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Author Contributions

Sung-Ae Cho (Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing)

So-min Ahn (Data curation; Formal analysis)

Woojin Kwon (Formal analysis; Data curation ; Writing – review & editing)

Tae-Yun Sung (Conceptualization; Supervision; Formal analysis; Writing – review & editing)

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Abstract

Background: Remimazolam is an ultrashort-acting benzodiazepine. Few studies have evaluated the effects of remimazolam-based total intravenous anesthesia (TIVA) on emergence agitation (EA). This study aimed to compare the incidence and severity of EA between TIVA using remimazolam and desflurane.

Methods: This prospective randomized controlled study enrolled 76 patients who underwent nasal surgery under general anesthesia. Patients were randomized into two groups of 38 each: desflurane-nitrous oxide (N_2O) (DN) and remimazolam-remifentanil (RR) groups. The same protocol was used for each group from induction to emergence, except for the use of different anesthetics during maintenance of anesthesia according to the assigned group: desflurane and nitrous oxide for the DN group and remimazolam and remifentanil for the RR group. The incidence of EA as the primary outcome was evaluated using three scales: Ricker Sedation-Agitation Scale, Richmond Agitation-Sedation Scale, and Aono's four-point agitation scale. Additionally, hemodynamic changes during emergence and postoperative sense of suffocation were compared.

Results: The incidence of EA was significantly lower in the RR group than in the DN group in all three types of EA assessment scales (all $P < 0.001$). During emergence, the change in heart rate differed between the two groups ($P = 0.002$). The sense of suffocation was lower in the RR group than in the DN group ($P = 0.027$).

Conclusions: RR reduced the incidence and severity of EA in patients undergoing nasal surgery under general anesthesia. In addition, RR was favorable for managing hemodynamics and postoperative sense of suffocation.

Keywords: Desflurane; Emergence agitation; General anesthesia; Intravenous anesthesia; Nasal surgery; Remimazolam.

Introduction

General anesthesia for otolaryngological surgery is frequently accompanied by agitation on awakening during recovery. In particular, nasal packing to prevent bleeding at the surgical site induces suffocation, often accompanied by intense excitement on awakening [1–3]. Excessive emergence agitation (EA) from anesthesia can cause serious problems, such as reoperation due to bleeding from the surgical site, fall from the operating bed, unintentional extubation of the endotracheal tube, and injury to the patient or medical staff [4].

In addition to the type of surgery, the type of anesthesia method (inhalational anesthesia or total intravenous anesthesia [TIVA]) and the timing and method of drug administration (bolus or continuous infusion) also affect EA [5–8]. Inhalational anesthetics with low blood/gas partition coefficients (desflurane and sevoflurane) are preferred general anesthetics because of their short wake-up time [9]. Of these, desflurane reduced the incidence of EA in adult patients undergoing orthognathic surgery compared with sevoflurane [9]. As an adjunct commonly used together with other inhalational anesthetics, the effect of nitrous oxide (N_2O) on EA varies depending on the study; however, it has been reported to be unrelated to EA or to attenuate EA [4]. Remimazolam is a novel ultrashort-acting benzodiazepine [10]. Remimazolam can be used as a component of TIVA for general anesthesia and is often used in combination with remifentanil. In a previous study, TIVA using propofol-remifentanil reduced EA in patients undergoing nasal surgery compared with the volatile induction and maintenance of anesthesia using sevoflurane and N_2O [11]. However, few studies have evaluated the effect of continuous infusion of remimazolam-remifentanil (RR) on EA as an anesthetic maintenance method [12].

We hypothesized that the effect of anesthesia maintenance through continuous intravenous administration of RR on EA would differ from that using desflurane-N_2O (DN). Therefore, this study aimed to compare the incidence and severity of EA between RR and DN as anesthesia maintenance

agents in adult patients undergoing nasal surgery.

