Comparison of Remifentanyl Concentrations with and without Dexmedetomidine for the Prevention of Emergence Cough after Nasal Surgery: A Randomized Double Blinded Trial

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Research article

Keywords: cough, dexmedetomidine, emergence, remifentanyl

Posted Date: October 8th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-74937/v1>

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Version of Record: A version of this preprint was published at BMC Anesthesiology on May 4th, 2021. See the published version at <https://doi.org/10.1186/s12871-021-01358-x>.

Abstract

Background: After nasal surgery, preventing emergence cough is critical. Emergence cough can provoke immediate postoperative bleeding, which leads to upper airway obstruction. In the present study, we compared the effect-site concentration (Ce) of remifentanyl for preventing emergence cough after propofol anesthesia when remifentanyl was or was not combined with dexmedetomidine after nasal surgery.

Methods: Forty-seven patients who underwent nasal surgery with propofol-remifentanyl anesthesia were randomly divided into a dexmedetomidine group (Group D, n=23) or a saline group (Group S, n=24). Group D and Group S were infused dexmedetomidine (0.5 µg/kg) or saline for 10 min before the completion of surgery. Remifentanyl was infused a predetermined Ce until extubation. Remifentanyl Ce for the prevention of cough in 50% of patients (EC₅₀) and 95% of patients (EC₉₅) was estimated using modified Dixon's up-and-down method and isotonic regression. Hemodynamic and recovery parameters were observed.

Results: The EC₅₀ of remifentanyl Ce in Group D was significantly lower than that in Group S (2.15 ± 0.40 ng/mL vs. 2.66 ± 0.36 ng/mL, $p = 0.023$). The EC₉₅ (95% CI) of remifentanyl Ce was also significantly lower in Group D [2.75 (2.67 - 2.78) ng/mL] than in Group S [3.16 (3.06 - 3.18) ng/mL]. Emergence and recovery parameters were comparable between the two groups.

Conclusion: The remifentanyl EC₅₀ for the prevention of cough after propofol-remifentanyl anesthesia was significantly lower (approximately 19%) when a combination of remifentanyl and 0.5 µg/kg dexmedetomidine was used than when remifentanyl infusion alone was used in patients undergoing nasal surgery. Therefore, the Ce of remifentanyl may be adjusted for the prevention of emergence cough when used in combination with dexmedetomidine.

Trial registration: ClinicalTrials.gov, NCT03622502, Registered August 9, 2018, <https://clinicaltrials.gov>

Background

Emergence cough after general anesthesia leads to serious adverse effects including surgical site bleeding, wound disruption, hemodynamic instability, and increased intracranial and intraocular pressure [1]. The prevention of cough in nasal surgery patients is especially important because cough can provoke immediate postoperative bleeding, which leads to upper airway obstruction [2].

Remifentanyl has emerged as a medication for cough prevention after general anesthesia. In prior studies, effective remifentanyl effect-site concentrations (Ce) under various conditions have ranged from 1.5 to 2.9 µg/mL [3–6]. Although an increasing dose of remifentanyl may effectively prevent cough, this drug also increases the incidences of adverse effects including respiratory depression, nausea and vomiting, or delayed emergence [3, 7]. Thus, to decrease remifentanyl's Ce and its side effects when administered alone, co-administration of other adjuvant drugs may prove useful.

Dexmedetomidine is a highly selective α_2 -agonist and acts as a sedative and analgesic, though it has little effect on respiratory depression even when used at maximum concentrations [8]. A low-dose combination of dexmedetomidine and remifentanyl administered prior to surgery is reportedly more effective in preventing emergence cough without respiratory depression than a low-dose of remifentanyl alone [9]. In addition, a low-dose combination of dexmedetomidine (0.5 $\mu\text{g/kg}$) and remifentanyl was not inferior to a high dose of remifentanyl alone for the prevention of emergence cough [10]. However, the effective remifentanyl Ce for the prevention of emergence cough have not been evaluated when administered with a single dose of dexmedetomidine.

The present study was the first to investigate the effective remifentanyl Ce on the prevention of emergence cough after propofol anesthesia in 50% of patients (EC_{50}) and in 95% of patients (EC_{95}) when remifentanyl and dexmedetomidine (0.5 $\mu\text{g/kg}$) were used versus remifentanyl alone in patients undergoing nasal surgery.

