

Efficacy of intraoperative dexmedetomidine infusion on emergence agitation and quality of recovery after nasal surgery

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Editor's key points

- Intraoperative continuous dexmedetomidine infusion ($0.4 \mu\text{g kg}^{-1} \text{h}^{-1}$) until extubation was effective in reducing the incidence of emergence agitation after nasal surgery.
- No delay of extubation or increasing incidence of other complications was observed after dexmedetomidine infusion.
- Use of dexmedetomidine produced more stable haemodynamic changes during extubation and enhanced patient-reported global quality of recovery at 24 h after surgery.

Background. Emergence agitation is common after nasal surgery. We investigated the effects of intraoperative dexmedetomidine infusion on emergence agitation and quality of recovery after nasal surgery in adult patients.

Methods. One hundred patients undergoing nasal surgery were randomized into two groups. The dexmedetomidine group (Group D, $n=50$) received dexmedetomidine infusion at a rate of $0.4 \mu\text{g kg}^{-1} \text{h}^{-1}$ from induction of anaesthesia until extubation, while the control group (Group C, $n=50$) received volume-matched normal saline infusion as placebo. Propofol ($1.5\text{--}2 \text{ mg kg}^{-1}$) and fentanyl ($1 \mu\text{g kg}^{-1}$) were used for induction of anaesthesia, and desflurane was used for maintenance of anaesthesia. The incidence of agitation, haemodynamic parameters, and recovery characteristics were evaluated during emergence. A 40-item quality-of-recovery questionnaire (QoR-40) was provided to patients 24 h after surgery.

Results. The incidence of agitation was lower in Group D than Group C (28 vs 52%, $P=0.014$). Mean arterial pressure and heart rate were more stable in Group D than in Group C during emergence ($P<0.05$). Time to extubation, bispectral index, and respiratory rate at extubation were similar between the groups. Global QoR-40 score at 24 h after surgery was higher in Group D (median [range], 183 [146–198]) compared with Group C (178 [133–196]) ($P=0.041$).

Conclusions. Intraoperative infusion of dexmedetomidine provided smooth and haemodynamically stable emergence. It also improved quality of recovery after nasal surgery.

Keywords: anaesthesia, general; complications, extubation trachea; pharmacology, dexmedetomidine; recovery, postoperative

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Emergence agitation from general anaesthesia may lead to self-extubation or removal of catheters, which can cause serious complications such as hypoxia, aspiration pneumonia, bleeding or reoperation.¹ Ear, nose, and throat (ENT) surgery is associated with a higher incidence of emergence agitation.² After nasal surgery, awake extubation is preferred because the airway is contaminated by blood, and the nasal airway is blocked with surgical packs.³ However, awake extubation may intensify emergence agitation.

Dexmedetomidine is a selective α_2 -receptor agonist and has sympatholytic, analgesic, and sedative properties.⁴ Infusion of dexmedetomidine reduces agitation from general anaesthesia in children^{5,6} and from ventilator weaning in ICU patients.^{7,8} However, the data related to the effects of dexmedetomidine on reducing agitation from general anaesthesia in adults are limited. Perioperative use of dexmedetomidine also

decreases postoperative opioid consumption, pain intensity, and antiemetic therapy.^{9–12} In addition, it has been revealed that intraoperative dexmedetomidine infusion reduces stress response and therefore improves quality of recovery after major spinal surgery.¹³

In this randomized, double blind, placebo-controlled study, we hypothesized that intraoperative use of dexmedetomidine until extubation would reduce emergence agitation in adult patients undergoing nasal surgery. Furthermore, we evaluated the effects of dexmedetomidine on quality of recovery after nasal surgery.