Materials and methods

This prospective randomized controlled study was conducted after being approved by the Institutional Review Board (IRB) of Konyang university hospital (KYUH 2021-08-008) and registered in the Korean Clinical Research Information Service (https://cris.nih.go.kr/; KCT0006528). This study followed the Consolidated Standards of Reporting Trials guidelines, and written informed consent was obtained from each participant and/or legal surrogate before the study was conducted. The study was conducted at a university hospital between August 2021 and June 2023.

Patients aged 19–65 years who underwent elective nasal surgery under general anesthesia with an American Society of Anesthesiologists (ASA) Physical Status I–II were included in this study. The exclusion criteria were as follows: emergency surgery; hemodynamic instability or respiratory failure; contraindications to the use of remimazolam (hypersensitivity to benzodiazepine drugs, glaucoma, alcohol or drug dependence, sleep apnea syndrome, renal failure, or liver failure); psychiatric history; and cognitive impairment.

All patients were randomly allocated to one of the two groups in a 1:1 ratio using online randomization software (Researcher Randomizer; www.randomizer.org). One was the group that used desflurane and N_2O (DN group), and the other used remimazolam and remifentanil (RR group) for the maintenance of general anesthesia.

Without premedication, the patients were allowed to enter the operating room after fasting for at least 8 h. With monitoring for electrocardiogram, non-invasive blood pressure, pulse oximetry, neuromuscular monitor with acceleromyography, and body temperature, anesthesia was induced with propofol (2 mg/kg) and fentanyl (0.5–1 μg/kg), followed by intubation after injecting rocuronium. Mechanical ventilation was used in the volume-controlled mode at a tidal volume of 8 ml/kg and a respiratory rate of 12 breaths/min. Anesthesia in the DN group was maintained with 3–8 vol% end-tidal concentrations of desflurane and 50% N_2O to maintain a bispectral index (BIS) of 40–60. In the

RR group, anesthesia was maintained with remimazolam 1–2 mg/kg/h with an effect-site concentration of remifentanil 2–4 ng/ml (Minto model) to maintain a BIS of 40–60 and systolic blood pressure within 80–120% of the preoperative value. The hemodynamic parameters were maintained during surgery using the same protocol in both groups. All patients underwent surgery in the supine position during the entire period of anesthesia, and they got the same regimen of patient-controlled analgesia for postoperative pain control. When intranasal packing was performed at the end of the surgery, administration of the anesthetic agent for maintenance was stopped, and the intravenous line connected to the anesthetic agent was flushed to remove the remnant agent in the intravenous line. The neuromuscular block was reversed with 2 mg/kg or 4 mg/kg sugammadex owing to neuromuscular function monitoring. Extubation was conducted after confirming BIS > 80, tidal volume ≥ 5 ml/kg, spontaneous respiratory rate 10–25/min, train of four ratio ≥ 0.9, and response to verbal commands. When there was no awakening 30 min after the end of anesthetic administration, a flumazenil 0.2 mg injection was planned. After extubation, all patients were transferred to the post-anesthesia care unit (PACU).

Measurements

EA was assessed using three types of EA assessment tools (i.e., Ricker Sedation-Agitation Scale [RSAS], Richmond Agitation-Sedation Scale [RASS], Aono's four-point agitation scale [AFPS]; Table 1) during the emergence period (the time interval between the discontinuation of all anesthetics administered and 5 min after extubation) by the attending anesthesiologists, and the highest score during the emergence period was recorded [1–3,9,11]. When the patient was observed with RSAS ≥ 5, RASS ≥ 2, and AFPS ≥ 3, it was considered to reflect EA and was recorded as an incidence of EA that was the primary endpoint of this study. Additionally, RSAS = 7, RASS ≥ 3, and AFPS = 4 were considered severe EA. During the emergence period, the time to spontaneous respiration, time to first awakening response, time to extubation from turning off anesthetics, and nasal bleeding grade (three

scales; 0 = no bleeding; 1 = dressing staining; 2 = persistent oozing or bleeding requiring repeat nasal packing) were recorded.

Variables related to hemodynamic parameters, including systolic blood pressure and heart rate, were collected before the induction of anesthesia (baseline), when turning off the anesthetic, at extubation, 2 min after extubation, and 5 min after extubation.

