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Optimal remifentanil effect-site concentration for preventing cough and hyperdynamic response during tracheal extubation after sevoflurane vs. desflurane: the REX trial

Abstract

Purpose: To evaluate the impact of three different effect-site concentrations of remifentanil [1.0, 2.0 and 2.5 ng.ml^{-1}] on cough, heart rate and systolic blood pressure during extubation after balanced anesthesia with desflurane or sevoflurane.

Design: Double-blinded controlled trial.

Setting: Operating room.

Patients: ASA I-II adults (n=451) who underwent elective procedures.

Interventions: Subjects were randomly assigned to maintain remifentanil effect-site concentrations at 1.0, 2.0 and 2.5 ng.ml^{-1} by a target control infusion system after receiving balanced general anesthesia with remifentanil and sevoflurane vs. desflurane.

Measurements: Cough severity (using a four-point intensity scale), heart rate and systolic blood pressure were registered during eye opening, tracheal extubation and 2.5 minutes after.

Main Results: Cough was significantly reduced in all groups of remifentanil at 2.0 and 2.5 ng.ml^{-1} during eye opening, tracheal extubation and 2.5 minutes after, when compared with 1.0 ng.ml^{-1} [Risk ratio (95% CI) at tracheal extubation 0.35 (0.23-0.53) and 0.33 (0.21-0.52) for desflurane; 0.50 (0.35-0.73) and 0.45 (0.30-0.73) for sevoflurane, respectively. $P < 0.001$]. There were no significant differences on heart rate or systolic blood pressure values at these time points for any of the studied groups.

Conclusion: In adult patients of elective procedures under balanced general anesthesia with sevoflurane or desflurane, maintaining a remifentanil effect-site concentration at 2.0-2.5ng.ml^{-1} significantly reduce the risk of cough but not hemodynamic responses during tracheal extubation.

Keywords: Remifentanil; Cough; Airway Extubation; Awakening; Balanced Anesthesia

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Introduction

Sympathetic stimulation is common during emergence from general anesthesia and awakening. Cough is particularly the most frequent reflex (38-96%) experienced by patients during tracheal extubation (TE), at least in part due to activation of airway mechanoreceptors.[1,2] An increase of venous, intracranial, ocular and abdominal pressures may be noted in patients with severe cough during TE.[3] Furthermore, cough may be associated with deleterious morbidities and other clinical surrogates of autonomic hyperactivity such as tachycardia and hypertension that eventually can precipitate ventricular overload, arrhythmias and myocardial ischemia in susceptible individuals.[4]

Many strategies have been studied to reduce cough and autonomic hyperactivity during TE. Studies comparing dexmedetomidine, esmolol and lidocaine by different approaches at this setting have shown no conclusive results about their specific benefits as monotherapies.[5,6] Total intravenous anesthesia (TIVA) seems to reduce these events thereby allowing a softer emergence when compared with balanced inhaled anesthesia,[7] but access in many countries to systems for simultaneous infusions, drug availability and costs are limiting factors for its widespread use.

Remifentanil is an ultra-short-acting opioid that has been used in multiple subpopulations as an effective intervention to mitigate some potentially harming autonomic reflexes in response to a variety of perioperative stimuli.[8,9] When remifentanil is administered by continuous infusion during emergence, it seems to be an effective intervention to decrease severe cough and hyperdynamic response during TE. A recently published work suggests that maintaining a remifentanil effect-site concentration (Ce) at 1.5 ng.ml^{-1} during TE in patients who received TIVA, reduced autonomic response and cough episodes from 90% to 40% without differences in time from TE to awakening.[10] In patients under balanced general anesthesia (BGA) there is moderate evidence that favors the use of remifentanil over several other agents for this purpose but little is known about the effects at different Ce when different inhaled anesthetics are used.[11,12]

In this randomized controlled trial, we aimed to evaluate the impact of three different Ce of remifentanil [1.0, 2.0 and 2.5 ng.ml^{-1}] on cough, heart rate (HR) and systolic blood pressure (SBP) at eye opening, TE and at 2.5 minutes after awakening in Oval patients who received BGA with sevoflurane or desflurane.

