Effects of tramadol on emergence agitation after general anesthesia for nasal surgery
A retrospective cohort study

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Abstract

Emergence agitation (EA) is common after nasal surgery. Strong opioids and N-methyl-D-aspartate (NMDA) receptor antagonists prevent EA. Tramadol also acts as an opioid receptor agonist and an NMDA receptor antagonist, but few studies have evaluated the effects of tramadol on EA. This retrospective study investigated whether tramadol is effective for reducing EA in adult patients undergoing nasal surgery.

Of 210 adult patients undergoing a nasal surgical procedure under general anesthesia, the medical records of 113 were analyzed retrospectively. The patients were divided into 2 groups: patients who received tramadol during the operation (tramadol group, n = 52) and patients who did not (control group, n = 61). The incidence of EA, recovery time, changes in hemodynamic parameters, postoperative pain scores, and adverse events were compared between the 2 groups.

The incidence of EA was higher in the control group than in the tramadol group (50.8% [31/61] vs 26.9% [14/52]; odds ratio 2.805; 95% confidence interval, 1.3 to 6.2; $P = .010$). Changes in systolic blood pressure in the 2 groups were similar, whereas changes in heart rate during emergence differed depending on the group ($P = .020$), although pairwise comparisons did not reveal any differences between the groups. Recovery time, postoperative pain scores, and adverse events were similar in the 2 groups.

In adult patients undergoing nasal surgery, tramadol infusion decreases the incidence of EA after sevoflurane anesthesia without delaying recovery or increasing the number of adverse events.

Abbreviations: ASA = American Society of Anesthesiologists, BIS = bispectral index, EA = emergence agitation, ENT = ear, nose, and throat, HR = heart rate, NMDA = N-methyl-D-aspartate, NRS = numerical rating scale, PACU = postanesthesia care unit, PAS = postanesthetic shivering, PONV = postoperative nausea and vomiting, RASS = Richmond Agitation-Sedation Scale, RSAS = Ricker Sedation-Agitation Scale, SBP = systolic blood pressure, TOF = train-of-four.

Keywords: emergence agitation, nasal surgical procedures, N-methyl-D-aspartate, tramadol

1. Introduction

Emergence agitation (EA) after nasal surgery is common,[1,2] which can lead to several problems, such as injury to the patient

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or medical staff, unplanned removal of a catheter or endotracheal tube, re-bleeding at the operation site, and delayed discharge.[3]

Various analgesics or sedatives have been introduced to prevent or treat EA.[4] Although EA disappears spontaneously as the patient recovers consciousness,[3] EA often requires additional nursing care and the administration of analgesics or sedatives.[4,5] Therefore, it is important to prevent EA by performing adequate postoperative pain control and eliminating risk factors for EA.[6] Drugs that have potent analgesic effects (fentanyl, remifentanil, and nefopam) or an analgesic effect with a sedative effect (ketamine and dexmedetomidine) help prevent EA after general anesthesia.[1,7–9] However, complete pain management does not guarantee the prevention of EA, as it can occur regardless of pain intensity.[10] Sedatives (propofol and benzodiazepine) have conflicting results in terms of EA according to the timing (premedication, at induction of anesthesia, or at the end of surgery) and manner (single bolus vs continuous infusion during anesthesia) of administration.[4,11] Because opioids have a respiratory depressant effect and sedatives may cause delayed recovery from anesthesia, careful observation after surgery is imperative.[4]

Tramadol is a synthetic opioid composed of a racemic mixture of (+) and (−) enantiomers that has analgesic efficacy for moderate to severe acute and chronic pain.[12] The racemate has better efficacy and fewer side effects than ether enantiomer alone, by the complementary action of the 2 enantiomers.[13] At clinically relevant dosages, tramadol also reduces the incidence of postoperative shivering, cough, and voiding urgency, without significant cardiovascular or respiratory adverse effects.[14–16]

