery time was significantly longer in group D ($p<0.01$).

**Conclusion:** Both dexmedetomidine and tramadol are effective in preventing CRBD and in postoperative analgesia. Dexmedetomidine is more potent than tramadol in the early period; however, it may delay post-anesthesia recovery time.

**Keywords:** Dexmedetomidine, tramadol, urinary catheterization, complications

## Introduction

Urinary catheterization is frequently performed in many surgeries, particularly urinary surgery. However, this intervention may cause a group of symptoms termed "catheter-related bladder discomfort" (CRBD), characterized by pain, a burning sensation in the suprapubic region, and a constant urge to urinate. CRBD increases the risk of postoperative complications by causing pain and agitation in the patient, delays the recovery period and increases the workload of health workers. Therefore, the prevention or treatment of CRBD at an early stage is essential.

Male sex and Foley catheter diameter (≥18F) are major risk factors for CRBD. Additionally, the type of surgery is also essential for CRBD, which is more common in urological or lower abdominal surgeries (1,2). Other reported risk factors are cesarean and urinary catheterization medical history, age <50 years, and absence of lubrication (3).

The main cause of urinary catheter-related discomfort is involuntary contractions of the detrusor muscle due to stimulation of muscarinic receptors, primarily type 3 receptors (M3 receptors). Several studies have shown that medical treatments including ketamine, tolterodine, oxybutynin, gabapentin, pregabalin, butylscopolamine,

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chlorpheniramine, tramadol, and dexmedetomidine, and methods such as botulinum toxin injection, adjustment of the catheter balloon diameter, local infiltration, and regional anesthesia are effective in preventing CRBD (1,4-9). Muscarinic receptor antagonists such as oxybutynin, tolterodine, and ketamine are the main drugs used to treat CRBD (10-12). Gabapentin has been reported to be effective in preventing CRBD by regulating the afferent signal input from the bladder and excitability of the sacral reflex center (13). Hyosin N-butyl bromide, also known as scopolamine, treats CRBD effectively by stopping painful cramps and spasms with its anticholinergic effect (14). However, the search for the ideal agent for preventing CRBD continues since no definitive conclusions can be drawn for routine use due to the small number of samples, surgical differences, and some anticholinergic and sedative side effects.

In this study, we evaluated and compared the effects of intraoperatively administered tramadol and dexmedetomidine on the incidence and severity of CRBD and their side effects. We also examined their analgesic activity.

## Materials and Methods

### Compliance with Ethical Standards

This prospective randomized controlled study was conducted between March and July 2020 after obtaining ethical committee approval from University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital (date: 05.08.2019, approval number: 69/15). The protocol for this clinical trial was registered at ClinicalTrials.gov (NCT04314050).

### Study Design

Internet-based randomization software (http://www.randomizer.org) was used to determine randomization assignments. Written informed consent was obtained from all patients. A total of 135 male patients with ASA I-II, aged between 18 and 70 years, scheduled to undergo elective retrograde intrarenal surgery (RIRS) and who would be undergoing a urinary bladder catheter were included in the study. Patients with preoperative double j stent and difficulty inserting the urinary catheter were excluded from the study. Moreover, patients with a history of bladder outlet obstruction, overactive bladder, neurogenic bladder, and patients with morbid obesity, liver or kidney insufficiency, diabetic neuropathy, chronic analgesic drug use, and cognitive impairment were excluded from the study.

To ensure standardization, we included only male patients and preferred one type of surgery. Urinary catheterization was performed using a 16-Fr Foley catheter with a lubricant gel and fixed to the leg without any traction-using sticking plaster. Additionally, as a routine practice of the urology clinic, a polyurethane 26 cm 4.7-F double j stent was applied to all patients after the RIRS operation.