Methods

The REX (Remifentanil during tracheal Extubation) trial was a double-blind randomized controlled trial that had IRB approval prior the recruitment of patients (Comité de Ética en Investigación Biomédica FVL/ Protocol No. 380/01/07/2013) and was originally registered with the number NCT03132519 at ClinicalTrials.gov. This study was conducted in ASA I-II adult patients (age > 18 years) who were intubated and received BGA with sevoflurane or desflurane for elective procedures. Subjects with history of uncontrolled hypertension, chronic cough, active or uncontrolled pulmonary disease, signs or history of difficult airway, recent respiratory infection, BMI above 30 $Kg.m^{-2}$, concomitant use of epidural catheter and those who had received some form of oral/intravenous pre-medication, beta-blockers or antitussives were excluded.

Subjects were divided into six arms using three different Ce of remifentanil (1.0, 2.0 or 2.5 $ng.ml^{-1}$) adjusted to real body weight during emergence and TE after inhaled anesthesia with sevoflurane or desflurane. The arms are explained as follows: (1) group sevo-1.0: Ce of remifentanil at 1.0 $ng.ml^{-1}$ after maintenance with sevoflurane; (2) group sevo-2.0: remifentanil 2.0 $ng.ml^{-1}$ after sevoflurane; (3) group sevo-2.5: remifentanil 2.5 $ng.ml^{-1}$ after sevoflurane; (4) group des-1.0: received remifentanil 1.0 $ng.ml^{-1}$ after maintenance with desflurane; (5) group des-2.0: remifentanil 2.0 $ng.ml^{-1}$ after desflurane; (6) group des-2.5: remifentanil 2.5 $ng.ml^{-1}$ after desflurane.

Patients who fulfilled the enrollment criteria and agreed to participate were randomly assigned by an independent operator to receive one of the interventions using a web-based system. Randomization was based on a balanced-block design program, stratifying by age and gender. Patients were blind to allocated intervention and anesthesiologists responsible for each of the cases were blind specifically to the assigned Ce but not to the inhaled gas (sevoflurane or desflurane).

Anesthesia management

Standardized induction of GA included fentanyl 1.5 $mcg.kg^{-1}$, lidocaine 1 $mg.kg^{-1}$, propofol 1.5 $mg.kg^{-1}$ and a neuromuscular blocker (cisatracurium 0.01 $mg.kg^{-1}$ or rocuronium 0.6 $mg.kg^{-1}$). Tracheal intubation was performed under direct laryngoscopy using 7.0- and 7.5-mm endotracheal tube for women and men, respectively. The tube cuff was inflated initially with air 3-4 ml and consecutive additional volumes of 1 ml were decided if leakage was noted until it disappeared. Volume/pressure controlled ventilation was adjusted to maintain end-expiratory carbon dioxide at 30-35 mmHg. Active warming by forced-air systems was used to maintain intraoperative core temperatures ranging from 36.0 to 36.5 ºC. Anesthetic maintenance was performed with sevoflurane/desflurane using a gas analyzer (Life Scope BSM-5135k. Nihon Kohden Corp. Japan) to keep gas end-tidal concentrations in the range of 0.6-0.7 age corrected iso-MAC[13] based on the concept of protection against intraoperative awareness at this range.[14] For administration of remifentanil infusion, a target Ce was set before induction based on Minto's PK/PD model programmed in the system Perfusor®Space (B.BRAUN Medical SA, Germany) trying to keep intraoperative Ce in the range of 2-4 $ng.ml^{-1}$.

All patients received a standardized prophylaxis for postoperative nausea and vomiting that included dexamethasone 4 mg immediately after the induction and ondansetron 4 mg at the end of the procedure. If there were no contraindications, a standardized multimodal transitional analgesia included i.v. diclofenac 1 $mg.kg^{-1}$ at the beginning of procedure and both methamizol 40 $mg.kg^{-1}$ and an intermediate half-life opioid (morphine 0.1 $mg.kg^{-1}$ or hydromorphone 0.02 $mg.kg^{-1}$) 20-30 minutes before awakening. Reversion of neuromuscular blockade was assessed 15-20 minutes before emergence by quantitative analysis of T_4/T_1 response to train-of-four stimuli (TOF-Watch SX, Ireland) and. Values < 90% were interpreted as residual curarization and reversion with neostigmine 20-30 $mcg.kg^{-1}$ and atropine 80 $mcg.kg^{-1}$ was performed.