In a recent comparative study of tramadol and dexmedetomidine in pediatric patients who underwent adenotonsillectomy,[17] the 2 led to comparable observational pain scores and pediatric anesthesia emergence delirium scores. The authors concluded that both drugs were effective for preventing EA. However, the 2 were not compared to a placebo in that study and the effects of the drugs on EA differed depending on the age of the subject (children vs adults), type of surgery, and timing and manner (single bolus vs continuous infusion) of drug administration. In 1 previous study, an intraoperative dexmedetomidine infusion (loading dose of 1 μg/kg, followed by a 0.1-μg/kg/h infusion) throughout the surgery reduced EA in children after ambulatory surgery under sevoflurane anesthesia,[18] whereas, in another study, adding a single dose of dexmedetomidine (1 μg/kg) to a remifentanil infusion at the end of the operation did not reduce EA compared to a remifentanil infusion alone in adults after orthognathic surgery.[19]

The effects of a single dose (2 mg/kg) of tramadol on EA in adult patients after nasal surgery have not been evaluated. Therefore, the present study investigated whether intraoperative tramadol administration would reduce the incidence of EA in adult patients undergoing nasal surgery under general anesthesia.

2. Materials and methods

This study was approved by the institutional review board of Konyang University Hospital, Daejeon, Korea (permit number KYUH 2018-04-006), and registered at the Korea Clinical Research Information Service (http://cris.nih.go.kr; permit number, KCT 0003327). Informed consent was waived due to the retrospective nature of the study. We retrospectively reviewed the medical records of patients who underwent elective nasal surgery under general anesthesia in our hospital between June 2017 and December 2017. Two anesthesiologists were in charge of anesthesia for the ear, nose, and throat (ENT) surgeries. Both anesthesiologists performed anesthesia using the same anesthetic agents, patient monitoring, and extubation criteria, according to our institutional protocol. However, 1 administered tramadol at the beginning of the operation for postoperative pain relief, and the other did not. Consequently, the patients were divided into 2 groups according to the use (tramadol group, $n=52$) or not (control group, $n=61$) of an intraoperative intravenous tramadol infusion. Exclusion criteria were age <19 or >65 years old, American Society of Anesthesiologists (ASA) physical status classification ≥ 3, combined surgery (e.g., nasal surgery and adenotonsillectomy), neuromuscular disorder, neuropsychological disorder, or cognitive disorder.

All patients received the same anesthetic technique except tramadol, and routine monitoring was applied, including electrocardiogram, noninvasive blood pressure (NIBP), pulse oximetry, bispectral index (BIS), end-tidal carbon dioxide (EtCO$_2$), and neuromuscular train-of-four (TOF). Premedication was not administered. General anesthesia was induced with 2 mg/kg intravenous propofol, and then endotracheal intubation was facilitated with 0.6 mg/kg rocuronium. After intubation, the patients were ventilated mechanically to maintain EtCO$_2$ of 30 to 40 mmHg. At the beginning of the operation, patients in the tramadol group received intravenous tramadol slowly over 1 to 3 minutes, whereas patients in the control group did not. Anesthesia was maintained during surgery with an oxygen/nitrous oxide mixture (60:40) and sevoflurane was adjusted to keep the BIS at 40 to 60. At the end of the nasal surgery, nasal packing and dressing were applied by the ENT resident, the

sevoflurane and nitrous oxide were turned off, and the patients were ventilated manually with 100% oxygen at 6 L/min. Sugammadex (Bridion, MSD, Seoul, Korea; 2 or 4 mg/kg) was injected to reverse the neuromuscular blockade using TOF stimulation on the adductor pollicis muscle. Extubation was performed after confirming spontaneous respiration (respiratory rate >12/min, tidal volume >5 mL/kg), TOF ratio ≥ 0.9, BIS >80, and response to verbal commands.