In the PACU, ~~the patients assessed~~ postoperative pain and sense of suffocation were assessed using a numerical rating scale (NRS, 11 points; 0 = no pain/no sense of suffocation, 10 = worst pain imaginable/worst sense of suffocation imaginable) based on the amount of analgesics and antiemetics used. All adverse events were analyzed.

Statistical analysis

In a preliminary study, the incidence of EA as the primary outcome was 85.7% in the DN group (n = 14) and 50% in the RR group (n = 14). With a power of 0.9 and a two-sided α-value of 0.05, 34 patients per group were required. Considering a dropout rate of 10%, 38 patients were enrolled in this study. The SPSS® Statistics software (ver. 27.0 for IBM Corp., Armonk, NY, USA) was used for the statistical analyses. Student's *t*-test or the Mann–Whitney *U* test was used to analyze continuous variables depending on the Kolmogorov–Smirnov normality test results. The χ^2 test, χ^2 test for trends (linear-by-linear association), or Fisher's exact test was used for analyzing categorical variables. After confirming the normality and Mauchly's sphericity results, repeated-measures analysis of variance was used to analyze the changes in systolic blood pressure and heart rate, followed by a t-test with Bonferroni correction. $P < 0.05$ was considered significant.

Results

A total of 88 patients were screened in the study. Among them, 12 patients were excluded owing to psychiatric medication (nine patients), hemodynamic instability (two patients), or emergency surgery (one patient). Finally, 76 patients (38 per group) were included in the analysis (Fig. 1).

Patient characteristics and intraoperative data are presented in Table 2. The variables in Table 2 were comparable between the two groups.

The recovery data and incidence of EA during the emergence period are presented in Tables 3 and 4. The incidence of EA as a primary outcome was significantly higher in the DN group than in the RR group in all three types of EA assessment scales: 84.2% vs. 44.7% by RSAS (relative risk 2.9; 95% CI for relative risk 1.4 to 6.1; effect size $h = 0.647$; $P < 0.001$), 65.8% vs. 21.1% by RASS (relative risk 2.5; 95% CI for relative risk 1.5 to 4.1; effect size $h = 0.938$; $P < 0.001$), and 63.2% vs. 21.1% by AFPS (relative risk 2.4; 95% CI for relative risk 1.5 to 3.8; effect size $h = 0.883$; $P < 0.001$). The incidence of severe agitation was also significantly higher in the DN group than in the RR group, with RSAS (28.9% vs. 5.3%; relative risk 2.0; 95% CI for relative risk 1.4 to 2.9; effect size $h = 0.671$; $P = 0.012$) and RASS (42.1% vs. 5.3%; relative risk 2.3; 95% CI for relative risk 1.6 to 3.4; effect size $h = 0.948$; $P < 0.001$). The times to spontaneous respiration, first awakening, and extubation were significantly longer in the RR group than in the DN group (all $P < 0.001$). The changes in systolic blood pressure and heart rate are shown in Fig. 2. The change in systolic blood pressure was comparable between the two groups; however, the change in heart rate differed between the two groups ($P = 0.002$), and heart rate at extubation and 2 min after extubation were significantly higher in the DN group than in the RR group ($P = 0.012$ and 0.036, respectively).

Postoperative data and adverse events are presented in Table 5. All variables other than the NRS for suffocation did not differ between the groups. The NRS score for suffocation was higher in the DN group than in the RR group ($P = 0.027$).

Discussion

The incidence of EA and severe EA after general anesthesia for nasal surgery were significantly lower in patients receiving RR anesthesia than in those receiving DN anesthesia. In addition to EA, RR showed hemodynamic stability on awakening and reduced the degree of suffocation after awakening compared to DN.

Nasal surgery causes a sense of suffocation due to intranasal packing after surgery and is accompanied by EA with various incidences [1–3]. The results of this study confirmed that EA occurred less frequently with RR than with DN through all three different assessment tools for EA evaluation in adults undergoing nasal surgery. To the best of our knowledge, this is the first study to suggest that RR, as a maintenance anesthetic agent, helps prevent EA. Additionally, the results of this study are more meaningful in that they were confirmed by applying all three representative EA assessment tools. To date, there is no single evaluation tool validated as an EA evaluation scale in the operating room or PACU, and the incidence of EA may vary significantly depending on the evaluation tool [4]. As a result, there was a possibility of drawing different conclusions depending on the assessment tool used. However, in this study, we attempted to increase the reliability of the research results by applying all three evaluation tools commonly used for EA evaluation.