At the end of procedure and once confirmed that inhaled gas administered was concordant with allocation, a previously trained operator non-implicated in the case set the TCI device according to the randomized assigned Ce and used a black sticker to cover the screen information. At the same time, anesthetic gas administration was discontinued, and vital signs recorded (T_0). Cough was evaluated by a blinded evaluator for eye opening to calling by name and a gentle stimulation over his/her shoulder when gas analyzer showed a concentration of 0.1 age corrected iso-MAC (usually 0.2 and 0.6 for sevoflurane and desflurane, respectively). If no response, consecutive stimulation was performed each minute until eye opening (T_1) and time for this event was recorded. TE was performed when 3/3 of the following responses to specific orders were obtained: Eye opening; mouth opening; inspiratory effort (T_2). Systolic blood pressure, heart rate and cough severity scale (1=no cough; 2=one episode of cough; 3=two episodes of cough or 4=severe/sustained cough) were registered during T_0-T_2 and 2.5 minutes post-extubation (T_3). Remifentanil infusion was discontinued during first 10 seconds after TE and infusion set was immediately disconnected from intravenous fluid line.

Communication with patients and verbal breathing incentive were maintained during all phases of emergence/extubation until 5 min after TE or when regular spontaneous ventilation was observed. All subjects were followed by the same blinded evaluator during the first 25 minutes after arriving at PACU. Pulse oximetry, respiratory rate (RR), heart rate (HR) and non-invasive blood pressure assessment and each 5-minute registration was maintained, seeking for possible events of hypoxemia (pulse oximetry SaO_2<90%), hypo-hypertension and bradypnea (RR<10 rpm). Registered information was transferred at the end of follow-up from written forms to a web-based database (BD-Clinic, FVL). Concealment to the team implicated in the management of the participants was assured during all phases of the protocol.

Sample size and statistical analysis

Analysis was aimed at testing for the null hypothesis that both proposed Ce of remifentanil (2.0 and 2.5 $ng.ml^{-1}$) were equivalent to 1.0 $ng.ml^{-1}$ to prevent cough response at TE. A sample size of 452 subjects (75 in each of the groups) was calculated based on previous papers reporting an incidence of cough of 63-65% with remifentanil Ce around 1 $ng.ml^{-1}$ to detect a relative risk reduction of 50% in the main outcome with a power of 80% and an overall type I error of 5%. Based on a potential benefit even at low infusion rates of remifentanil, we decide to use Ce 1.0 $ng.ml^{-1}$ as controls for each of the halogenate groups. Main outcomes effect data were performed according to intention-to-treat principle.

An initial exploratory analysis was conducted to describe the variables. Continuous data were summarized as mean and standard deviation or median and interquartile rank when appropriate and analyzed using the student's t-test or Kruskal-Wallis test, respectively. Categorical variables were summarized as frequencies and analyzed using the *Chi-Square* test. Cough probabilities were assessed for each of the interventional groups with their corresponding relative risk and 95% confidence interval. Two-way ANOVA for repeated measures

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were performed to compare changes on SBP and HR at the four time-points of study. One-way ANOVA and adjustments by Kruskal-Wallis test were used for comparison between groups and secondary outcomes. All statistical computations were performed using STATA/SE 10.1 (StataCorp, TX, USA) and statistical significance was considered for *p*-values ≤0.05. This manuscript adheres to the applicable CONSORT guidelines.[15]

Results

Between November 2013 and February 2015, 502 patients were enrolled and randomly assigned to one of the six interventional groups. Fifty-one subjects had to be excluded due to changes in surgical or anesthetic plan (n=43) and missing data during follow-up (n=8). Finally, 451 subjects [sevo-1.0 (n=75); des-1.0 (n=74); Sevo-2.0 (n=75); Sevo-2.5 (n=75); Des-2.0(n=76) and Des-2.5 (n=76)] were included in the analysis (Figure 1). Abdominal and head/neck surgeries were the most commonly performed procedures (40.3 and 33.3%, respectively). Global demographic characteristics and baseline clinical variables did not show statistically significant differences between groups. Adjusted iso-MAC end-tidal gas concentration at eye opening was 0.09 (0.08-0.1) and 0.09 (0.09-0.13) % for sevoflurane and desflurane, respectively, without intra-group differences (Table 1).

