Butorphanol Mitigates Emergence Agitation in Patients Undergoing Functional Endoscopic Sinus Surgery: A Randomised Controlled Clinical Trail

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Research article

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Abstract

Background: This study explored the effectiveness of preoperative intravenous injection of butorphanol in the alleviation of emergence agitation (EA) in patients undergoing functional endoscopic sinus surgery (FESS).

Methods: Patients (n = 708) were randomized into two groups. The butorphanol group (Group B, n=358) received butorphanol infusion (20 ug/kg) before anaesthesia induction, while the control group (Group C, n=350) received an equal volume of normal saline infusion. General anaesthesia was induced with sufentanil, propofol and rocuronium, and was maintained with sevoflurane and remifentanil. Vasoactive drugs maintained the haemodynamic indices within 20% of the baseline.

Results: The incidence of EA (Group B vs. C: 24.3 vs. 31.4%, P = 0.034). The times to spontaneous breathing (26.5 min vs. 23.7 min, P = 0.011), verbal response (36.0 min vs. 33.4 min, P = 0.012) and extubation (31.0 min vs. 28.7 min, P = 0.025) were longer in Group B, and the grade of cough (0.33 vs. 0.43, P = 0.024) at extubation in Group B was lower than that in Group C (P = 0.024). The mean arterial pressure at the end of the operation (P = 0.004) and at 5 min after extubation (P = 0.008) was higher and hypotension was less prominent (0.6% vs. 2.6%, P = 0.030) in Group B.

Conclusions: Preoperative intravenous injection of butorphanol decreased the incidence of EA after FESS, and provided smooth and haemodynamically stable emergence without extending the stay in post-anaesthesia care unit.

Trial registration: Clinicaltrials.gov, NCT03398759. Registered 21 December 2017, https://www.clinicaltrials.gov/ct2/show/NCT03398759?term=03398759&draw=2&rank=1

Background

Emergence agitation, also known as emergence delirium, is a common symptom after ear, nose, and throat (ENT) surgery under general anaesthesia, especially in children and patients over 65 years old, characterised by aimless restlessness, hallucination, delusion, inconsolable crying or moaning, disorientation and incoherence[1–5]. Although the exact mechanism of EA has not been clarified after decades of research, its incidence varies from 5–80% and can be affected by many factors, such as age, gender, types of operation, volatile anaesthetics, benzodiazepine pre-medication, preoperative anxiety, postoperative pain, and others[6–9]. EA can increase the risk of injury, pain, haemorrhage, self-extubation, or removal of catheters. This can lead to serious complications, such as hypoxia, aspiration pneumonia, bleeding, or re-operation[1, 2, 8]. Although many strategies had been proven helpful to the reduction of the incidence of EA, like α2-adrenoreceptor agonists[10, 11], total intravenous anaesthesia[12], and multi-modal analgesia[13], these preventive strategies often yielded inconsistent results depending on the methodology of the study and the patients assessed[14], and led to residual sedation and haemodynamic changes that resulted in prolonged post-anaesthesia care unit (PACU) stay.

Butorphanol is a mixed agonist–antagonist opioid with strong κ-receptor agonist and weak μ-receptor antagonist activities[15]. It is commonly used for the management of cancer, postoperative, gynaecological, and obstetric pain. Additionally, butorphanol elicits less pronounced respiratory depression and sedation effects. This renders it as a good medication for the alleviation of agitation. However, there is no clinical evidence that confirms the effectiveness of butorphanol.

In this randomised, double-blind, placebo-controlled study, we evaluated the hypothesis that preoperative intravenous injection of butorphanol would reduce the incidence of EA in adult patients undergoing FESS. Furthermore, we evaluated the effects of butorphanol on the quality of recovery after FESS.

Methods

This single-centre, prospective, randomised, double-blinded clinical trial was conducted at the Renji Hospital (affiliated to the Shanghai Jiaotong University School of Medicine) from February 2018 to May 2020. This study was approved by Renji Hospital Ethics Committee (2017 − 159) and was registered at clinicaltrials.gov (NCT03398759). Written informed consent was obtained from all patients before inclusion.