The patients were randomized into three groups: tramadol (group T), dexmedetomidine (group D), and control (group C). No premedication was given. Standard general anesthesia with a laryngeal mask was applied to all patients, and 1 g paracetamol was administered intravenously (i.v.) for postoperative analgesia. After anesthesia induction, group D was infused with dexmedetomidine (Hipnodex™; Haver Pharma Drug Inc., Istanbul, Turkey) at a loading dose of 1 μg $kg^{-1}$ (diluted in 100 ml of 0.9% saline-10 minute i.v. infusion) followed by a continuous infusion of 0.5 μg $kg^{-1}$ $h^{-1}$ at the end of the surgery. In group T, tramadol (Tramosel™; Haver Pharma Drug Inc., Istanbul, Turkey) 1.5 mg $kg^{-1}$ diluted in 100 mL of 0.9% saline was given by slow infusion during the last 30 min of the surgery. No additional drugs were administered to the patients in the control group. The patients who were extubated at the end of the operation were transferred to the post-anesthesia care unit (PACU).

### Patient Evaluation and Follow-up

The patients were evaluated using the Ramsay sedation scale (RSS) and the modified aldrete score (MAS) on admission to the PACU. The RSS is the most commonly used sedation scale in intensive care units and scores sedation at six levels (15). The ideal sedation level is two. Patients with a sedation scale of ≥4 were considered deeply sedated. MAS is used to check whether the patient is ready for discharge from the PACU after anesthesia. MAS assesses patients' motor activity, respiration, blood pressure, consciousness, and oxygenation over 10 points (16). Nine points are required for discharge from the PACU. Patients whose evaluation scores reached 9 points were transferred to the ward. The time from admission to PACU until MAS ≥9 was recorded as recovery time.

Patients who were informed about CRBD symptoms preoperatively were evaluated for the incidence and severity of CRBD at postoperative $0^{th}$ ($t_0$), $1^{st}$ ($t_1$), $3^{rd}$ ($t_2$), and $6^{th}$ ($t_3$) hours in the PACU and ward. The severity of CRBD was assessed in four grades: none, when patients did not complain of any CRBD; mild, when reported by patients only on questioning; moderate, when reported by patients on their own (without asking and any behavioral response); and severe, when reported by patients on their own along with behavioral responses (severely agitated) (5,17,18). Patients who complained of moderate or severe CRBD were considered CRBD-positive. As part of our routine clinical practice, we administered 20 mg

of hyoscine N-butyl bromide (Buscopan®, Sanofi Health Products Ltd, Istanbul, Turkey) as rescue therapy (19,20).

Patients were evaluated for postoperative pain using a numerical rating scale (NRS). The patient was asked to score their pain between 0 (no pain) and 100 points (worst imaginable pain) at $t_0$, $t_1$, $t_2$, and $t_3$ (21). Rescue dexketoprofen (Arveles, UFSA Pharmaceutical Industry and Trade Inc., Istanbul, Turkey) 50 mg was administered when the NRS was >60. Additionally, major adverse effects such as nausea, vomiting, dry mouth, and intraoperative hypotension or bradycardia were recorded.

### Statistical Analysis

The Statistical Package for the Social Sciences (SPSS version 22.0, Chicago, IL, USA) was used for statistical analysis. P<0.05 was considered significant. The normality of continuous data was assessed using a one-sample Kolmogorov-Smirnov test. The homogeneity of variances was tested using Levene's test. Numerical variables were summarized as mean ± standard deviation (SD) or median (IQR), and categorical variables as frequencies and percentages. For the comparison of continuous variables, the Kruskal-Wallis test was used in the triple group comparison and the Mann-Whitney U test was used for paired group comparisons.

The sample size for the research was estimated on the basis of a preliminary experiment according to the incidence of CRBD in a range from 0.17 to 0.5 between the three groups. To obtain significance of $\alpha$=0.05 and 90% power (1-$\beta$=0.9), the required sample size per group was at least 41. Considering the possibility of dropout, we included 135 patients in this study.

## Results

During the study period, 169 patients were assessed for eligibility, and 34 were excluded (Figure 1), so 135 patients (45 in each group) were analyzed. Reasons for exclusion included history of bladder disease (n=10), refusal to participate (n=4), language barrier (n=5), cognitive disorder (n=6), and pre-existing catheter before surgery (n=9).