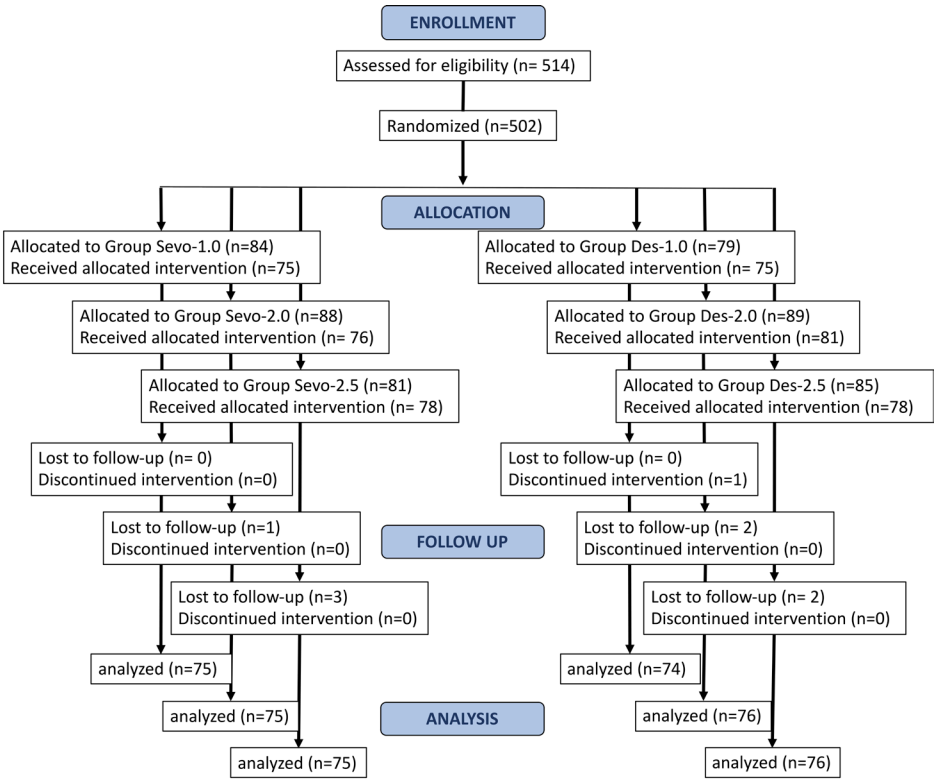

Figure 1 Consort Diagram

Table 1 Demographics

	Global	Sevo-1.0	Sevo-2.0	Sevo-2.5	Des-1.0	Des-2.0	Des-2.5	*P*-Value
Age, years	40.47 ± 11.89	36.40 ± 12.92	39.29 ± 12.20	40.67 ± 11.74	44.67 ± 10.79	42.11 ± 11.35	36.68 ± 12.29	0.09
Weight, kg	67.91 ± 12.86	61.87 ± 13.97	66.69 ± 12.35	68.34 ± 11.95	64.87 ± 9.99	69.09 ± 12.21	67.38 ± 12.81	0.36
Height, cm	164.92 ± 8.98	164.00 ± 9.74)	164.62 ± 8.51	165.00 ± 9.34	161.87 ± 8.02	165.22 ± 8.79	164.82 ± 9.46	0.86
BMI, kg/m2	24.84 ± 3.26	22.84 ± 3.51	24.49 ± 3.33	25.04 ± 3.09	24.84 ± 4.02	25.16 ± 2.89	24.68 ± 3.70	0.19
Gender								
Female, n (%)	248 (54.9)	40 (53.3)	43 (57,3)	42 (56)	39 (52.7)	44 (57.8)	40 (52.6)	0.53
Type of surgery, n (%)								0.48
Head and neck	150 (33.3)	26 (33.3)	22 (30.4)	28 (37.4)	23 (31.4)	25 (32.9)	26 (34.2)	
Abdominal	182 (40.3)	27 (36)	32 (41.3)	30 (40.4)	33 (44.7)	31 (40.7)	29 (38.1)	
Orthopedic	119 (26.4)	22 (30.7)	21 (28.3)	17 (22.6)	18 (24.3)	20 (26.3)	21 (27.6)	
End tidal iso-MAC at eye opening¶	0.09 (0.08-0.1)	0.11 (0.1-0.13)	0.10 (0.1-0.11)	0.15 (0.12-0.16)	0.10 (0.9-0.11)	0.09 (0.05-0.1)	0.10 (0.04-0.1)	0.35