Participants

Patients aged 18–65 years and American Society of Anaesthesiologists (ASA) physical status class I–II, who were scheduled for FESS under general anaesthesia were included in the study. The excluding criteria are: (1) body mass index (BMI) > 30 kg/m^2, (2) cerebral disease or patients with a history of neurological and psychiatric diseases, including Alzheimer disease, stroke, epilepsy and psychosis, (3) bradycardia (heart rate < 60 beats per minute for any reasons), (4) gastrointestinal ulcer, (5) urinary incontinence, (6) asthma or chronic obstructive pulmonary disease, (7) allergy to butorphanol, (8) auditory or vision disorders, (9) unwillingness to comply with the protocol or procedures, (10) inability to communicate in Chinese Mandarin.

Randomisation and blinding

A biostatistician who did not participate in the data management and statistical analyses generated the random sequences. The PROC PLAN programme (SAS, version 9.0) was used to generate the sample randomisation sequence using 1:1 allocation with block 90 and a length = 8. The results of the randomisation were sealed in sequentially numbered envelopes. Consecutively recruited patients were assigned to Groups B or C. Group B received an intravenous injection of butorphanol (trade name Nuoyang, produced by Jiangsu Hengrui Pharmaceutical Co., Ltd.) at a dose of 20 ug/kg (diluted with normal saline to 1 g/L) before anaesthesia induction, while Group C received an equal volume of normal saline infusion as the placebo at the same time point. The investigator, attending anaesthetist, surgeons, recovery, ward nurses, and patients were blinded to group assignment.

Sample size estimation

The sample size was calculated based on the estimated differences of EA incidence between the two groups with PASS (ver. 11.0) (two independent proportions, z-test). With an alpha = 0.05, power = 0.8, an expected reduction in the EA incidence from 35–25%[16], degree-of-freedom = 1 and attrition rate = 10%, we estimated that 358 patients were needed in each group.

Study design

Routine monitors, including the electrocardiogram, pulse oxygen saturation (SpO_2), non-invasive arterial pressure and end-tidal CO_2 ($ETCO_2$) were applied upon patient arrival in the operating room. The room temperature was kept at 20 °C–24 °C during the operation. Before the induction of anaesthesia, the patient was injected with a drug labelled “experimental drug” according to the patient’s weight (20 ug/kg of butorphanol or the same volume of normal saline). General anaesthesia was induced by the combined use of sufentanil (0.5 ug/kg), propofol (2 mg/kg) and rocuronium (0.6 mg/kg). The orotracheal intubation was then performed, the tidal volume of mechanical ventilation was set to 6–8 ml/kg, and the ventilation frequency was adjusted to 12–15 times/min to maintain $ETCO_2$ between 35–40 mmHg (1 mmHg = 0.133 kPa). Anaesthesia was maintained with sevoflurane based on 1.3 age-adjusted minimum alveolar concentration (MAC) combined with remifentanil (0.2–0.5 ug/kg/min) to maintain the bispectral index (BIS) (A-2000TM SP, Aspect Medical Systems, Norwood, MA, USA) values between 40–60. Vasoactive drugs were used to maintain the haemodynamic indices of patients within 20% of the baseline.

After entering the PACU, the arterial pressure, electrocardiogram and SpO_2 were monitored continually, and the patients were mechanically ventilated. All patients were given atropine (15 ug/kg) and neostigmine (50 ug/kg) to antagonise the residual muscle relaxation. Extubation was performed when patients began breathing spontaneously and were able to respond to verbal requests sensitively and accurately. Patients were discharged from the PACU when their Aldrete score $\geq$ 9[17].

Emergence duration is defined as the time spent in the PACU. During emergence, the level of agitation was evaluated by a nurse using the Ricker sedation–agitation scale (SAS). The agitation score of patient was recorded based on the following: 1 = minimal or no response to noxious stimuli, 2 = arousal to physical stimuli but no communication, 3 = difficult to arouse but awaken to verbal stimuli or gentle shaking, 4 = calm and follows commands, 5 = anxious or physically agitated and calm to verbal instructions, 6 = requiring restraint and frequent verbal reminding of limits, and 7 = pulling at tracheal tube, trying to remove catheters or striking staff members[18]. EA was defined as the highest SAS score $\geq$ 5 during emergence, and SAS score > 5 was defined as severe EA[1]. Delayed sedation is considered to occur if SAS score $\leq$ 3 upon arrival in PACU. When the SAS score $\geq$ 5, intermittent intravenous injection of propofol 0.5 mg/kg was performed until the symptoms of agitation disappeared.