2.1. Measurements

In our hospital, since November 2015, the attending anesthetist (nurse) routinely evaluates EA during emergence and records it on the electronic medical record. Until 2016, the Richmond Agitation-Sedation Scale (RASS, 10-point scale) was used for this EA evaluation,[1] but since 2017 the Ricker Sedation-Agitation Scale (RSAS, 7-point scale; 1=unarousable, 2=very sedated, 3=sedated, 4=calm and cooperative, 5=agitated and calm to verbal instructions, 6=very agitated requiring restraint, 7=pulling at tracheal tube, trying to remove catheters, or striking the staff) has been used.[20] The main reason for changing the assessment tool was that the RSAS allows the evaluator to evaluate EA more quickly and easily because there are fewer evaluation items compared to the RASS.

Emergence was defined as the interval between turning off the inhalation anesthetics (sevoflurane and nitrous oxide) and 5 minutes after extubation. Each patient's peak RSAS score was recorded during emergence. EA was defined as RSAS ≥ 5 during emergence. The intervals between turning off the inhalation anesthetic and the first awakening response, verbal response, and extubation were analyzed. Hemodynamic parameters (systolic blood pressure [SBP] and heart rate [HR]) at different time points (before anesthesia, the end of surgery, extubation, and 5 minutes after extubation) were also collected and analyzed.

All patients were transferred to the post-anesthetic care unit (PACU). In the PACU, NIBP, HR, and oxygen saturation were monitored. Postoperative pain was evaluated using an 11-point numerical rating scale (NRS, 0=no pain, 10=worst pain imaginable). If patients complained of pain and required analgesics or if the NRS score was ≥ 5, fentanyl (0.5–1 μg/kg) was injected at the discretion of the attending anesthesiologist. If the patient had nausea or vomiting, 10 mg metoclopramide was administered intravenously. All adverse events recorded in the electronic medical chart were analyzed.

2.2. Statistical analyses

The primary endpoint was the incidence of EA, which was 54% in a previous study conducted in patients undergoing nasal surgery.[1] Assuming that a 50% reduction in the incidence of EA would be clinically relevant, a sample size of 51 patients in each group was calculated with a power of 0.8 and α-value of 0.05 (2-sided).

Data were analyzed using SPSS software (ver. 18.0 for Windows; SPSS Inc., Chicago, IL). The normality of the distribution of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables were analyzed using Student t test or the Mann–Whitney U test and are expressed as mean±standard deviation or median (interquartile range), as appropriate. Categorical variables such as sex, ASA physical status classification, incidence of EA, number of patients who received analgesics in the PACU, and adverse events were analyzed using the χ^2 or Fisher exact test and are expressed as
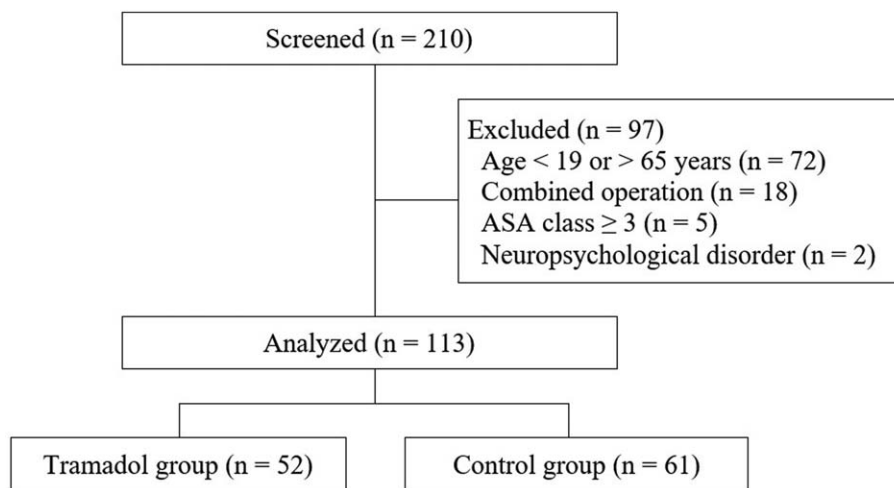
Figure 1. Flow diagram. ASA = American Society of Anesthesiologists.

number (%) or number, as appropriate. Type of surgery and RSAS were analyzed using the χ^2 test for trends (linear-by-linear association) and are expressed as numbers. Changes in SBP and HR were analyzed using repeated-measures analysis of variance, followed by a t test with the Bonferroni correction. A P value <.05 was considered significant.