Data are expressed as mean ± standard deviation

¶: Data are expressed as median and interquartile ranks

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When compared to controls, cough was significantly reduced in all groups of remifentanil Ce 2.0 and 2.5 ng.ml^{-1} at eye opening, TE and 2.5 minutes after awakening [risk ratio (95%CI) at ET for sevo-2.0: 0.50 (0.35-0.73), sevo-2.5: 0.45 (0.30-0.73), des-2.0: 0.35 (0.23-0.53), des-2.5: 0.33 (0.21-0.52); P<0.001], without differences between sevoflurane and desflurane (Figure 2). There were no significant differences on HR (beats per minute at TE 75.5 ± 12.4 for sevo-1.0, 79.7 ± 20.2 for sevo-2.0, 81.2 ± 16.1 for sevo-2.5, 77.1 ± 21.6 for des-1.0,78.8 ± 19.4 for des-2.0, and 88.4 ± 22.7 for des-2.5) and SBP (mmHg at TE 110.3 ± 13.3 for sevo-1.0, 103.3 ± 19.2 for sevo-2.0, 102.4 ± 18.1 for sevo-2.5, 104.3 ± 17.6 for des-1.0,105.5 ± 16.8 for des-2.0, and 103.7 ± 19.6 for des-2.5) mean values at these time points for any of the studied groups (Figure 3).

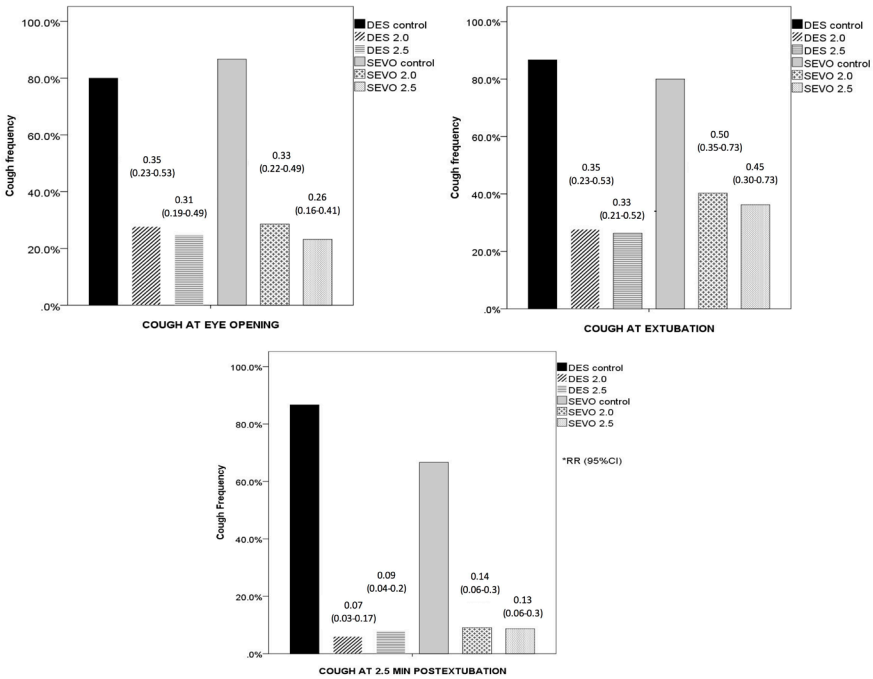

Figure 2 The frequency of cough and calculated risk ratio (95% confidence interval) at eyes opening, tracheal extubation and 2.5 minutes after with three different effect-site concentrations of remifentanil in patients under balanced inhaled anesthesia with sevoflurane vs. desflurane**.**