The demographic data of the patients was similar (Table 1). Among the three groups, there was no significant difference in the incidence and severity of CRBD at the first assessment ($t_0$) in the PACU (p=0.934 and p=0.467, respectively). However, they were significantly lower in group D at $t_1$ (p=0.0006 and p=0.032, respectively) than in the other groups. The incidence and severity of CRBD were similar between groups T and D (p=0.334 and p=0.708; p=0.557 and p=0.168, respectively) and were significantly lower than those in group C at $t_2$ and $t_3$ (p=0.0007 and p=0.005; p=0.002 and p=0.0001, respectively) (Figure 2, Table 2).

The median NRS scores were significantly lower in groups T and D than in group C at $t_0$ and $t_1$ (p=0.0001 and p=0.005, respectively), and they were similar in groups T and D (p=0.848 and p=0.365, respectively). There was no significant difference in NRS scores between the groups at $t_2$ and $t_3$ (p=0.910 and p=0.491, respectively) (Table 3).

The postoperative recovery time was significantly longer in group D than in the other groups (p=0.0001), and it was similar in groups T and C (p=0.075) (Table 3).

Deep sedation was not observed in these patients. No drug-related adverse effects were observed in any patient.

## Discussion

We observed that tramadol was as effective as dexmedetomidine in reducing the frequency and severity of CRBD and postoperative pain. However, dexmedetomidine was more effective than tramadol in the early period.

Tramadol is a centrally acting, synthetic opioid analgesic with M1 and M3 muscarinic receptor inhibitory effects. In a previous study comparing the dose-response effect of tramadol, 1.5 mg $kg^{-1}$ was reported to be more effective than 1 mg $kg^{-1}$ in treating CRBD and reducing postoperative pain (17). Agarwal et al. (22) showed that 1.5 mg $kg^{-1}$ i.v. tramadol, administered 30 min before extubation, decreased the incidence and severity of CRBD (50%) at all time points ($0^{th}$, $1^{st}$, $2^{nd}$, and $6^{th}$ hours) and provided a 20% reduction in postoperative fentanyl consumption. However, a recent study reported that butorphanol effectively lowered the CRBD score and reduced postoperative pain compared with 1.5 mg $kg^{-1}$ of tramadol in non-urological surgery (23). However, the sedation score was higher in the butorphanol group.

In this study, we observed that tramadol did not affect the incidence and severity of CRBD in the first hour; still, it reduced the incidence and severity of CRBD by 17-31% in the $3^{rd}$ and $6^{th}$ hours postoperatively. Tramadol, consisting of two enantiomers [(+) tramadol, (-) tramadol], each with a different mechanism of action, turns into an active metabolite after metabolism. The pharmacokinetics and pharmacodynamics of tramadol can vary due to a delay of action depending on its transport from the plasma to the central nervous system and pharmacodynamic interactions between its two enantiomers and its active metabolites (24,25). Although the information about the onset of action and elimination half-life of the i.v. form of tramadol is not unclear, intramuscular injection and 30-minute i.v. infusion are considered bioequivalent in terms of systemic effects. Accordingly, it may take up to 1.5 h to reach the serum peak value for tramadol (26). As explained above, this may be because the drug cannot reach its serum peak level in the early period.