We assessed the grade of cough during extubation based on a four-point scale (0 = no cough, 1 = single cough, 2 = persistent cough lasting < 5 s; and 3 = persistent cough lasting $\geq$ 5 s or bucking). The length of the period following PACU admission to spontaneous breathing, verbal response and extubation were recorded. The respiratory rate at the time of extubation was also measured. We recorded the

haemodynamic parameters including heart rate (HR) and mean arterial pressure (MAP) before anaesthesia induction, at intubation, at the end of operation, at extubation, 5 min after extubation, and before leaving the PACU. Desaturation (SpO_2 < 95%), laryngospasm and other complications (bradycardia, tachycardia, hypotension and hypertension) were also recorded during the operation and emergence.

In the PACU, score on an 11-point numerical rating scale (NRS) for pain (0 = no pain and 10 = worst pain imaginable), and score on a 4-point nausea and vomiting scale (0 = no nausea, 1 = mild nausea, 2 = severe nausea requiring antiemetics, and 3 = retching, vomiting, or both) were evaluated after extubation. Patients were given an injection of sufentanil (5 ug) when NRS was ≥ 4.

Outcomes

The primary outcome was the incidence of EA defined as the highest SAS score ≥ 5 during emergence. The secondary outcomes were the hemodynamic (HR and MAP) changes at different time points. We also analysed the operation details (duration of surgery and anaesthesia, amount of intraoperative fluid, amount of sufentanil and remifentanil, and intraoperative blood loss), recovery characteristics, and adverse events during the operation and emergence.

Statistical analysis

Statistical analyses were performed using the software SPSS (ver. 26.0, SPSS, Inc., Chicago, IL, USA). The normality of distribution was assessed based on the Shapiro–Wilk test. According to the normality of the data, the continuous variables were compared by the Student's t- or Mann–Whitney U tests, and the categorical variables were evaluated using the χ^2 or Fisher's exact test. Repeat-measure variables (HR and MAP) were analysed using repeated measures ANOVA with Bonferroni correction. A P-value < 0.05 was considered statistically significant. All values were expressed as mean (SD), median (range), or number (%).

Results

A total of 733 patients were assessed for eligibility and enrolled in the study. Of these, 25 patients refused to participate. In total, 708 patients were randomised and they all completed the study (Fig. 1). Patient characteristics and operation details were similar between the two groups (Table 1).

Table 1
Patient characteristics and operation details. Values are mean (SD), median (range) or number (%). B, butorphanol; C, control with normal saline. Grade of blood loss: 1, blood loss ≤ 100 ml; 2, blood loss ≤ 200 ml; 3, blood loss > 200 ml.

	Group B (n = 358)	Group C (n = 350)	P-value
Age (yr)	51 (18–65)	51 (18–65)	0.937
Gender (M/F)	223 (135)	211 (139)	0.584
Height (cm)	167 (8)	167 (8)	0.855
Weight (kg)	66 (10)	66 (11)	0.287
BMI	23.62(2.73)	23.35 (2.69)	0.209
ASA (I/II)	245 (113)	240 (110)	0.969
Comorbidities			
Hypertension	61 (17.0%)	49 (14.0%)	0.264
Diabetes	15 (4.2%)	19 (5.4%)	0.441
Heart diseases	32 (8.9%)	23 (6.6%)	0.239
Duration of anesthesia (min)	80 (37)	84 (39)	0.226
Duration of surgery (min)	60 (35)	63 (37)	0.288
Amount of intraoperative fluid (ml)	863 (231)	876 (236)	0.384
Crystal fluid	749 (90)	755 (99)	0.422
Colloidal fluid	113 (209)	120 (214)	0.666
Grade of blood loss	1 (1–3)	1 (1–3)	0.572
Amount of sufentanil (ug)	21 (3)	21 (3)	0.122
Amount of remifentanil (ug)	663 (395)	702 (522)	0.324

The incidence of EA was significantly lower in Group B than in Group C (24.3% vs. 31.4%, P = 0.034). Three patients in Group B and one patient in Group C exhibited severe EA (0.8% vs. 0.3%, P = 0.632), while there was no significant difference (Fig. 2).