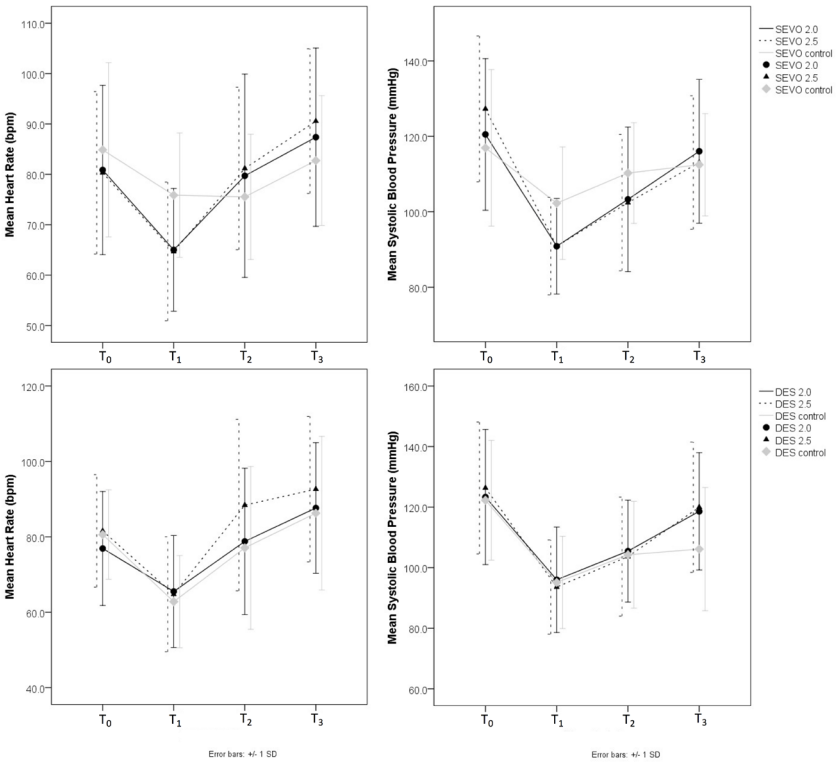

Figure 3 Heart rates (beats per minute) and systolic blood pressures (in mmHg) at baseline (T_o), eyes opening (T_1), tracheal extubation (T_2) and 2.5 minutes post-extubation (T_3) with three different effect-site concentrations of remifentanil in patients under balanced inhaled anesthesia with sevoflurane vs. desflurane.

Citation: Ariza F, Cruz G, Castaño D, et al. Optimal remifentanil effect-site concentration for preventing cough and hyperdynamic response during tracheal extubation after sevoflurane vs. desflurane: the REX trial. *J Anesth Crit Care Open Access.* 2023;15(3):93–99. DOI: 10.15406/jaccoa.2023.15.00560

Time from gas discontinuation to eye opening [7.22 ±2.38 minutes for sevo-1.0, 11.66 ± 4.55 minutes for sevo-2.0, 11.99 ± 5.41 minutes for sevo-2.5, *P*=0.002] and TE [8.12 ± 2.44 minutes, 12.07 ±4.65 minutes, 12.52 ± 5.50 minutes, respectively; *p*=0.007] was significantly prolonged in all sevoflurane groups when compared with controls but not for desflurane [6.51 ± 3.44 minutes for des-1.0, 9.94 ± 8.37 minutes for des-2.0, 8.60 ± 4.69 minutes for des-2.5; *P* = 0.14. and 6.84 ± 3.47, 10.38 ± 8.41, 9.06 ± 3.47 minutes, respectively; *P* = 0.13]. Hypertension was the most frequent adverse event at post-anesthesia care unit (PACU). Although respiratory rates at 2.5 and 5 minutes after TE were similar, 3 cases of mild-to-moderate hypoxemia (SaO2 85-90%) were detected at arrival to PACU, which adequately responded to verbal incentive and oxygen supplementation without significant differences between groups (Table 2).

Table 2 The effect of three different effect-site concentrations of remifentanil [1.0, 2.0 and 2.5 ng.ml^{-1}] after sevoflurane vs. desflurane on times from halogenate discontinuation to eye opening, tracheal extubation and postoperative early complications