EA shows different results depending on the timing of injection (preoperative or end of surgery) and method of administration (bolus or infusion), even for the same drug [6–8]. In addition, there are differing opinions regarding whether the method of anesthesia affects EA [11,13–15]. Our study differs from previous studies as it is the first to compare RR and inhalational anesthetics. Additionally, in a recently published study comparing propofol and remimazolam in hip surgery for older adult patients, remimazolam-sufentanil showed a lower incidence of EA than propofol-sufentanil, and positive effects can be expected when applied to patients undergoing nasal surgery in the future [16].

According to previous studies on benzodiazepines, midazolam premedication via bolus injection increased EA; however, continuous infusion during nasal surgery reduced EA, similar to dexmedetomidine infusion [4,17]. Midazolam pretreatment was ineffective against EA owing to its short half-life, but there are reports that a bolus of midazolam administered before ophthalmic surgery in pediatric patients helped with EA [17]. Therefore, in addition to the pharmacological properties of midazolam itself, different patient groups (pediatrics vs. adults), type of surgery, and administration time may have affected thed results of previous studies. Moreover, the mechanism by which remimazolam, a recently approved benzodiazepine, reduces EA has not been precisely elucidated. Remimazolam is an ultrashort-acting benzodiazepine that rapidly offsets sedation through rapid biotransformation and elimination and is structurally similar to midazolam; however, it has a side chain with an ester bond attached to the diazepine ring and is quickly hydrolyzed in the liver. Unlike alpha-hydrocyclidazolam, a midazolam metabolite, remimazolam metabolites show only 1/400 of its potency [18,19]. Therefore, no active metabolites remained on awakening. Despite these characteristics, the awakening time of remimazolam is longer than that of propofol and inhalational anesthetics [120,21]. In contrast, desflurane is a representative inhalational anesthetic with rapid emergence from general anesthesia so that patients do not have enough time to recognize their current situation, such as unfamiliar environments, surgical pain, or discomfort in the tracheal tube [20]. According to our results, recovery time, including the time to spontaneous respiration, first awakening time, and extubation, was significantly longer in the RR group than in the DN group. The etiology of EA is multifactorial [4], and although delayed emergence does not necessarily decrease EA [9], the results of our study suggest that delayed emergence may have partially contributed to the decrease in EA and are supported by studies that have suggested rapid emergence as a risk factor for EA [22,23]. Additionally, inhalational anesthetics are more vulnerable to postoperative nausea and vomiting than TIVA that can cause agitation [4,24]. Although our results did not show a difference in nausea, these

characteristics may have affected the difference in EA between the two agents.

As postoperative pain is also a significant risk factor for EA, continuous IV remifentanil administration in the RR group may have partially contributed to the reduction in EA. However, balanced anesthesia using remifentanil and inhalational anesthetic showed no difference in EA incidence or even increased EA compared to inhalational anesthesia alone [25,26]. In our study, the results related to postoperative pain did not differ between the two groups. Therefore, it is difficult to explain the difference in the incidence of EA between the two groups solely on the analgesic effect of remifentanil.

Additionally, several emergence profiles of remimazolam were simultaneously confirmed. There was a difference of 2 min until the first appearance of spontaneous breathing, 3 min until the first awakening, and 4 min until extubation in the current study; however, this showed a similar or slightly slower recovery than in the previous study [12]. However, in previous studies, flumazenil was used to awaken all the patients. Therefore, if flumazenil had been used in all patients in this study, awakening would have been faster than the current results. However, flumazenil may affect the incidence of EA; thus, further studies on the use of flumazenil are needed. Nevertheless, in this study, considering that extubation was possible within 10 min on an average (there were no patients with delayed emergence for more than 30 min), we consider that remimazolam can be without causing significant delayed emergence in actual clinical practice.