Methods

This study was approved by the Internal Review Board of Yonsei University Medical Center and was registered at

<http://clinicaltrials.gov> (registration number NCT01513772). Between February 2012 and August 2012, we enrolled 100 consecutive patients, aged 20–58 yr and ASA class I–II, who underwent general anaesthesia for elective nasal surgery in which nasal packing on each side was used until 24 h after surgery. Written informed consent was obtained from all patients before randomization. Patients were not admitted to the study if any of the following criteria were present: known or suspected allergy to α_2 -adrenergic agonist or non-steroidal anti-inflammatory drugs; use of monoamine oxidase inhibitors or adrenergic blocking drugs; history of uncontrolled hypertension; heart block greater than first degree; cognitive impairment; chronic use of antipsychotic medications; kidney or liver disease; and body mass index $\geq 30 \text{ kg m}^{-2}$.

Patients were randomly assigned into two groups by computer-generated random numbers. The dexmedetomidine group (Group D, $n=50$) received dexmedetomidine (Precedex[®] $100 \mu\text{g ml}^{-1}$, Hospira, Inc., Rocky Mount, IL, USA) at a rate of $0.4 \mu\text{g kg}^{-1} \text{ h}^{-1}$ from induction of anaesthesia until extubation, while the control group (Group C, $n=50$) received volume-matched normal saline infusion as placebo. Dexmedetomidine was diluted with normal saline to a concentration of $4 \mu\text{g ml}^{-1}$ in 50 ml. Dexmedetomidine or normal saline was prepared by an anaesthetist who did not participate in data collection. The investigator, attending anaesthetist, surgeons, recovery, ward nurses, and patients were blinded to group assignment.

All patients were premedicated with i.m. midazolam 0.04 mg kg^{-1} 30 min before induction of anaesthesia. Just before induction of anaesthesia, patients were given i.v. glycopyrrolate 0.1 mg . Routine monitors, including electrocardiogram, pulse oxygen saturation (SpO_2), non-invasive arterial pressure, and end-tidal CO_2 (E_{CO_2}) were applied and monitored at 5-min intervals. General anaesthesia was induced by combined use of fentanyl $1 \mu\text{g kg}^{-1}$ and propofol $1.5\text{--}2 \text{ mg kg}^{-1}$, after loading 4 ml kg^{-1} of crystalloid solution. After the administration of rocuronium bromide $0.6\text{--}0.8 \text{ mg kg}^{-1}$, orotracheal intubation was performed using a 6.5- and 7.5-mm tracheal tube for women and men, respectively. Mechanical ventilation was maintained with an 8 ml kg^{-1} tidal volume, and ventilation frequency was adjusted to maintain E_{CO_2} between 4.6–5.3 kPa in 50% O_2/air . Maintenance of anaesthesia was done with desflurane, which was regulated 0.6–1.4 age-adjusted minimal alveolar concentration (MAC) in order to maintain either bispectral index (BIS; A-2000[™] SP, Aspect Medical System, Norwood, MA, USA) value of 40–60 or minimum bleeding in the operation field. Bradycardia [heart rate (HR) $< 40 \text{ beats min}^{-1}$] was treated with i.v. atropine 0.5 mg . Tachycardia (HR $> 110 \text{ beats min}^{-1}$) was treated with i.v. esmolol in 10 mg increments. Hypotension [mean arterial pressure (MAP) $< 60 \text{ mm Hg}$] was treated with i.v. ephedrine at 6 mg increments. At the time of nasal packing, i.v. ketorolac 30 mg was administered to both groups.

Once the surgery was complete, oral suction was performed, and reversal agents (glycopyrrolate 0.004 mg kg^{-1} and neostigmine 0.02 mg kg^{-1}) were given after confirming

the return of neuromuscular function using train-of-four peripheral nerve stimulation. Following these steps, desflurane was turned off (defined as ‘time zero’ in the emergence process) in both groups, and mechanical ventilation was then converted to manual ventilation with 100% oxygen at 8 litre min^{-1} . The patients were not disturbed, except by continual verbal requests to open their eyes. All other stimuli were prevented. Extubation was performed when patients began breathing spontaneously and were able to respond to verbal requests with a BIS value of > 70 . After extubation, dexmedetomidine, or saline was stopped.