3. Results

In total, 210 patients underwent nasal surgery between June 2017 and December 2017. Among them, 97 patients were excluded: 72 were <19 or >65 years of age, 18 received a combined operation, 5 were ASA physical status classification ≥ 3, and 2 had a history of a neuropsychological disorder. Consequently, 113 patients were included in the final analysis (tramadol group = 52, control group = 61) (Fig. 1). The patient and operative characteristics of the 2 groups were similar (Table 1).

The RSAS during emergence differed significantly between the 2 groups (P = .014). The incidence of EA was significantly higher in the control group than in the tramadol group (50.8% [31/61] vs 26.9% [14/52], respectively; odds ratio 2.805; 95% confidence interval, 1.3–6.2; P = .010) (Table 2). Differences in time of

recovery from discontinuing the inhalation anesthetic to the first awakening response, verbal response, and extubation were not significant between the 2 groups (Table 2). The postoperative NRS pain score and number of patients who required rescue analgesics or antiemetics in the PACU were similar between the 2 groups (Table 2).

Changes in SBP in the 2 groups were similar, whereas changes in HR over time differed significantly between the groups overall (P = .020); however, pairwise comparisons at each time point revealed no differences between the 2 groups (Fig. 2).

The adverse events recorded are listed in Table 3 and did not differ between the groups.

4. Discussion

Administering tramadol intraoperatively was effective for reducing the incidence of EA without delaying recovery or increasing the frequency of adverse events after sevoflurane anesthesia in adult patients undergoing nasal surgery. However, administering the tramadol infusion at the beginning of nasal

Table 1

Demographic and operative characteristics.

	Tramadol group (n=52)	Control group (n=61)	P
Age, yr	42.7±13.8	42.1±14.1	.817
Sex, male/female	31/21	43/18	.225
Height, cm	165.2±8.5	166.4±8.3	.452
Weight, kg	67.6±11.8	68.8±12.3	.619
ASA, I/II	20/32	28/33	.425
Type of surgery			.214
Septoplasty	4 (7.7%)	5 (8.2%)	
ESS	14 (17.9%)	25 (41.0%)	
Septoplasty+ESS	34 (65.4%)	31 (50.8%)	
Duration of anesthesia, min	73.5 (61.0–92.3)	69.0 (60.5–97.0)	.481
Duration of surgery, min	49.5 (36.0–69.5)	45.0 (35.0–61.5)	.443
Intraoperative fluids, mL	225 (150–300)	200 (150–250)	.156

Data are mean±standard deviation, median (interquartile range), number or number of patients (%).
ASA = American Society of Anesthesiologists physical status classification; ESS = endoscopic sinus surgery.

Table 2

Recovery data.

	Tramadol group (n=52)	Control group (n=61)	P
RSAS (3/4/5/6/7)	8/30/5/7/2	1/29/16/11/4	.014*
Emergence agitation	14 (26.9%)	31 (50.8%)	.010†
Time to first awakening response, min	5.6±2.5	5.1±2.9	.346‡
Time to verbal response, min	7.9±2.7	7.3±3.0	.259‡
Time to extubation, min	9.5±2.6	9.2±3.0	.527‡
In PACU			
NRS for pain	3 (2.0–5.0)	3 (2.5–5.0)	.639§
Analgesics	17 (32.7%)	19 (31.1%)	.861†
Antiemetics	1 (1.9%)	3 (4.8%)	.624‖