HR and MAP during operation and emergence are shown in Fig. 3. HR and MAP were similar in both groups at baseline. Furthermore, no HR difference was observed between the two groups. However, the MAP in Group B demonstrated more stable haemodynamic changes at the end of surgery (P = 0.004, Bonferroni corrected) and at 5 min after extubation (P = 0.008, Bonferroni corrected) compared with Group C.

Parameters related to emergence in the PACU are listed in Table 2. The time from entering PACU to spontaneous breathing (26.5 min vs. 23.7 min, P = 0.011), verbal response (36.0 min vs. 33.4 min, P = 0.012) and extubation (31.0 min vs. 28.7 min, P = 0.025) was longer in Group B compared with Group C. No difference was observed between the groups in respiratory rate at extubation, nor were there differences in the grade of nausea, while the grade of cough was lower in Group B compared with Group C (P = 0.024). Moreover, the two groups yielded similar pain scores, administration of analgesics and the length of PACU stay.

Table 2
Recovery characteristics. Values are mean (SD), median (range) or number (per cent). B, butorphanol; C, control with normal saline; NRS, numerical rating scale; PACU, post-anaesthetic care unit.

	Group B (n = 358)	Group C (n = 350)	P-value
Time to spontaneous breathing (min)	26.5 (13.7)	23.7 (13.0)	0.011
Time to verbal response (min)	36.0 (14.5)	33.4 (13.9)	0.012
Time to extubation (min)	31.0 (13.5)	28.7 (12.7)	0.025
Respiratory rate at extubation (min^{-1})	16 (3)	16 (3)	0.373
Grade of cough at extubation	0.33 (0.58)	0.43 (0.66)	0.024
Grade of nausea after extubation	0 (0–3)	0 (0–3)	0.685
Residual sedation in PACU	56 (15.6%)	43 (12.3%)	0.148
NRS for pain in PACU	1 (0–4) / 1.5 (0.7)	1 (0–4) / 1.6 (0.9)	0.434
Analgesics in PACU	13 (3.6%)	21 (6.0%)	0.141
Length of PACU stay (min)	50.2 (13.3)	49.2 (12.6)	0.262

There was no difference between the groups regarding the incidence of hypertension, hypotension, tachycardia and bradycardia during the operation. During the PACU, there were fewer patients with hypotension in Group B (0.6% vs. 2.6%, P = 0.030) (Table 3). No patients experienced respiratory depression, severe desaturation (SpO_2 < 90%) and laryngospasm during emergence.

Table 3
Adverse events. Values are number (per cent). B, butorphanol; C, control with normal saline.

	Group B (n = 358)	Group C (n = 350)	P-value
Intraoperative complications			
Hypertension	33 (9.2%)	26 (7.4%)	0.389
Hypotension	50 (14.0%)	55 (15.7%)	0.513
Tachycardia	7 (2.0%)	15 (4.3%)	0.074
Bradycardia	136 (38.0%)	130 (37.1%)	0.816
PACU complications			
Desaturation (Spo2 < 95%)	5 (1.4%)	6 (1.7%)	0.733
Hypertension	24 (6.7%)	25 (7.1%)	0.818
Hypotension	2 (0.6%)	9 (2.6%)	0.030
Tachycardia	19 (5.3%)	17 (4.9%)	0.785
Bradycardia	34 (9.5%)	25 (7.1%)	0.257

Discussion

This prospective, double-blinded, randomised study indicated that preoperative intravenous infusion of butorphanol was effective in reducing the incidence of EA after FESS and making haemodynamics relatively more stable without extending the length of PACU stay.