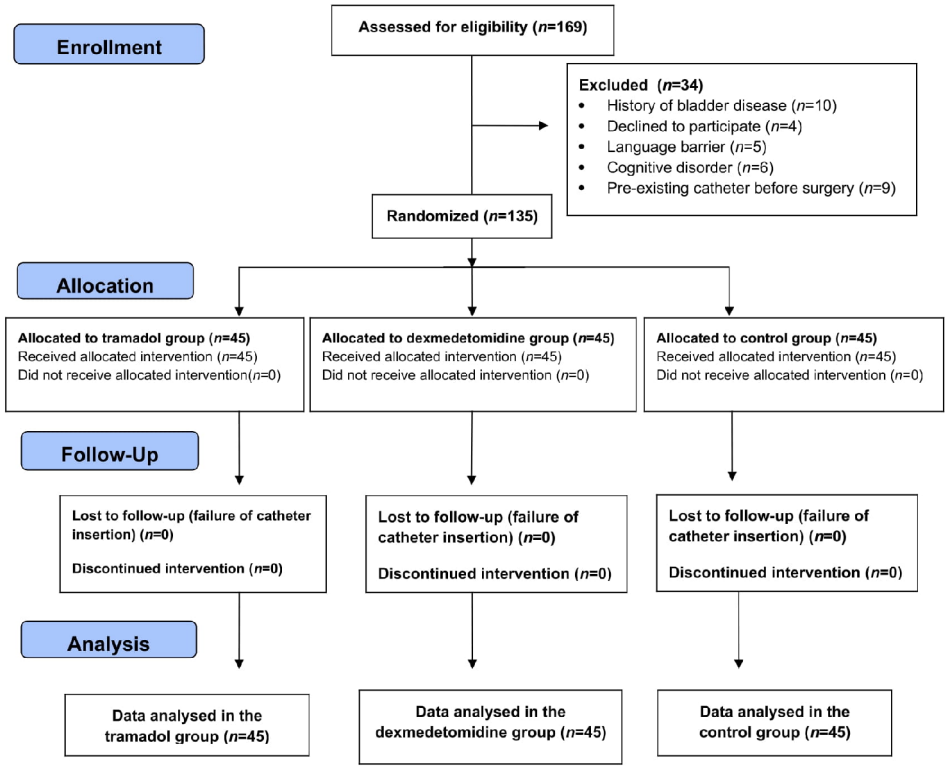


**Figure 1.** CONSORT diagram

Dexmedetomidine, a selective α-2 adrenoceptor agonist, has analgesic, sympatholytic, and sedative properties (27). The research by Takizuka et al. (28) found an inhibitory effect of dexmedetomidine on the M3 receptor; the impact of dexmedetomidine on CRBD has been the subject of research. Previous studies have shown that dexmedetomidine is effective in preventing CRBD and reducing the frequency and severity of CRBD, and is also effective in alleviating postoperative analgesia (18,29-32). A recent meta-analysis, which included seven studies on different types of surgery, concluded that intraoperatively administered dexmedetomidine reduced the frequency and severity of CRBD in the early postoperative period without having any serious side effects (33). Consistent with other studies, our results showed that intraoperatively administered dexmedetomidine effectively prevents CRBD and reduces the frequency and severity of CRBD by 20-33%.

A previous study comparing the effects of lidocaine and dexmedetomidine on CRBD prevention found that lidocaine and dexmedetomidine reduce the frequency of CRBD in the early period but have no effect on the severity of CRBD (34). Another study comparing dexmedetomidine with ketamine reported that both agents had similar analgesic effects on CRBD, but dexmedetomidine was more acceptable regarding its side-effect profile (35). In this study comparing dexmedetomidine and tramadol, we found that the two drugs had similar efficacy. However, dexmedetomidine is more effective than tramadol in the first hour, suggesting that its antimuscarinic effect is more significant than tramadol in the early period. This may be related to dexmedetomidine's being a selective

**Table 1. Patients' demographic data**

| | Group T (n=45) | Group D (n=45) | Group C (n=45) | p-value |
|---|---|---|---|---|
| Age (year) (mean ± SD) | 44±9 | 40±12 | 40±12 | 0.241* |
| ASA I/II (n) | 17/28 | 16/29 | 18/27 | 0.910** |
| Stone size [median (IQR)] | 10 (8-12) | 10 (8-12) | 10 (9-12) | 0.460** |

*: Anova test; **: Kruskal-Wallis test
IQR: Interquartile range, SD: Standard deviation

M3 receptor inhibitor. Furthermore, we consider that the antimuscarinic effect of dexmedetomidine is prolonged, as suggested by other studies, although the half-life of dexmedetomidine after infusion for 60 min has been reported to be approximately 30 min (33,36).

At the first evaluation ($t_0$) in the PACU, there was no significant difference between the groups regarding CRBD severity and frequency. However, the incidence of CRBD was low in all the groups at $t_0$. This may be due to ongoing anesthetic activity in the first postoperative minutes, as seen in a recent study that compared tramadol and tapentadol, an opioid-derived analgesic (37).