Previous studies have also confirmed the hemodynamic stability of remimazolam, such as reduced post-induction hypotension; however, hemodynamic stability during emergence has not been confirmed [12]. In this study, remimazolam showed significant hemodynamic stability on awakening compared with desflurane; in particular, the heart rate was stable, possibly because of less increase in sympathetic tone in the RR group during emergence because of decreased EA. Lower EA and stimulation for suffocation in the RR group may be due to the slower emergence time of remimazolam

than that of desflurane. They may have been caused by remimazolam that can potentiate the analgesic effect of remifentanil [27]. In contrast, the possibility of drowsiness after emergence, with or without flumazenil, has been occasionally reported when using remimazolam [12]. Although the definition of awakening may have been met according to the study criteria, re-sedation or drowsiness may have occurred because this study did not define re-sedation, and there is no clear definition of re-sedation [28]. Therefore, caution against re-sedation is necessary when using remimazolam.

This study had some limitations. First, in the RR group, remifentanil was also used to maintain anesthesia. Therefore, it is difficult to determine which drug, remimazolam or remifentanil, contributed more to EA reduction in the RR group. However, given the short context-sensitive half-life of remifentanil and the inconsistent results of remifentanil on EA in previous studies [4,25,26], the reduction of EA in this study may have been mainly due to the continuous intravenous administration of remimazolam. Second, as this study was conducted for evaluating EA until 5 min after extubation, the period of assessment for EA may affect the incidence of EA. Thirdly, although the depth of anesthesia was controlled by applying the same BIS target value in both groups in this study, intraoperative nociception monitoring was not applied. Therefore, differences in the level of nociception between the two groups cannot be ruled out that may have influenced the results of this study. Lastly, because this study was conducted in healthy adults, further studies in pediatric or older adult patients are needed. Remimazolam might be a useful drug for older people owing to its hemodynamic stability and free metabolism in the kidney and liver.

In conclusion, as an anesthetic maintenance agent, RR reduced the incidence of EA compared with inhalational anesthesia using DN. Additionally, RR is superior in managing hemodynamics during the emergence and management of suffocation after surgery compared to inhalational anesthesia using DN.

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Table 1. Assessment tools for emergence agitation

Ricker sedation agitation scale [11]		
Score	Category	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down on verbal instructions
4	Calm, cooperative	Calm, easily arousable, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands
Richmond agitation sedation scale [11]		
Score	Category	Description
4	Combative	Overtly combative, violent, immediate danger to staff
3	Very agitated	Pulls or removes tubes or catheters; aggressive
2	Agitated	Frequent non-purposeful movement, fights ventilator
1	Restless	Anxious but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Sustained awakening to voice (≥ 10 s)

-2	Light sedation	Briefly awakens with eye contact to voice (< 10 s)
-3	Moderate sedation	Movement or eye opening to voice but no eye contact
-4	Deep sedation	No response to voice but movement or eye opening to physical stimulation
-5	Cannot be aroused	No response to voice or physical stimulation

Aono's four-point agitation scale [29]

Score	Description
1	Calm (conversation)
2	Not calm but could be easily calmed
3	Not easily calmed, moderately agitated or restless
4	Combative, excited, or disoriented