Emergence is defined as the time interval from ‘time zero’ to 2 min after extubation. During emergence, the level of agitation was evaluated using the Ricker sedation-agitation scale,¹⁴ and each patient’s maximum agitation score was recorded: 1=minimal or no response to noxious stimuli; 2=arouse to physical stimuli but does not communicate; 3=difficult to arouse but awakens to verbal stimuli or gentle shaking; 4=calm and follows commands; 5=anxious or physically agitated and calms to verbal instructions; 6=requiring restraint and frequent verbal reminding of limits; and 7=pulling at tracheal tube, trying to remove catheters or striking at staff. Emergence agitation was defined as any score on the sedation-agitation scale ≥ 5 . Dangerous agitation was defined as a sedation-agitation scale score = 7.^{1 14}

Grade of cough during emergence was assessed using a four-point scale (0=no cough; 1=single cough; 2=persistent cough lasting $< 5 \text{ s}$; and 3=persistent cough lasting $\geq 5 \text{ s}$ or bucking). The length of the period from ‘time zero’ to first verbal response and extubation were recorded. Respiratory rate and BIS at the time of extubation were measured. HR and MAP were recorded before induction of anaesthesia, 10 min after the start of operation, 30 min after the start of operation, at the end of operation, at extubation, and 2 min after extubation. Desaturation ($\text{SpO}_2 < 90\%$), laryngospasm and other complications were recorded during emergence.

In the post-anaesthetic care unit (PACU), residual sedation (sedation-agitation scale score ≤ 3 at arrival in PACU), score on an 11-point numerical rating scale (NRS) for pain (0=no pain and 10=worst pain imaginable), and score on a four-point nausea and vomiting scale (0=no nausea; 1=mild nausea; 2=severe nausea requiring antiemetics; and 3=retching, vomiting, or both) were evaluated. When NRS was ≥ 5 or if patients requested analgesics, additional injections of fentanyl $1 \mu\text{g kg}^{-1}$ were given. If a patient’s score on the nausea and vomiting scale was ≥ 2 , i.v. ondansetron 4 mg was given. Patients were discharged from the PACU when their Aldrete score was ≥ 9 .¹⁵

The quality of recovery was assessed 24 h after surgery using a 40-item quality-of-recovery questionnaire (QoR-40).¹⁶ Five dimensions of recovery are included within the QoR-40: emotional state (9 items), physical comfort (12 items), psychological support (7 items), physical independence (5 items), and pain (7 items). Each item is graded on a five-point score, and global scores range from 40 (extremely poor quality of recovery) to 200 (excellent quality of recovery).

Statistical analysis

The sample size calculation was based on the primary end-point of this study, the incidence of agitation. In a previous study, the incidence of emergence agitation after ENT general surgery was 55.4%.² With the assumption that dexmedetomidine infusion would reduce emergence agitation by 50% (α of 0.05 and a power of 80%), 48 subjects were required in each group. We included 50 patients per group to allow for possible dropouts.

Statistical analyses were performed using PASW Statistics 18 (SPSS, Inc., Chicago, IL, USA) or SAS software 9.2 (SAS, Inc., Cary, NC, USA). The normality of distribution was assessed with a Q-Q plot and the Shapiro-Wilk test. Parametric data were analysed with the independent *t*-test, and non-parametric data were analysed using the Mann-Whitney *U*-test. Categorical variables were evaluated using the χ^2 - or Fisher's exact test when appropriate. Repeat-measure variables (MAP and HR) were analysed using linear mixed models with a Bonferroni correction. All values were expressed as mean (SD), median (range), or the number of patients (%). A *P*-value of <0.05 was considered statistically significant.