Methods

The present prospective trial was done with the approval of the Ajou University Hospital Institutional Review Board (AJIRB-MED-OBS-18-170) and registered at ClinicalTrials.gov (ref no.: NCT03622502). Written informed consent was obtained from all participants. Patients with American Society of Anesthesiologists (ASA) physical status scores of 1 or 2 between the ages of 19 to 65 years who had planned septoplasty or endoscopic sinus surgeries were enrolled. Participant exclusion criteria were a potentially difficult airway (Mallampati class 3 or 4), use of angiotensin converting enzyme-inhibitors, severe obesity (body mass index $> 35 \text{ kg/m}^2$), current smoker, a recent upper airway infection, asthma, and uncontrolled hypertension. According to a randomization generator (<http://www.random.org>), patients were randomized into a saline group (Group S) or a dexmedetomidine group (Group D).

After patients entered the operating room (no premedication), anesthetic monitoring including non-invasive blood pressure (BP), electrocardiogram, and pulse oximetry monitoring was applied. To monitor the depth of anesthesia, a bispectral index (BIS) sensor was also applied to the patient's forehead. For anesthesia induction, target-controlled infusion (TCI) was started (propofol Ce of 5.0 $\mu\text{g/mL}$ and remifentanyl Ce of 4.0 ng/mL) using an infusion device (Orchestra, Fresenius Vial, France). Two min after administration of rocuronium (0.6 mg/kg), endotracheal intubation was performed using a cuffed tube (inner diameter of 7.5 mm in males and 7.0 mm in females) with a cuff pressure of 20–25 mmHg.

Anesthesia was maintained with propofol Ce of 2.0–3.0 $\mu\text{g/mL}$ and remifentanyl Ce of 3.0–5.0 ng/mL . Anesthetic depth was adjusted from a BIS value of 40 to 60. Intraoperative heart rate (HR) and BP were adjusted to within 20% of baseline (before induction of anesthesia). When HR dropped below 45 bpm, atropine (0.5 mg) was administered. When mean BP decreased to less than 20% of baseline mean BP, ephedrine (6 mg) was administered.

Dexmedetomidine (0.5 µg/kg) in Group D and the same volume of normal saline in Group S were infused over 10 min using a syringe pump before completion of surgery. Upon completion of surgery, propofol infusion was halted. Throughout emergence, remifentanyl infusion of predetermined Ce was continued for at least 15 min until extubation. Drugs were administered by one researcher (JY Kim) according to the patient's group identity (dexmedetomidine or normal saline and a pre-determined Ce of remifentanyl). Patients' degree of muscle relaxation was assessed using train-of-four (TOF) monitoring. When the TOF ratio was more than 90%, neostigmine (0.02 mg/kg) and glycopyrrolate (0.004 mg/kg) were injected. Subsequently, assisted ventilation with 100% of inspired oxygen was initiated in response to spontaneous patient breathing. When the patient opened their eyes spontaneously or in response to a verbal command, we confirmed that their spontaneous breathing was sufficient and removed their endotracheal tube. Thereafter, remifentanyl was stopped and a facial mask delivering 100% oxygen was applied. The patient was transferred to a post-anesthetic care unit (PACU) after confirming the adequacy of their consciousness and respiration over a 5-min period. In the PACU, the patient was assessed for postoperative nausea and vomiting (PONV). Patient pain was evaluated using a numeric rating scale (NRS), which ranges from 0 (no pain) to 10 (worst possible pain). If the patient suffered from pain rated worse than a 5 or requested painkiller administration, fentanyl (50 µg) was injected. Sedation was also evaluated using a modified Wilson sedation scale [11]. When the modified Aldrete score was ≥ 9 , patients were transferred to the ward [12].

Patients were sequentially enrolled using a Dixon's up-and-down allocation approach, as previously [13]. Patient enrolment continued until both groups reached at least 20 patients and six success-failure pairs. Cough was defined as a sudden expulsion of air with abdominal muscle contraction and classified into one of four grades (grade 0: no cough, grade 1: single cough, grade 2: more than one episode of non-sustained cough, grade 3: sustained and repetitive cough). Cough was assessed from the end of surgery to 5 min after extubation. The Ce of remifentanyl was initiated with 2.0 ng/mL in each group. The next patient's Ce of remifentanyl was determined by the previous patient's cough response. If the patient had no cough or a single cough (grade 0 or 1), we defined this as successful prevention of cough, and the pre-determined Ce of remifentanyl for the next patient was lowered by 0.4 ng/mL. If cough was not successfully prevented (grade 2 or 3), we determined the result to be a failure at preventing cough, and the pre-determined Ce of remifentanyl for the next patient was increased by 0.4 ng/mL.