The incidence of CRBD varies between 47% and 90% (1,7,11,13,17,22,38). In contrast, Binhas et al. (39) reported the incidence of CRBD as 47% in a study investigating the incidence and risk factors of CRBD in patients requiring intraoperative urinary catheterization under general anesthesia. However, in their study of patients who underwent percutaneous nephrolithotomy, Agarwal et al. (12) reported the incidence of CRBD as 92% in the control group at the postoperative 2nd hour. The incidence of CRBD was 40% in the control group at $t_1$ and $t_2$ in this study. The reason for the low incidence compared to the general literature may be the inclusion of only moderate and severe symptoms of CRBD.

The patients were also assessed for postoperative pain at the same intervals. Similar to the results reported in the literature, both agents were effective for postoperative analgesia. In this study, the patients' pain levels were not very high because the surgical procedure is less painful than invasive procedures such as percutaneous nephrolithotomy.

Although previous studies have reported tramadol-related side effects such as nausea (56%), vomiting (40%), and dexmedetomidine-related side effects such as dry mouth (3%), nausea (11%), and rarely, hypotension and bradycardia attacks, no side effects were observed in this study (18,22,23,32,33). This may be because the tramadol was diluted and administered as a slow infusion and the dexmedetomidine infusion was short because of the short operation time.

There is no consensus on the effect of dexmedetomidine on postoperative recovery time; the general opinion is that it prolongs recovery time (29,40-42). The recovery period was significantly longer in the dexmedetomidine group than in the other groups. However, since the recovery time was limited to a maximum of 20 min, we considered that it would not pose a problem regarding patient safety.

Tramadol and dexmedetomidine can easily be administered and prevent CRBD without any side effects, making them superior to other treatments. This study may help establish a common intraoperative approach to prevent CRBD early, especially in patients at risk of CRBD.

**Study Limitations**

Firstly, the administration of drugs was arranged according to the end time of the operation. However, the inability to accurately predict the end time of the operation limited our study. Therefore, it would be appropriate to record the duration of the surgery. Secondly, we evaluated

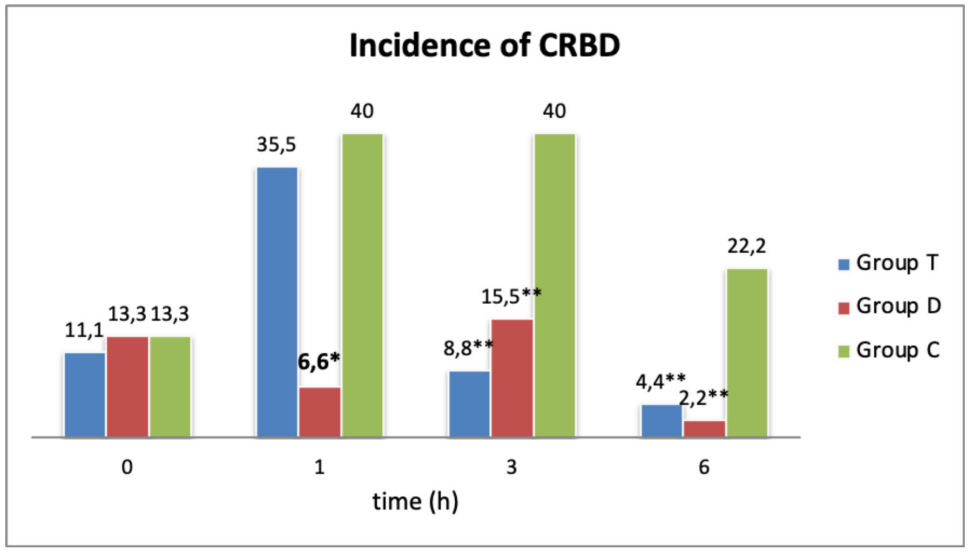


**Figure 2.** Incidence of CRBD. Dexmedetomidine is more effective in reducing the frequency of CRBD in the early period. Data are presented as n (%). Chi-square test; *p<0.001, for comparison between group D vs. groups T and C, **p<0.01, for comparison between groups T and D vs. group C and p>0.05 for comparison between group T vs. D