Results

A total of 108 patients were assessed for eligibility and 100 subjects were enrolled in the study. After randomization, the participants either received dexmedetomidine or saline

during surgery. All patients completed the study (Fig. 1). Patient characteristics and operative procedures were similar between the two groups (Table 1).

The incidence of emergence agitation was lower in Group D than in Group C (28% vs 52%, $P=0.041$), while dangerous agitation was not different between the groups (Fig. 2). Agitation subsided within 5 min after extubation in all patients.

Age-adjusted MAC of desflurane was not different between the groups during the surgery (0.9 ± 0.2 in both groups at 10 min after the start of surgery and 0.9 ± 0.2 in Group D vs 1.0 ± 0.2 in Group C at 30 min after the start of surgery). At the completion of surgery, it was 0.9 ± 0.2 in Group D and 0.9 ± 0.1 in Group C. Other parameters related to emergence from general anaesthesia and recovery in the PACU are provided in Table 2. The time from desflurane discontinuation to extubation (8.7 min in Group D vs 7.8 min in Group C, $P=0.092$) was not different, even though the time to verbal response was longer in Group D compared with Group C (8.1 min vs 7.0 min, $P=0.044$). There were no differences between the groups in respiratory rate or BIS at the time of extubation, nor were there differences in coughing during emergence. Pain scores and administration of analgesics and antiemetics in the PACU were not different between the groups. Length of PACU stay was similar in both groups even though two patients in Group D had residual sedation (sedation-agitation scale score=3) upon arrival in the PACU. There were no complications, including