During the operations, data on the Ce for propofol and remifentanyl, mean BP, HR, pulse oximetry saturation (SpO₂), BIS value, respiratory rate, and end-tidal CO₂ (EtCO₂) were collected at seven time points, namely, baseline (T0), immediately before (T1) and after (T2) the start of dexmedetomidine or saline infusion, upon operation completion (T3), at eye opening (T4), and immediately (T5) and 5 min (T6) after extubation. In addition, the intraoperative use of medications to control BP or HR was recorded.

Cough was assessed by one researcher (HY Kim), from whom patients' group allocations and the predetermined Ce of remifentanyl was concealed. The times elapsed between stopping propofol administration to eye opening (time to eye opening) and from stopping propofol administration to extubation (time to extubation) were recorded. For 5 min after extubation, bradypnea (respiratory rate < 8

breaths/min), laryngospasm, and desaturation ($\text{SpO}_2 < 95\%$) were recorded. In the PACU, respiratory rate, PONV, pain scores using the NRS, Aldrete score, sedation scale, and stay duration were recorded.

Statistical analyses

The EC_{50} and EC_{95} of remifentanyl for preventing cough in Group D were the primary study outcomes. To obtain the EC_{50} by Dixon's up-and-down method, at least six success-failure pairs and 20 patients were needed [14]. The EC_{50} of remifentanyl was defined as the mean value of the mid-point for each failure-to-success pair. To obtain the EC_{95} of remifentanyl, the isotonic regression method using a pooled-adjacent-violators algorithm and a bootstrapping approach was also used, as previously [15]. No overlap between two EC_{95} values at 95% confidence interval (CI) was considered a significant difference [16].

Categorical variables were analyzed using the chi-squared or Fisher's exact tests, and continuous variables were analyzed using independent t-tests or Mann-Whitney U tests. Measured variables were repeatedly analyzed using the linear mixed model (LMM). When the model revealed a significant interaction between group and time, a post-hoc analysis was performed to identify time points which differed significantly. Data are shown as means $\pm$ standard deviations (SDs), medians (interquartile range, IQR), or numbers (frequency). A *P*-value less than 0.05 was considered significant. Statistics were analyzed with SPSS (version 25.0, IBM Corporation, Armonk, NY, USA) and R (version 3.2.5).

Results

Forty-eight patients were enrolled between August 2018 and March 2019. One patient was withdrawn due to incorrect initiation of dexmedetomidine, leaving 23 patients in Group D and 24 patients in Group S who completed the study (Fig. 1). Preoperative patient characteristics and intraoperative details were comparable between the two groups (Table 1).

Table 1
Preoperative and intraoperative patient characteristics.

	Group D (n = 23)	Group S (n = 24)	P-value
Sex, male n (%)	14 (61)	19 (79)	0.636
Age, years	40 ± 12	40 ± 14	0.875
Weight, kg	74 (66–84)	73 (64–76)	0.442
Height, cm	170 (160–176)	172 (166–182)	0.248
ASA classification (I/II), n	19/4	18/6	0.724
Operation time, min	35 (25–40)	30 (25–44)	0.765
Anesthesia time, min	70 (60–75)	70 (60–89)	0.579
Values are mean ± SD, median (25th – 75th IQR), or number (%).			
ASA, American Society of anesthesiologist			

Successes and failures to prevent emergence cough in consecutive patients are shown in Fig. 2. EC₅₀s were calculated by Dixon's method from eight failure-success pairs in Group D and from seven failure-success pairs in Group S. The EC₅₀ for remifentanyl was significantly lower in Group D than in Group S (2.15 ± 0.04 vs. 2.66 ± 0.36 ng/mL, respectively, P = 0.023). The EC₉₅ (95% CI) for remifentanyl was also significantly lower in Group D than in Group S [2.75 (2.67–2.78) vs. 3.16 (3.06–3.18) ng/mL, respectively], and their 95% CIs did not overlap.

During surgery, repeated measure variables including MBP, HR, SpO₂, BIS value, and EtCO₂ had similar trends over time in both groups (all p values > 0.05) (data not shown). The number of patients who were administered ephedrine did not differ between the two groups [9 (39.1%) in Group D vs. 11 (45.8%) in Group S, p = 0.642]. One patient in Group D received atropine.