Data are mean±standard deviation, median (interquartile range), number or number (%). RSAS = Ricker sedation-agitation scale, NRS = numerical rating scale (0 = no sense of pain, 10 = worst imaginable sense of pain).
* χ^2 test for trends (linear-by-linear association).
† χ^2 test.
‡ Student's t test.
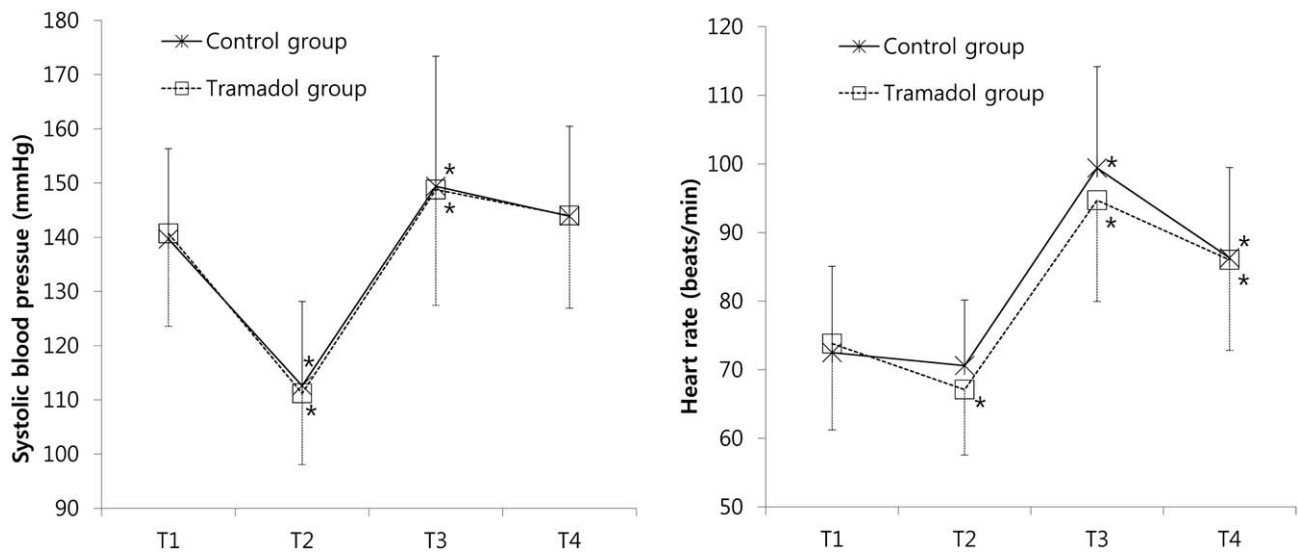§ Mann–Whitney U test, ‖ Fisher's exact test.

Figure 2. Changes in systolic blood pressure and heart rate. Values are presented as mean ± standard deviation. $^{*}P < .05$ compared to baseline in each group (Bonferroni corrected). T1 = before induction of anesthesia (baseline), T2 = at the completion of surgery, T3 = at extubation, T4 = 5 minutes after extubation.

surgery did not decrease the postoperative NRS pain score or the requirement for analgesics in the PACU.

The precise etiology of EA has not been identified, but multiple pathophysiological abnormalities in dopaminergic, noradrenergic, serotonergic, and γ-aminobutyric acid pathways have been suggested to be associated with the etiology of agitation.[21] Many factors affect the incidence of EA. Although some inconsistent results have been reported, factors that increase EA include younger (18–39 years) or older (≥65 years) age, male sex, use of an inhalation anesthetic with a low blood/gas partition coefficient (e.g., sevoflurane and desflurane), oral cavity and ENT surgery, longer-duration operation, postoperative pain, postoperative nausea, and vomiting (PONV), the presence of a tracheal tube, the presence of a urinary catheter or gastric tube, and voiding urgency.[2,4,6,11] The use of potent opioids (fentanyl or remifentanil), non-narcotic analgesics (nefopam), local anesthetics (lidocaine), N-methyl-D-aspartate (NMDA) receptor antagonists (magnesium sulfate and ketamine), α2-aderenoreceptor agonists (clonidine and dexmedetomidine) generally prevents EA.[1,4,7–9,22]