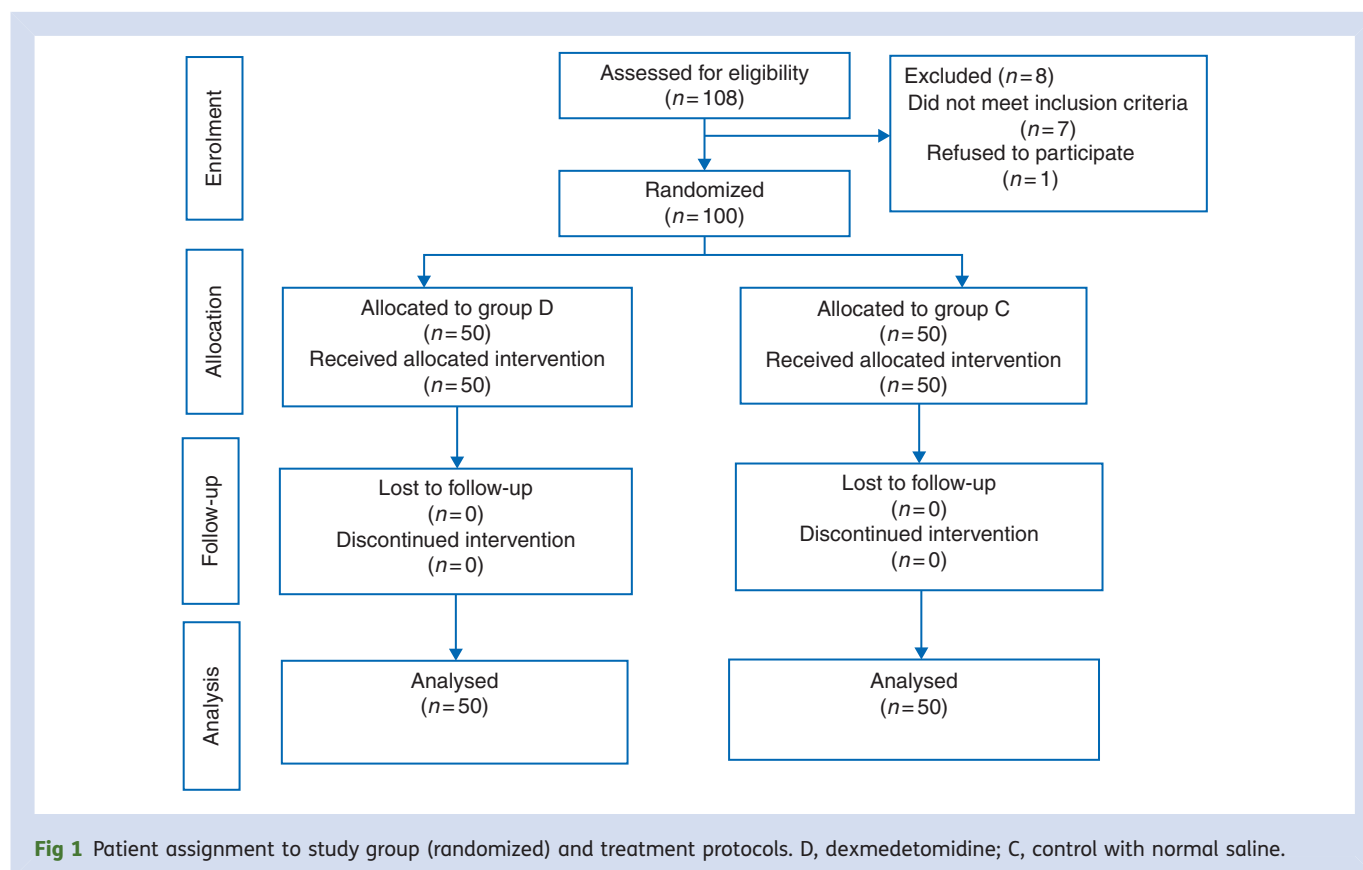


Table 1 Patient characteristics and operation details. Values are mean (SD), median (range) or number (%). D, dexmedetomidine; C, control with normal saline; study drug means dexmedetomidine or normal saline

	Group D (n=50)	Group C (n=50)	P-value
Age (yr)	32 (20–58)	33 (20–58)	0.863
Gender (M/F)	37 (13)	35 (15)	0.656
Height (cm)	169 (10)	169 (8)	0.956
Weight (kg)	66 (12)	66 (11)	0.894
Hypertension	1 (2%)	1 (2%)	1.000
Type of surgery			0.952
Septoplasty	23 (46%)	24 (48%)	
Ethmoidectomy, both	6 (12%)	5 (10%)	
Septoplasty and ethmoidectomy	18 (36%)	19 (38%)	
Septorhinoplasty	3 (6%)	2 (4%)	
Duration of surgery (min)	51 (25)	57 (29)	0.282
Infusion duration of study drug (min)	77 (29)	73 (27)	0.534
Amount of intraoperative fluid (ml)	506 (216)	524 (227)	0.689

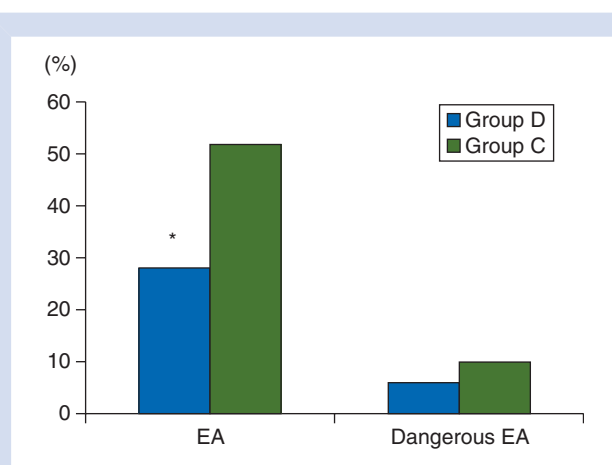


Fig 2 Incidence of emergence agitation and dangerous emergence agitation. D, dexmedetomidine; C, control with normal saline; EA, emergence agitation. Emergence is defined as the period from the end of surgery to 2 min after extubation. Agitation is defined as a sedation-agitation scale score of ≥ 5 . Dangerous agitation is defined as a sedation-agitation scale score = 7. * $P=0.041$ compared with Group C.

desaturation or laryngospasm, during emergence or while in the PACU.