Prior studies reported that the incidence of EA in adult patients after general anaesthesia can reach 20% [8, 19]. Male gender, type of surgery, inhalation anaesthetics, postoperative pain, and the presence of tracheal and/or urinary catheters are known risk factors for EA[1–4, 8]. The incidence of EA after ENT surgery is even higher, almost up to 55.4%[19]. Owing to the obstruction of the habitual respiratory channels caused by gauze filling in the nasal cavity to stop bleeding after FESS, it is preferred to awake extubation after general anaesthesia[20]. However, awake extubation can lead to a higher agitation incidence. Postoperative pain, as well as the suffocation caused by the gauze strips and blood clots may be the possible reasons for the high incidence of EA after FESS[21].

The harm of EA is tremendous. It can increase the probability of respiratory and circulatory complications and internal bleeding owing to the excitement of sympathetic nerve, although some patients can relieve themselves. In severe cases, the surgical incision may be ruptured and the intravenous access and drainage tube may fall off suddenly, leading to the failure of the operation[8]. At the same time, the occurrence of EA increases the burden of the medical staff and reduces the satisfaction of patients with disease treatment. At present, analgesic and sedative drugs (such as fentanyl, tramadol, propofol, etc.)

are commonly used to prevent and treat EA clinically, but there is a risk of respiratory inhibition or delayed recovery[22–24]. Butorphanol is an opioid receptor agonist–antagonist. Its metabolites can act on κ-receptors and have dual effects of activation and antagonism on μ-receptors. It mainly interacts with these receptors in the central nervous system to indirectly exert anaelgesic, sedative and other pharmacological effects. Patients have no discomfort such as agitation and anxiety. Butorphanol usually exerts its effects after intravenous injection within a timeframe of 3–5 min. Its elimination half-life is 2.5–3.5 h, and its analgesic potency is 5–8 times higher than that of morphine[25–27]. However, respiratory inhibition rarely occurs, and the incidence of adverse reactions is significantly lower than that of morphine and fentanyl. Based on these characteristics, it may become an ideal drug for postoperative reduction of EA.

Some studies found that among the many causes of EA, postoperative pain may be the most important reason for inducing and aggravating agitation during emergence[19]. Butorphanol attracted our attention in the prevention and treatment of EA owing to the fact that it induces sedation and analgesia without respiratory depression. In this study, we demonstrated that administration of butorphanol before anaesthesia induction can effectively reduce the incidence of EA after FESS. We believed that the anaelgesic and sedative effects of butorphanol are the main reasons for reducing the incidence of EA. In our research, the operation duration was approximately 2–3 h. Therefore, the anaelgesic and sedative effects of butorphanol were still working on during the emergence duration. This made patients more tolerant to the sense of asphyxia caused by the tracheal catheters and habitual airway blockage. However, in our study, the incidence of EA in the control group was 31.4%, lower than that in previously reported studies[3, 9]. This may be attributed to the fact that we gave patients an adequate amount of analgesics during the perioperative period to manage the perioperative pain more efficiently. This could be reflected by the NRS score. In our study, both the highest and mean NRS scores in the control group were lower than those in previously reported results[3, 9]. Research studies concerning butorphanol in combination with other drugs used to reduce the incidence of EA are also in progress. Lin et al.[28] found that butorphanol combined with ketamine was more effective than butorphanol or ketamine alone on postoperative EA in patients with gastric cancer.

The time to spontaneous breathing, verbal response and extubation was longer in Group B than Group C, while the residual sedation and length of PACU stay yielded no differences. Compared with Group C, the grade of cough at extubation in Group B was lower. These results may be attributed to the sedative effect of butorphanol. This medication induced patients in a more appropriate state of sedation, and their recoveries were better and without PACU duration prolongations.

While HR was similar in both groups during operation and emergence, the MAP at the end of the operation and at 5 min after extubation were significantly higher in Group B. The incidence of hypotension during PACU in Group B was significantly lower compared with that of Group C. These results indicated that the haemodynamics of patients who received a preoperative intravenous injection of butorphanol were more stable during the perioperative period.

There are several limitations associated with this study. First, we only studied the effectiveness of butorphanol on the incidence of EA in patients aged 18–65 who underwent FESS. Additional studies are warranted for other types of surgery and for children or patients over 65 years. Second, in this study, only one experimental drug dose was set, so we do not know whether a lower or higher dose of butorphanol can reduce the incidence of EA as well.