This study included several risk factors that may increase EA, such as the use of sevoflurane, nasal surgery, and the presence of a tracheal tube during the EA assessment period. Although

sevoflurane and desflurane are well-known risk factors for EA,[4] sevoflurane resulted in a higher rate of EA in adults in a comparative study with desflurane.[23] Moreover, sevoflurane anesthesia increases the risk for EA by more than 2-fold after nasal surgery compared to total intravenous anesthesia.[2] Clinically silent sevoflurane-induced epileptogenic activity has been suggested to be a cause of EA after sevoflurane anesthesia.[22] Nasal surgery is significantly associated with a higher incidence of EA compared to other types of surgery,[6] but the cause is unclear. In 2 previous studies, the postoperative pain was not intense; the median NRS pain score assessed in the PACU was only 2 points in patients undergoing nasal surgery;[1,24] our results are similar. Those 2 studies also reported a reduced incidence of EA by infusing experimental drugs, such as dexmedetomidine and nefopam, and the incidences of PONV in the control groups were not higher than those of the experimental groups.[1,24] A sense of suffocation due to nasal packing was suspected to be the cause of the increased incidence of EA in those studies. However, in another retrospective study of 792 adult patients who underwent nasal surgery, nasal packing was not a risk factor for EA.[2] By contrast, the presence of a tracheal tube is a consistent and strong risk factor for EA in adults.[2,3,6]

Tramadol is an atypical centrally acting opioid that acts on multiple receptors and exhibits various effects. It non-selectively activates μ-, κ-, and δ-opioid receptors as an opioid agonist, and acts as a norepinephrine-serotonin reuptake inhibitor at monoamine receptor sites.[25,26] Furthermore, it inhibits the NMDA receptor, M1 and M3 muscarinic acetylcholine receptors, and nicotinic acetylcholine receptors.[15,16] The analgesic potency of intravenous tramadol is approximately 1-tenth that of morphine.[26] The analgesic effect of tramadol results from activation of the μ-opioid receptor and inhibition of serotonin and noradrenaline reuptake.[17] Although postoperative pain is an important risk factor for EA,[6,8] it is difficult to explain the ability of tramadol to reduce EA through an analgesic effect alone because postoperative pain was not severe in either group in our study.

Ketamine, magnesium sulfate, and nefopam show efficacy in preventing postanesthetic shivering (PAS)[14,27] and EA regard-

Table 3

Adverse events.

	Tramadol group (n=52)	Control group (n=61)	P*
Headache	5 (9.6%)	2 (3.3%)	.245
Dizziness	4 (7.7%)	2 (3.3%)	.411
Nausea	1 (1.9%)	3 (4.8%)	.624
Vomiting	0 (0%)	0 (0%)	NA
Confusion	1 (1.9%)	0 (0%)	>.999
Residual sedation	0 (0%)	1 (1.6%)	>.999
Dry mouth	0 (0%)	0 (0%)	NA
Shivering	0 (0%)	0 (0%)	NA

Data are numbers (%). NA = not applicable.
* Fisher's exact test.

less of their analgesic potency.[1,4,9,22] Tramadol also suppresses the severity and incidence of PAS.[14] All of these drugs antagonize the NMDA receptor. PAS is associated with increased intraocular and intracranial pressure as well as increased metabolic rate;[27] thus, it may lead to discomfort during recovery from anesthesia. These results imply that the EA-reducing effects of tramadol may be mediated, in part, by the NMDA receptor. In addition, tramadol markedly suppresses the cough response and improves emergence quality.[15] The authors speculated that the antitussive effects of tramadol may be caused by multiple actions at NMDA, opioidergic, serotonergic, and muscarinic receptors. Furthermore, tramadol has a preventive effect on catheter-related bladder discomfort, or voiding urgency, by acting as an M1 and M3 muscarinic acetylcholine receptor antagonist;[16] voiding urgency and suprapubic discomfort due to voiding urgency may potentiate EA. Thus, we speculate that various positive effects of tramadol, such as postoperative pain relief, cough suppression, reduction of PAS, and reduction of voiding urgency, may contribute to preventing EA.