MAP and HR during operation and emergence are shown in Figure 3. Intraoperative MAP and HR were similar in both groups. However, Group D demonstrated more stable haemodynamic changes during the emergence period compared

Table 2 Recovery characteristics. Values are mean (SD), median (range) or number (per cent). D, dexmedetomidine; C, control with normal saline; BIS, bispectral index; NRS, numerical rating scale; PACU, post-anaesthetic care unit. Time to verbal response or extubation is defined as the time period from desflurane discontinuation to verbal response or extubation. Residual sedation is defined as sedation-agitation scale score ≤ 3 at arrival in PACU. Grade of cough: 0, no cough; 1, single cough; 2, cough persistence < 5 s; 3, persistent cough for ≥ 5 s or bucking. Emergence is defined as the period from end of surgery to 2 min after extubation

	Group D (n=50)	Group C (n=50)	P-value
Time to verbal response (min)	8.1 (2.9)	7.0 (2.5)	0.044
Time to extubation (min)	8.7 (2.9)	7.8 (2.6)	0.092
Respiratory rate at extubation (min^{-1})	17.0 (4.5)	17.5 (4.4)	0.633
BIS at extubation	81.5 (5.7)	83.2 (5.6)	0.145
Grade of cough during emergence	2 (0–3)	2 (0–3)	0.469
Residual sedation in PACU	2 (4%)	0	0.495
NRS for pain in PACU	2 (0–6)	2 (0–8)	0.061
Analgesics in PACU	4 (8%)	8 (16%)	0.218
Antiemetics in PACU	3 (6%)	9 (18%)	0.065
Length of PACU stay (min)	16.2 (5.3)	16.4 (5.5)	0.897

with Group C (Bonferroni corrected $P<0.05$). During the operation, ephedrine was administered to seven patients in Group D and four patients in Group C ($P=0.338$), while esmolol was administered to six patients in Group C and no patients in Group D ($P=0.027$). No patient in either group experienced bradycardia.

The QoR-40 score at 24 h after surgery are demonstrated in Table 3. The median global score in Group D was 183 (range: 146–198). This was significantly higher than the QoR-40 score of 178 (range: 133–196) for Group C ($P=0.041$). Group D demonstrated higher scores in pain dimension compared with Group C ($P=0.030$).

Discussion

The results of this prospective double-blind randomized study suggest that intraoperative continuous dexmedetomidine infusion ($0.4 \mu\text{g kg}^{-1} \text{h}^{-1}$) until extubation was effective in reducing the incidence of emergence agitation after nasal surgery without delay of extubation or increasing incidence of other complications. Furthermore, intraoperative use of dexmedetomidine produced more stable haemodynamic changes during extubation and enhanced patient-reported global quality of recovery at 24 h after surgery.

Emergence agitation has been reported in up to 20% of adult patients after general surgery.^{1 2} Male gender, type of