Conclusions

In conclusion, preoperative butorphanol infusion decreased the incidence of EA for adult patients who underwent FESS and provided smooth and haemodynamically stable emergence without a concomitant prolongation of the PACU stay.

Abbreviations

EA: Emergence agitation; FESS: Functional endoscopic sinus surgery; PACU: Post-anaesthesia care unit; ENT: Ear, nose, and throat; SAS: Sedation–agitation scale; HR: Heart rate; MAP: mean arterial pressure; NRS: Numerical rating scale.

Declarations

Competing interest

The authors declare that they have no competing interests.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contribution

Study design: SYQ, DSS, XRH; Study conduct: SYQ, WBD, WTT, LZ, XRH; Data analysis: SYQ, DSS, XRH; Manuscript preparation: SYQ, DSS, XRH; Data interpretation: SYQ, WBD, WTT, YZZ, LZ; Manuscript revision: all authors.

Ethics approval and consent to participate

This study was approved by Renji Hospital Ethics Committee (2017-159). Participants gave written informed consent prior to the study scenario.

Consent for publication

Not applicable.

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Statement

Our study adheres to CONSORT guidelines.

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Figures

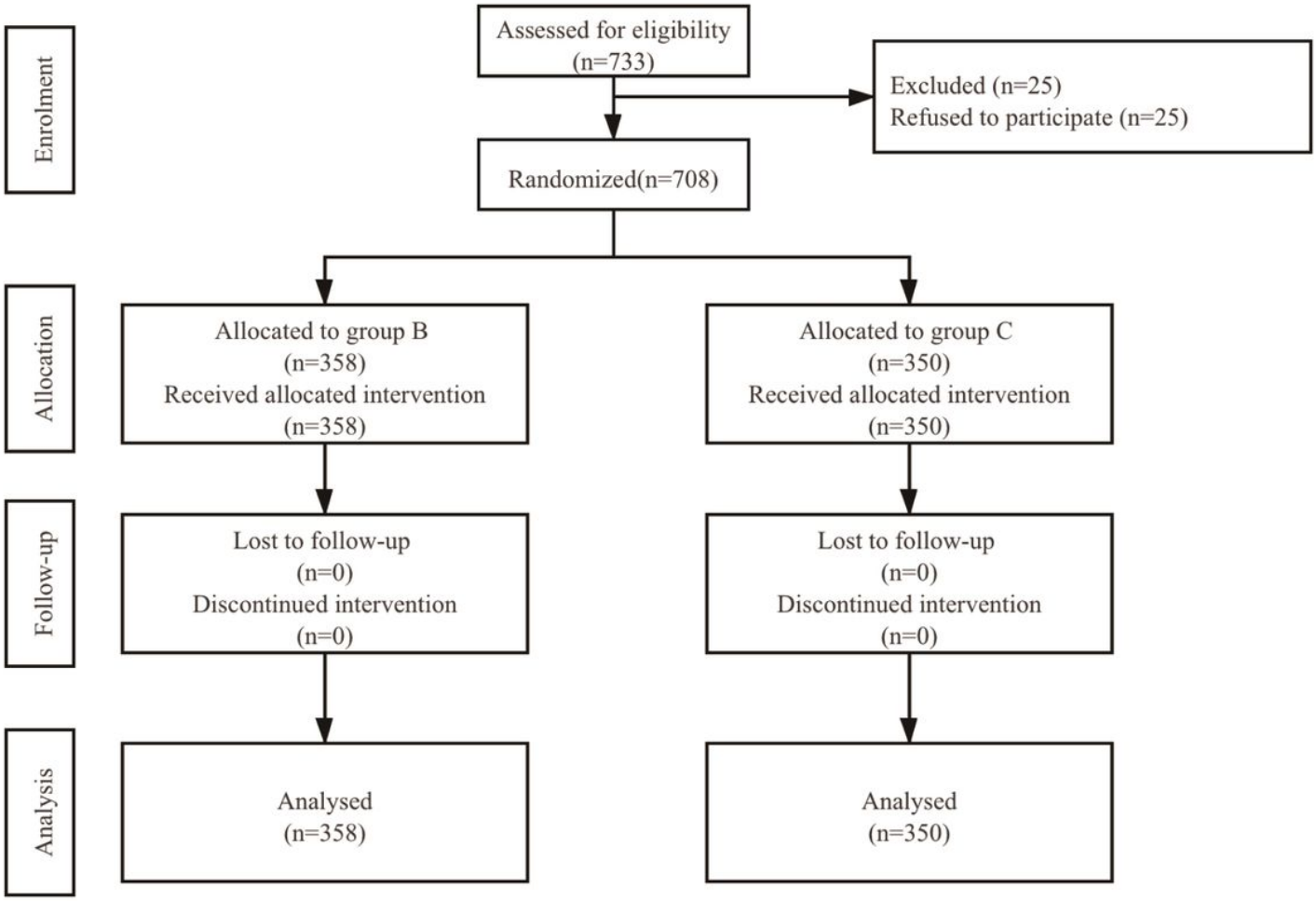

Figure 1

Patient assignment to study group (randomized) and treatment protocols. B, butorphanol; C, control with normal saline.