Optimal doses and the timing of administration are important to reduce side effects while achieving the desired effects of tramadol. The efficacy and adverse events related to tramadol are dose-related in a dose-response fashion.[13] Intravenous 1 to 2 mg/kg tramadol successfully reduces PAS, catheter-related bladder discomfort, and cough during recovery from anesthesia.[15,16,28] Intravenous administration of 3 mg/kg tramadol has been suggested to be the most appropriate dose for acute pain control of moderate to severe intensity with minimal adverse effects in adult patients.[13] However, considering the postoperative NRS pain scores in this study and previous studies,[1,8,24] postoperative pain after nasal surgery is mild, so routine administration of 3 mg/kg tramadol seems unnecessary to prevent postoperative pain. On the other hand, our results on EA suggest that the administration of 2 mg/kg tramadol is of value in patients undergoing nasal surgery, especially those with risk factors for EA because EA itself may cause serious problems as well as dissatisfaction among patients, caregivers, and medical staff.[3,6,17,18]

Although the optimal timing of tramadol administration to reduce the incidence of EA has not yet been determined, 30 minutes before the end of the operation seems most appropriate considering the onset of action (within 10 minutes), time to peak effect (about 30 minutes), and action duration (2–4 hours) of tramadol.[16,26] However, in our study, tramadol was administered at the beginning of surgery based on the short operation time (median, 49.5 minutes in the tramadol group and 45 minutes in the control group) because it was difficult for the anesthesiologist to accurately predict the point 30 minutes before the end of the operation. In addition, it was administered slowly over several minutes to prevent side effects, such as hypotension caused by peripheral vasodilation due to a rapid bolus injection.[13,26] SBP and HR did not differ between the 2 groups as measured before induction of anesthesia, at the end of surgery, at extubation, and 5 minutes after extubation (Fig. 2). At the end of the operation and particularly during extubation, the somewhat higher HR in the control group may have reflected elevated sympathetic tone due to the higher incidence of agitation in the control group compared to the tramadol group, rather than a direct effect of tramadol on HR in the tramadol group. Parenteral administration of tramadol has no clinically significant disturbing effect on HR or blood pressure.[12,15,17]

This study has some limitations due to its retrospective nature and the pharmacological properties of tramadol. First, although the effects of tramadol in reducing cough, PAS, and voiding urgency have been surmised to contribute to tramadol's preventive effects on EA, these effects have not been fully evaluated by close observations and direct or indirect questioning methods in this study. In addition, cough, PAS, and voiding urgency are easily overlooked side effects that occur during emergence. Future prospective studies should evaluate the correlation between EA and these factors. Second, tramadol was initially administered at a dose of 2 mg/kg for postoperative pain relief, not for preventing EA. Therefore, it is necessary to investigate the most appropriate dose to alleviate EA in the future. Finally, tramadol acts on a variety of receptors and thus interacts with other drugs, such as serotonin antagonists (ondansetron), opioid antagonists (naloxone), monoamine oxidase inhibitors, and α_2-aderenoreceptor antagonists.[25] The effects of tramadol on EA are unclear in such cases.

In conclusion, administration of 2 mg/kg tramadol intravenously at the beginning of surgery was effective for decreasing the incidence of EA in adult patients undergoing nasal surgery with sevoflurane anesthesia and did not delay recovery or increase the incidence of adverse events.

Author contributions

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