During emergence, time to eye opening, time to extubation, and respiration rate did not differ between the two groups. Bradypnea within 5 min of extubation occurred in six patients in Group D and in nine patients in Group S (P = 0.401). This bradypnea was transient in all patients and recovered with respiratory encouragement (Table 2).

Table 2
Emergence and recovery parameters.

	Group D (n = 23)	Group S (n = 24)	P-value
During emergence			
Time to eye opening, sec	560 (490–670)	565 (453–714)	0.975
Time to extubation, sec	670 (630–750)	690 (540–795)	0.775
Respiration rate, breaths/min			
Immediately after extubation	10 (9–12)	12 (9–13)	0.412
5 min after extubation	12 (12–13)	12 (10–13)	0.360
Bradypnea, n (%)	6 (26)	9 (38)	0.401
In the post-anesthesia care unit			
Pain score, NRS	2 (2–3)	2 (2–3)	0.644
Rescue analgesics, n (%)	2 (10)	2 (9)	0.456
PONV, n (%)	4 (18)	2 (9)	0.414
Duration of stay, min	30 (30–40)	30 (30–40)	0.745
Values are median (25th – 75th IQR), or number (%).			
NRS, numeric rating scale (0 = none, 10 = the worst); PONV, postoperative nausea and vomiting			

In the PACU, postoperative pain scores, the number of patients receiving rescue analgesics, PONV, and duration of stay did not differ between the two groups. Respiratory rate, Aldrete scores, and sedation scale scores also did not interact significantly with time and group (data not shown).

Discussion

In the present study, we evaluated remifentanil's Ce for the prevention of emergence cough after propofol anesthesia administration with and without co-administration of dexmedetomidine (0.5 µg/kg). The combined infusion of dexmedetomidine and remifentanil significantly reduced remifentanil EC₅₀ and EC₉₅ measures by 19% and 13%, respectively, compared to remifentanil infusion alone. In addition, the combined use of these drugs did not delay the time to awakening or extubation and did not aggravate respiratory depression.

Cough is mediated by peripheral nerve terminals within the airway walls and by central vagus afferent nerves in the nodose ganglia or bodies of the jugular [17, 18]. Several antitussive agents are known to inhibit peripheral cough pathways (e.g. local anesthetics), central cough pathways (e.g. gamma-aminobutyric acid agonists), or both cough pathways (e.g. opioids) [17, 18]. Of these, remifentanil is the antitussive agent of choice for use during anesthesia due to its uniquely rapid action without

accumulation [7]. However, although remifentanyl has a dose-dependent antitussive effect, it also has dose-dependent adverse effects such as respiratory depression, muscle rigidity, nausea and vomiting, pruritus, or delayed emergence [3, 7].

In recent years, the application of dexmedetomidine as a sedative and analgesic which does not cause respiratory depression has grown [19]. Given this, several studies have assessed the efficacy of dexmedetomidine for the prevention of cough [20–24]. At present, there have been conflicting results regarding the antitussive effects of dexmedetomidine. Several studies have reported that dexmedetomidine may not prevent cough better than remifentanyl, midazolam, or even saline [20–22]. However, other studies have reported that dexmedetomidine may prevent cough better than placebo (saline) [23, 24] and that it may have dose-dependent antitussive effects [23]. Although the efficacy of dexmedetomidine as an antitussive agent has not been fully evaluated, dexmedetomidine combined with remifentanyl may be more effective at preventing cough than remifentanyl alone [9, 10]. However, studies have reported that the combined use of dexmedetomidine and remifentanyl to prevent cough during emergence lead to delayed emergence compared to the use of remifentanyl alone [9, 10]. Therefore, clarifying what dose of remifentanyl should be used in combination with dexmedetomidine to prevent cough during emergence remains necessary.

The present study revealed differences of 0.4–0.5 ng/mL between the remifentanyl EC_{50} and EC_{95} between the two groups. In addition, a reduced C_e of remifentanyl when dexmedetomidine was combined did not delay emergence time (from eye opening to extubation) compared to the use of remifentanyl alone. In the present study, the remifentanyl EC_{95} after nasal surgery when remifentanyl was used alone was 3.16 ng/mL. This remifentanyl C_e was a substantially higher dose than that reported previously in the context of thyroid surgery (2.14 ng/mL) or brain tumour surgery (2.51 ng/mL) [25, 26]. Meanwhile, Choi et al. [4] found that the ideal remifentanyl EC_{95} for preventing cough after nasal surgery was 2.94 ng/mL, comparable to that reported here. Choi et al. suggested that coughing was more frequent after nasal surgery than other type of surgery, potentially because of chronic inflammation in the nasal mucosa, perioperative mechanical irritation, and pharyngolaryngeal stimulation by blood. Thus, the type of surgery could be one factor which determines the ideal remifentanyl C_e for preventing emergence cough.