*CRBD: Catheter-related bladder discomfort*

| Table 2. Severity of CRBD | | | | | |
|---|---|---|---|---|---|
| | | $t_0$ | $t_1$ | $t_2$ | $t_3$ |
| Group T n (45) | **No** | 17 | 11 | 17 | 32 |
| | **Mild** | 23 | 18 | 24 | 11 |
| | **Moderate** | 4 | 11 | 4 | 2 |
| | **Severe** | 1 | 5 | 0 | 0 |
| Group D n (45) | **No** | 18 | 15 | 17 | 25 |
| | **Mild** | 21 | 27 | 21 | 19 |
| | **Moderate** | 4 | 2 | 7 | 1 |
| | **Severe** | 2 | 1 | 0 | 0 |
| Group C n (45) | **No** | 24 | 14 | 10 | 12 |
| | **Mild** | 15 | 13 | 17 | 23 |
| | **Moderate** | 4 | 9 | 14 | 8 |
| | **Severe** | 2 | 9 | 4 | 2 |
| p-value | * | 0.467 | **0.032** | **0.005** | **0.0001** |
| | ** | 0.972 | **0.015** | 0.708 | 0.168 |
| | a | 0.272 | 0.883 | **0.003** | **0.0001** |
| | β | 0.301 | 0.031 | **0.010** | **0.001** |

Dexmedetomidine and tramadol decrease the severity of CRBD
CRBD: Catheter-related bladder discomfort, $t_0$: 0 h, $t_1$: 1 h, $t_2$: 3 h, $t_3$: 6 h postoperatively
*: Kruskal-Wallis test for comparison between three groups
**: Mann-Whitney u test for in comparison between group T vs. D
a: Mann Whitney test for in comparison between group T v.s C
β: Mann-Whitney u test for in comparison between group D vs. C
Bold values denote statistical significance at the p<0.05 level

| Table 3. Patients' postoperative pain scores (NRS) and post-anesthesia recovery times | | | | |
|---|---|---|---|---|
| | **Group T** | **Group D** | **Group C** | **p-value** |
| $t_0$ | 10 (10-10) | 10 (10-10) | 10 (10-30) | **0.0001*** 0.848** |
| $t_1$ | 10 (10-30) | 10 (10-40) | 30 (10-50) | **0.005*** 0.365** |
| $t_2$ | 30 (10-40) | 20 (10-40) | 20 (10-40) | 0.910* |
| $t_3$ | 10 (10-20) | 10 (10-30) | 20 (10-30) | 0.491* |
| Recovery time (min) | 10 (10-15) | 15 (15-20) | 10 (10-15) | **0.0001**[a] 0.075** |

Dexmedetomidine may delay post-anesthesia recovery time
NRS: Numeric rating scale; $t_0$: 0 h, $t_1$: 1 h, $t_2$: 3 h, $t_3$:6 h postoperatively
NRS and recovery time expressed as median (Interquartile range)
*: Kruskal-Wallis test for comparison between groups T and D vs. group C
**: Mann-Whitney U test for comparison between groups T vs. D
a: Kruskal-Wallis test for comparison between group D vs. groups T and C

only the efficacy of tramadol and dexmedetomidine in preventing CRBD. The dose-response relationship and efficacy of the treatment were not evaluated. Finally, it was difficult for the patients to differentiate between postoperative surgical pain and CRBD. We considered that acetaminophen, which we used for postoperative analgesia, may have masked the CRBD symptoms, although its effect on relieving postoperative CRBD has not been reported.

## Conclusion

Intraoperative tramadol and dexmedetomidine administration are useful agents for the prevention and treatment of CRBD and postoperative analgesic activity. The effect of dexmedetomidine on CRBD is more potent than that of tramadol in the early period. However, dexmedetomidine may delay post-anesthesia recovery time.

### Ethics

**Ethics Committee Approval:** Ethical committee approval was obtained from University of Health Sciences Turkey, Diskapi Yildirim Beyazit Training and Research Hospital (date: 05.08.2019, approval number: 69/15).

**Informed Consent:** Written informed consent was obtained from all patients.

**Peer-reviewed:** Externally and internally peer-reviewed.

### Authorship Contributions

Concept: F.O.S., A.D., Design: F.O.S., A.D., Data Collection and/or Processing: F.K.A., O.Y.M., R.P., F.S., Analysis and/or Interpretation: F.O.S., F.K.A., Literature Research: O.Y.M., F.S., Writing: F.O.S., R.P., A.D.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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