Table 2. Patient characteristics and intraoperative data

Variable	Group DN (n = 38)	Group RR (n = 38)	P-value
Age (yr)	47.0 (26.0, 55.0)	46.5 (36.0, 55.0)	0.582
Sex (M/F)	21/17	25/13	0.481
Weight (kg)	68.0 (58.0, 75.0)	69.4 (60.1, 77.0)	0.490
Height (cm)	165.4 ± 8.8	165.6 ± 8.5	0.942
ASA physical status (I/II)	10/28	5/33	0.249
Duration of surgery (min)	63.5 (50.0, 82.0)	59.0 (43.0, 73.0)	0.127
Duration of anesthesia (min)	80.0 (68.0, 103.0)	82.5 (65.0, 91.0)	0.666
Duration of anesthetics administration (min)	73.5 (59.0, 104.0)	75.0 (60.0, 95.0)	0.533
Intraoperative fluid (ml)	300.0 (200.0, 400.0)	400.0 (300.0, 500.0)	0.020
Nasal packing at the end of surgery (one/both)	3/35	3/35	> 0.999
Use of additional agent			
Nicardipine	10 (26.3%)	6 (15.8%)	0.399
Ephedrine	21 (55.3%)	23 (60.5%)	0.816
Esmolol	13 (34.2%)	4 (10.5%)	0.028
Atropine	1 (2.6%)	0 (0.0%)	> 0.999
Flumazenil	0 (0%)	0 (0%)	> 0.999

Data are expressed as the mean ± standard deviation, median (Q1, Q3), number, or number (%). DN: desflurane-nitrous oxide, RR: remimazolam-remifentanil, ASA: American Society of Anesthesiologists.

Table 3. Recovery data during the emergence period

Variable	Group DN (n = 38)	Group RR (n = 38)	P-value
Awakening time (min)			
Time to spontaneous respiration	4.0 (3.0, 5.0)	6.0 (4.0, 8.0)	< 0.001
Time to first awakening time	4.0 (4.0, 6.0)	7.0 (5.0, 9.0)	< 0.001
Time to extubation	6.0 (5.0, 7.0)	10.0 (8.0, 12.0)	< 0.001
Nasal bleeding grade (0/1/2)	17/16/5	23/12/3	0.373

Data are expressed as the mean ± standard deviation, median (Q1, Q3), number, or number (%). DN: desflurane-nitrous oxide, RR: remimazolam-remifentanil.

Table 4. Incidence of emergence agitation during the emergence period

	Group DN (n = 38)	Group RR (n = 38)	Relative risk (95% CI)	Effect size *h*	P-value
Emergence agitation by					
RSAS	32 (84.2%)	17 (44.7%)	2.9 (1.4, 6.1)	0.647	< 0.001
RASS	25 (65.8%)	8 (21.1%)	2.5 (1.5, 4.1)	0.938	< 0.001
AFPS	24 (63.2%)	8 (21.1%)	2.4 (1.5, 3.8)	0.883	< 0.001
Severe emergence agitation by					
RSAS	11 (28.9%)	2 (5.3%)	2.0 (1.4, 2.9)	0.671	0.012
RASS	16 (42.1%)	2 (5.3%)	2.3 (1.6, 3.4)	0.948	< 0.001
AFPS	10 (26.3%)	3 (7.9%)	1.7 (1.2, 2.6)	0.507	0.065

Data are expressed as the number (%). DN: desflurane-nitrous oxide, RR: remimazolam-remifentanil, , RSAS: Ricker Sedation-Agitation Scale, RASS: Richmond Agitation-Sedation Scale, AFPS: Aono's four-point agitation scale.

Table 5. Postoperative data and adverse events

Variable	Group DN (n = 38)	Group RR (n = 38)	P-value
NRS for pain	4.0 (2.0, 6.0)	3.0 (2.0, 5.0)	0.411
Usage of fentanyl	9 (23.7%)	11 (28.9%)	0.794
NRS for suffocation	5.0 (2.0, 7.0)	2.0 (0.0, 5.0)	0.027
Usage of antiemetics	1 (2.6%)	0 (0%)	1.000
Adverse event			
Nausea	3 (7.9%)	0 (0%)	0.239
Vomiting	0 (0%)	0 (0%)	
Dizziness	1 (2.6%)	0 (0%)	1.000
Headache	4 (10.5%)	6 (15.8%)	0.734
Desaturation	0 (0%)	0 (0%)	
Laryngospasm	0 (0%)	0 (0%)	
Sore throat	2 (5.3%)	2 (5.3%)	1.000
Hypersalivation	0 (0%)	0 (0%)	

Data are expressed as the median (Q1, Q3) or number (%). DN: desflurane-nitrous oxide, RR: remimazolam-remifentanil, NRS: numeric rating scale.