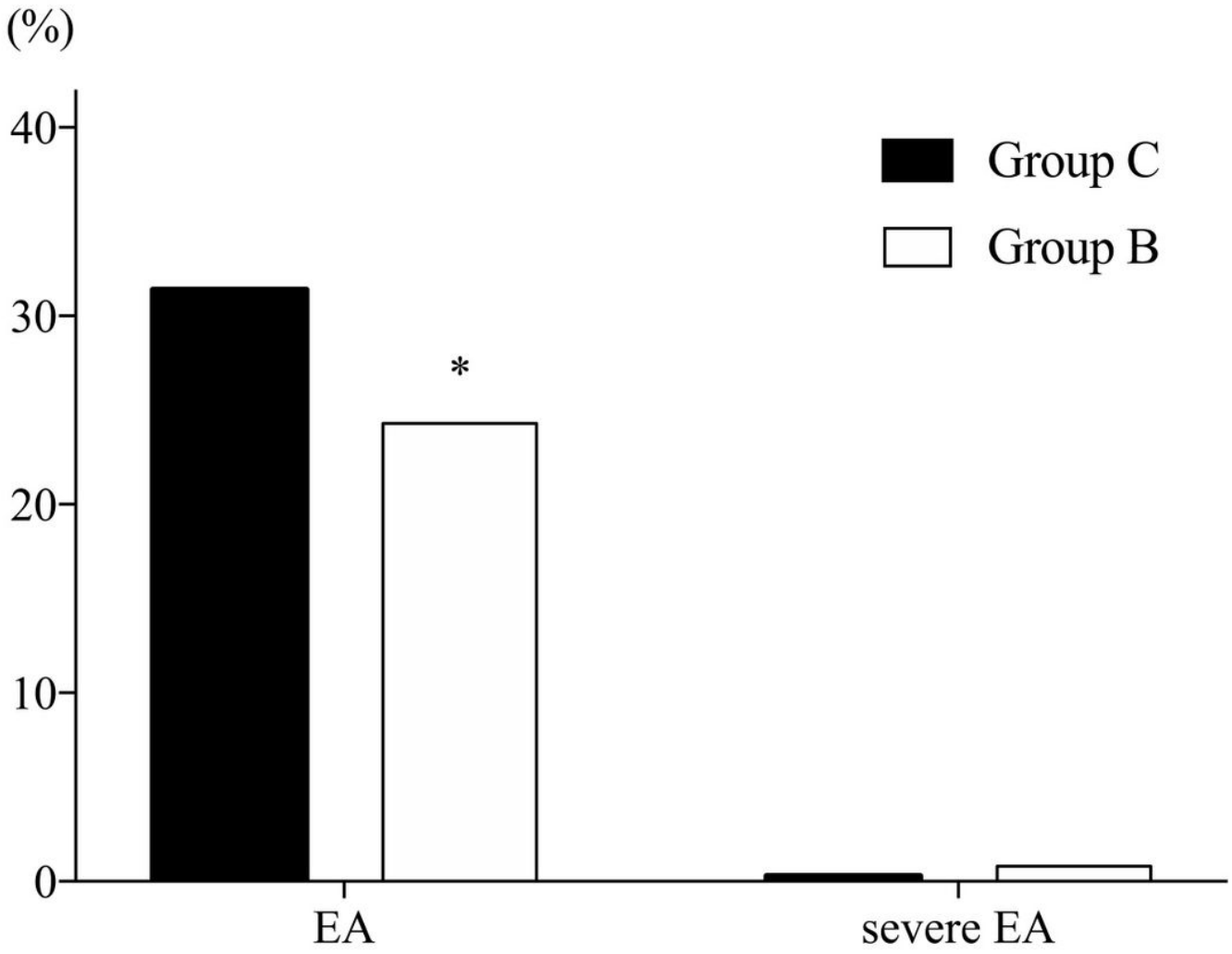

Figure 2

Incidence of emergence agitation. B, butorphanol; C, control with normal saline; EA, emergence agitation. Emergence is defined as the time spent in the PACU. Agitation is defined as a sedation-agitation scale score ≥5. Severe agitation is defined as a sedation-agitation scale score >5. *P=0.034 compared with Group C.

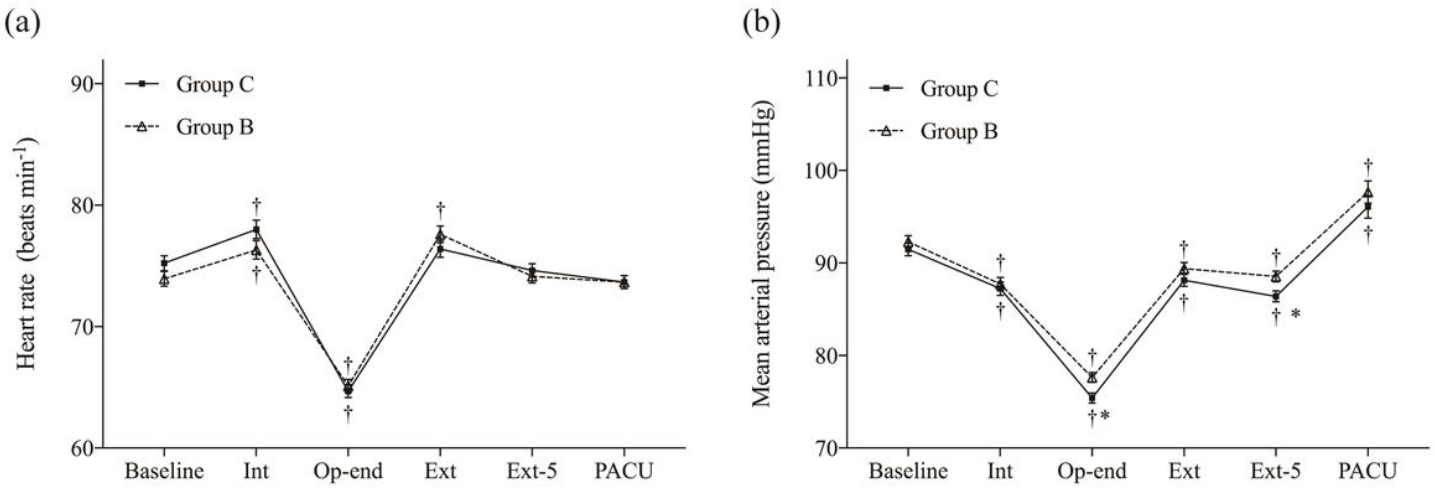

Figure 3

Haemodynamic changes during the operation and emergence. (a) HR, and (b) MAP. Baseline, before anaesthesia induction; Int, intubation; Op-end, end of operation; Ext, extubation; Ext-5, 5 min after extubation; PACU, before leaving PACU. Data are expressed as mean (SD). *P<0.05 compared with Group C (Bonferroni corrected). †P<0.05 compared with baseline in each group (Bonferroni corrected).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010FlowDiagram.doc
- CONSORT2010Checklist.doc