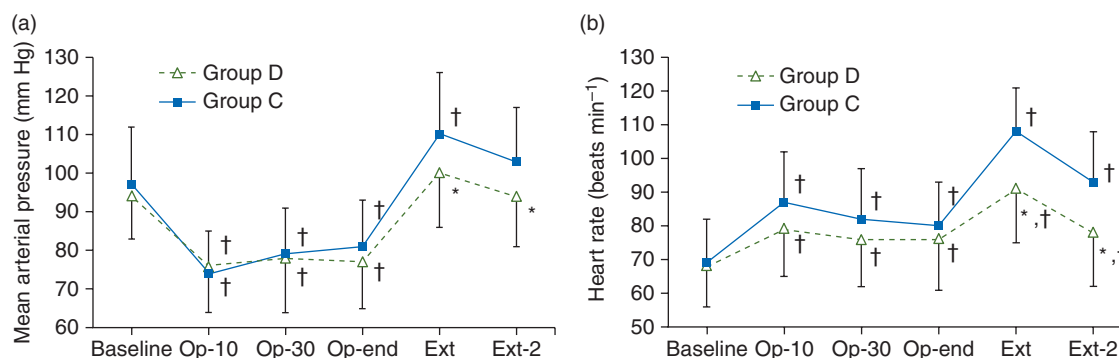


Fig 3 Haemodynamic changes during operation and emergence. (a) MAP, and (b) HR. Baseline, before anaesthetic induction; Op-10, 10 min after the start of operation; Op-30, 30 min after the start of operation; Op-end, end of operation; Ext, extubation; Ext-2, 2 min after extubation. Data are expressed as mean (SD). * $P < 0.05$ compared with Group C (Bonferroni corrected). † $P < 0.05$ compared with baseline in each group (Bonferroni corrected).

Table 3 QoR-40 dimensions and global scores. Values are median (range). D, dexmedetomidine; C, control with normal saline

	Group D (n=50)	Group C (n=50)	P-value
QoR-40 dimensions			
Emotional state	40 (33–45)	40 (25–45)	0.107
Physical comfort	53 (39–60)	52 (38–58)	0.358
Psychological support	35 (28–35)	35 (23–35)	0.073
Physical independence	24 (14–25)	24 (10–25)	0.094
Pain	32 (22–35)	30 (17–35)	0.030
Global QoR-40	183 (146–198)	178 (133–196)	0.041

surgery, inhalation anaesthetics, presence of tracheal tube and preoperative benzodiazepine medication are risk factors for postoperative agitation in adults.^{1,2} Emergence agitation is especially common after ENT surgery, where 55.4% of patients experienced agitation.² High incidence of emergence agitation after ENT surgery may be attributable to a sense of suffocation.¹⁷ In our study, we only included patients who were expected to have a higher risk of emergence agitation for the following reasons: the patient required each-side nasal packing, a tracheal tube was used, benzodiazepine premedication and inhalation anaesthetics were administered. As expected, in Group C, the incidence of emergence agitation was 52%, which is similar to a previously reported result.²

Dexmedetomidine induces sedation and analgesia without respiratory depression.⁴ Therefore, it has been used for preventing emergence agitation. Intraoperative administration of dexmedetomidine reduced emergence agitation in children by 57–70% compared with control groups.^{5,6,18,19} Consistent with previous results,^{5,6,18,19} dexmedetomidine was also effective in reducing emergence agitation by 46% in adults.

Even though time to verbal response was significantly longer in Group D than Group C, time to extubation was not significantly different between the two groups. This may be because of higher incidence of agitation in Group C. Extubation is sometimes delayed during agitation because of security of airway patency. In our study, the longest time to extubation was 19 min, in a subject who received dexmedetomidine infusion for 112 min. Meanwhile, maximum duration of dexmedetomidine infusion was 161 min, and extubation was performed 10 min after desflurane was discontinued. As dexmedetomidine dose not depress respiratory drive in spite of its sedative property, maintenance of dexmedetomidine infusion until extubation may be safe considering the results that the mean BIS value at extubation was 82 and mean respiratory rate was 17 min⁻¹ in Group D. However, the sedative effect of dexmedetomidine may not be enough to prevent cough after nasal surgery using desflurane anaesthesia. Use of desflurane for maintenance of anaesthesia was reported to result in faster emergence, but higher incidence of coughing compared with sevoflurane.²⁰

In our study, no patient had agitation in the PACU and two patients in Group D had residual sedation (sedation-agitation scale score=3, difficult to arouse but awakens to verbal stimuli or gentle shaking) at arrival in the PACU. However, these two patients were fully awake 10 min after arrival and stayed in the PACU for 15 and 26 min, respectively. Their lengths of PACU stay were clinically acceptable.