Figure legends

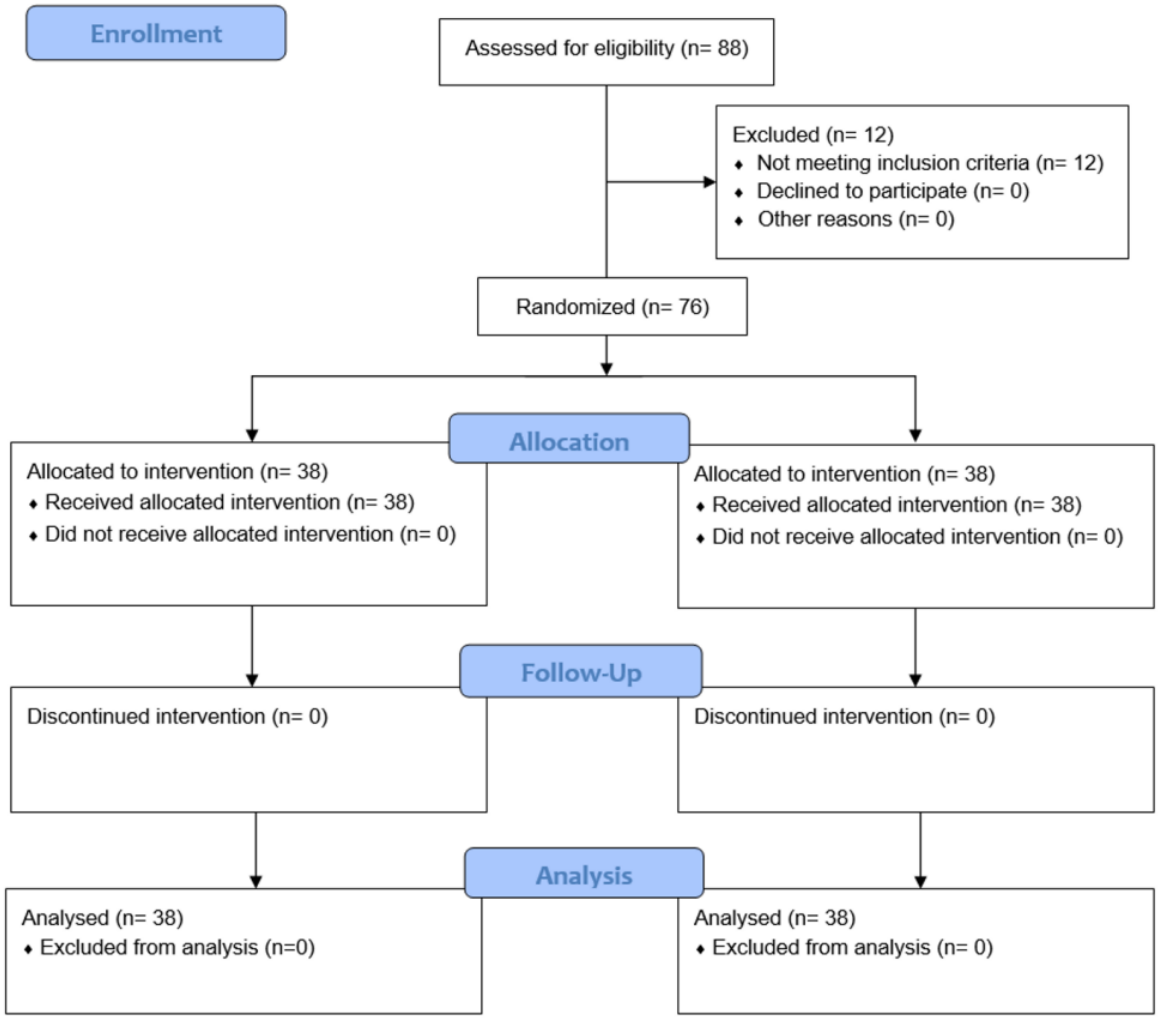

Fig. 1. Flow diagram of study

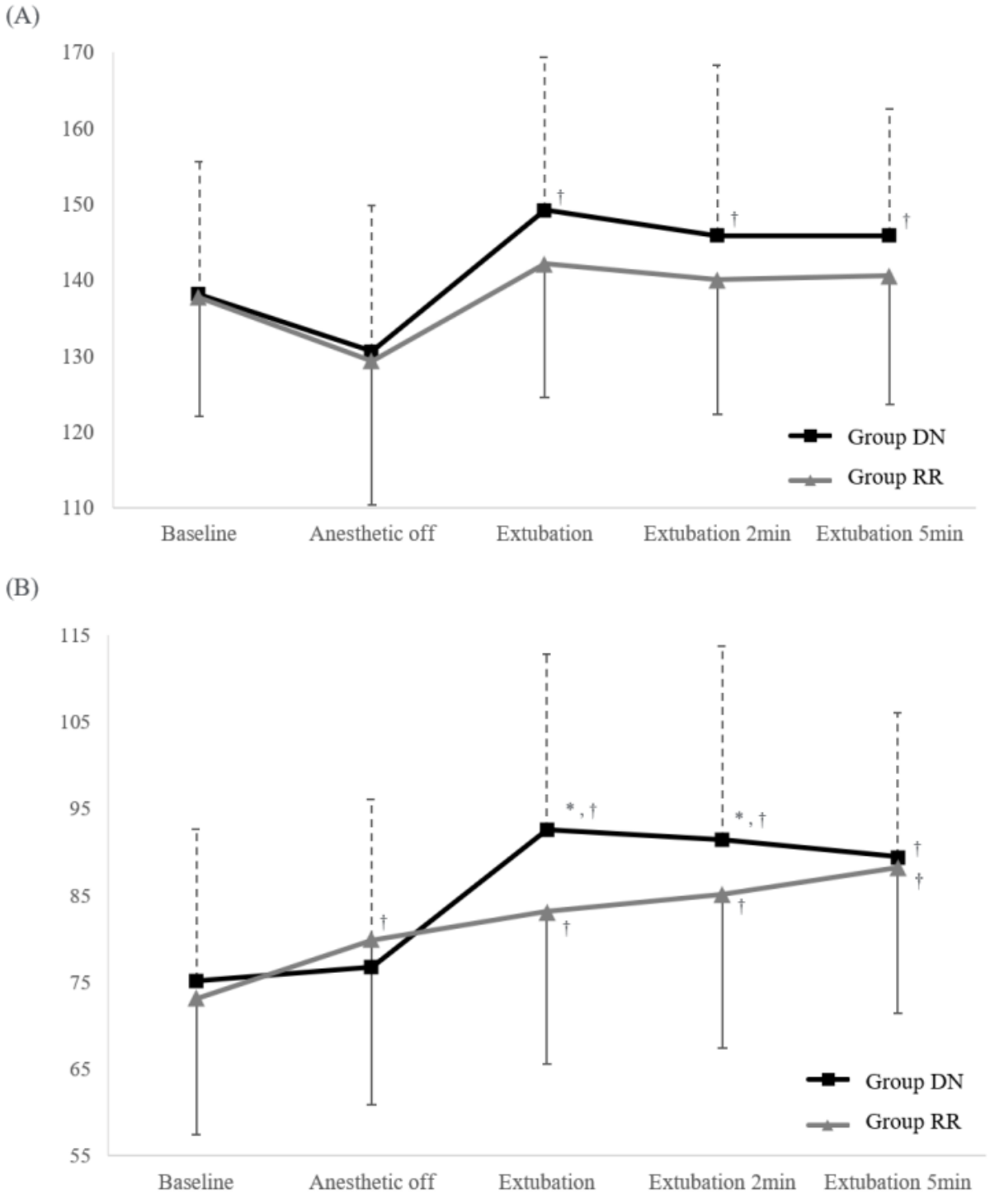

Fig. 2. Systolic arterial pressure and heart rate during emergence. (A) systolic arterial pressure, (B) heart rate. * $P < 0.05$ between the desflurane-N_2O (DN) and remimazolam-remifentanil (RR) groups, † $P < 0.05$ between the baseline values.