Despite our findings, the use of high concentrations of remifentanyl (e.g., above 3.0 ng/mL) for the prevention of cough may not be practical given that remifentanyl infusion during emergence under propofol anesthesia may increase the hypnotic effects of propofol and respiratory depression [27]. In a previous study, remifentanyl infusion at 3.0 ng/mL during laryngomicroscopic surgery after propofol anesthesia led to a higher incidence of hypoventilation and longer extubation time during emergence than remifentanyl infusion at 2.6 ng/mL or less [6]. This result indicates that the combined use of dexmedetomidine and remifentanyl for preventing emergence cough is feasible in clinical settings.

In the present study, the combined use of remifentanyl and dexmedetomidine did not attenuate hemodynamic changes during extubation better than remifentanyl alone. This is in contrast to previous reports in which hemodynamic changes were attenuated better with combined dexmedetomidine

(0.5 µg/mL) and remifentanyl (1 ng/mL) than with remifentanyl infusion alone [9]. The mean C_{es} for remifentanyl in the present study were 2.1 in Group D and 2.5 ng/mL in Group S. Remifentanyl attenuated hemodynamic changes during emergence in a dose-dependent manner [5]. Thus, relatively high doses of remifentanyl may have offset the cardiovascular effects of dexmedetomidine. Meanwhile, recovery profiles including respiratory rate were not different between the two groups, paralleling findings from a previous study by Kim et al. [10]. Kim et al. [10] suggested that remifentanyl plays a major role in regulating respiratory profiles when combined with dexmedetomidine because it does not worsen the respiratory depression caused by remifentanyl.

The present study has several limitations. First, although the Dixon' up-and-down method allows for good median estimation, it is a simple strategy. Because such median estimations depend on the chosen pairs (e.g. success-failure pairs or failure-success pairs) and clinical circumstances, the EC_{50} is a relative and not absolute value. Second, this study's sample size was determined using the Dixon' up-and-down allocation approach and may therefore be insufficient to confirm differences in secondary outcomes between the two groups. Third, all cases included in this study were performed under propofol anesthesia. Therefore, different results may emerge in cases which utilize inhalational anesthesia.

Conclusions

The C_e for remifentanyl for the prevention of emergence cough after propofol anesthesia administration was significantly lower when a single dose of dexmedetomidine (0.5 µg/kg) was co-infused with remifentanyl than when remifentanyl was administered alone in nasal surgery patients.

Abbreviations

ASA: American Society of Anesthesiologists; BIS: bispectral index; BP: blood pressure; C_e : effect-site concentration; CI: confidence interval; EC_{50} : effective concentration in 50% of patients; EC_{95} : effective concentration in 95% of patients; $ETCO_2$: end-tidal CO₂; HR: heart rate; IQR: interquartile range; LMM: linear mixed model; NRS: numeric rating scale; PACU: post-anesthetic care unit; PONV: postoperative nausea and vomiting; SD: standard deviations; SPO_2 : pulse oximetry saturation; TCI: target-controlled infusion; TOF: train-of-four

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Ajou University Hospital Institutional Review Board (AJIRB-MED-OBS-18-170). Written informed consent was obtained from all subjects participating in the trial. The trial was registered prior to patient enrollment at ClinicalTrials.gov (ref no.: NCT03622502).

Consent for publication

All data published here are under the consent for publication. Written informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The datasets generated and analyzed during the present study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

Funding

Not applicable.

Authors' contributions

HYK: data collection, manuscript drafting and editing. HJK: study design, and interpretation. DL: formal analysis. JHL: data collection and analysis. SKM: supervision. JYK: study design, manuscript drafting and editing. All of the authors have read and approved the manuscript.

Acknowledgements

Not Applicable.

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Figures

Figure 1

The CONSORT flow diagram

Figure 2

Effect-site concentration of remifentanyl by Dixon's methods in Group D(A) and in Group S(B)

Supplementary Files

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