Dexmedetomidine can cause haemodynamic changes including hypotension (30%), hypertension (12%), and bradycardia (9%).²¹ In previous studies of emergence agitation, the protocols for dexmedetomidine administration were diverse (e.g. only loading of 0.5 µg kg⁻¹, only infusion of 0.2 µg kg⁻¹ h⁻¹, or loading of 2 µg kg⁻¹ followed by infusion of 0.7 µg kg⁻¹ h⁻¹).^{5,6,18,19} Because hypertension is common after administration of the loading dose of dexmedetomidine,²² we administered a continuous infusion of 0.4 µg kg⁻¹ h⁻¹ without a loading dose, which was also

effective in reducing agitation during weaning from mechanical ventilation in critically ill patients.⁷ Intraoperative MAP and HR tended to be lower in Group D compared with Group C, however, there were no significant differences between the groups. Furthermore, incidence of hypotension that required ephedrine treatment was not different between the groups and none of the patients in Group D had bradycardia. Risk of bradycardia with dexmedetomidine may be offset by a dose-dependent increase in HR with desflurane.

Maintenance of dexmedetomidine until extubation provided more stable haemodynamic changes during emergence in our study. However, in a previous study, in which dexmedetomidine infusion of $0.2 \mu\text{g kg}^{-1} \text{h}^{-1}$ was maintained during extubation, MAP and HR were not different between the dexmedetomidine and control groups.⁶ These different results may be attributed to the different age groups of the patients (adults vs children), or differing infusion concentration ($0.4 \mu\text{g kg}^{-1} \text{h}^{-1}$ vs $0.2 \mu\text{g kg}^{-1} \text{h}^{-1}$).

Global QoR-40 scores were significantly higher in Group D compared with Group C. Among the five dimensions in the QoR-40, pain was the most significantly improved among Group D patients. The effect of intraoperative dexmedetomidine infusion on patient-perceived quality of recovery has been investigated in only a few studies. After laparoscopic bariatric surgery, in which a nine-item questionnaire was used for assessing quality of recovery, $0.2\text{--}0.8 \mu\text{g kg}^{-1} \text{h}^{-1}$ of dexmedetomidine was not associated with improved quality of recovery.⁹ However, after major spinal surgery, $0.5 \mu\text{g kg}^{-1} \text{h}^{-1}$ of dexmedetomidine was associated with improved quality of recovery as measured by the 40-item questionnaire that was used in our study.¹³ The QoR-40 is a useful objective measurement of quality of recovery after anaesthesia and surgery, and it is the only assessment tool that fulfils all of the eight quality-of-recovery criteria—appropriateness, reliability, validity, responsiveness, precision, interpretability, acceptability, and precision.^{16 23}

There are several limitations to this study. First, we cannot rule out the possible effects of pain and preoperative anxiety on emergence agitation. However, severity of pain might be similar between the groups during emergence because NRS for pain and use of additional analgesics in the PACU was not different between the groups. Additionally, preoperative anxiety has been reported to have no relationship with postoperative agitation.¹ Secondly, we did not conduct a preoperative QoR-40 questionnaire. However, preoperative values might be similar in both groups because we included in both groups patients who were 20–58 years old, were classified into ASA class I–II, and did not have cognitive impairment or a history of chronic use of antipsychotic medications. Thirdly, it is uncertain whether the beneficial effects of dexmedetomidine persisted beyond 1 day after nasal surgery because QoR-40 scores were only collected at 24 h after surgery. Fourthly, as sample size calculation was based on the incidence of emergence agitation, sample size may not be enough to check quality of recovery. Therefore, the significantly higher Global QoR-40 scores observed in Group D may be underpowered.

In conclusion, maintenance of intraoperative dexmedetomidine infusion ($0.4 \mu\text{g kg}^{-1} \text{h}^{-1}$) until extubation provided smooth and haemodynamically stable emergence without complications after nasal surgery. Furthermore, it improved the quality of recovery 1 day after surgery.

Declaration of interest

None declared.

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