	Sevo-1.0	Sevo-2.0	Sevo-2.5	*P*-value	Des-1.0	Des-2.0	Des-2.5	*P*-value
Time to eye opening, min¶	7.22 ± 2.38	11.66 ± 4.55	11.99 ± 5.41	**0.002**	6.51 ± 3.44	9.94 ± 8.37	8.60 ± 4.69	0.14
Time to extubation, min¶	8.12 ± 2.44	12.07 ± 4.65	12.52 ± 5.50	**0.007**	6.84 ± 3.47	10.38 ± 8.41	9.06 ± 3.47	0.13
RR at 2.5 min after TE	13(9-14)	12 (10-12)	10 (9-12)	0.20	11 (10-12)	10 (10-12)	10.5 (9-12)	0.93
RR at 5 min after TE	12 (9-14)	12 (10-16)	12 (10-16)	0.99	10 (10-14)	12 (10-14)	12 (10-14.5)	0.72
Complications				0.31				0.49
Hypoxemia, n (%)	0	0	2 (2.6)		0	1 (1.3)	0	
Hypertension, n (%)	0	2 (2.6)	0		0	1 (1.3)	3 (3.9)	
Bleeding, n (%)	0	0	0		0	0	0	
Others, n (%)	0	2 (2.6)	0		0	0	0	

¶Data are expressed as mean ± standard deviation

Statistically significant values are presented in bold

RR, respiratory rate; TE, tracheal extubation

Discussion

Cough and hyperdynamic signs are frequent events during awakening of intubated individuals under general anesthesia. This study showed a significant reduction in the risk of cough during emergence and TE when remifentanil Ce is maintained at 2.0 and 2.5 ng.ml^{-1} for adult patients under BGA with sevoflurane or desflurane. Moreover, we evidenced that awakening and TE were longer in time in patients previously exposed to sevoflurane. Additionally, no significant differences in HR or SBP were noted with respect to remifentanil Ce 1.0 ng.ml^{-1} as compared with higher Ce values at baseline, eye opening, TE and 2.5 minutes after. There were no significant differences in safety profile at PACU for any of the studied groups, independently of the anesthetic gas used.

Coughing during anesthetic emergence and TE is due to activation of sensory nerve terminals of the trachea and larynx with subsequent conduction along vagal afferences to brainstem and medulla, resulting in motor vagal responses of the glottis, respiratory muscles and diaphragm. Sensory/afferent pathways of cough reflex (unmyelinated Fibers C) respond to a variety of mechanical and chemical stimuli related with an overexpression of capsaicine-sensitive TRP vanilloid 1 (TRPV1), TRP ankyrin 1 (TRPA1) and metabotropic (bradykinin and trypsin) receptors that have been extensively described in previous papers.[16,17] Fentanyl (as was used during anesthetic induction) has been described as a cause of postoperative cough.[18,19] Although morphine and hydromorphone have antitussive effects due to their action on μ receptors, they can also induce cough, specially morphine, due to its effect on histamine release.[20,21] Remifentanil has none of this side effects, letting the antitussive effect on μ receptors to predominate.[21]

On the other side, hyperdynamic response to TE is associated with an increase of adrenaline plasma concentrations as a consequence of brainstem and cortical activation, resulting in an increase in HR and systemic/pulmonary vascular resistance.[22] A variety of strategies have been proposed to reduce the response to TE.[23-25] Remifentanil has been used in this setting as unique or combined approach with many of these drugs. For example, Park JS et al showed that remifentanil at Ce 2.0 ng.ml^{-1} during emergence is superior to dexmedetomidine to blunt cough but not hemodynamic response.[26] A recent RCT found that a combination of these two drugs (1.0 ng.ml^{-1} and 0.50 mcg.kg^{-1}) was more effective to blunt these two autonomic responses when compared individually.[27] Based on our findings about the effectiveness of remifentanil to prevent cough as opposed to limitations blunting hemodynamic responses during TE, further large multicenter studies assessing susceptible population are encouraged.

Our work was focused in BGA as this is the most frequent anesthetic approach worldwide. Inhaled anesthesia supposes a higher autonomic response during emergence and TE when compared with TIVA even when propofol and remifentanil are at low Ce values.[28,29] This differential response to TIVA is presumed to be at least in part due to a potent sympathetic inhibitory effect of propofol and pharmacokinetic/pharmacodynamics (PK/PD) interactions.[30,31] When remifentanil infusion is maintained until TE, an additional reduction of cough and hemodynamic changes has been found, concluding that this is a simple but effective strategy to optimize anesthetic emergence and awakening. At this respect, a study by Jun et al. showed that remifentanil Ce 1.0 and 1.5 ng.ml^{-1} at TE after balanced anesthesia with sevoflurane reduced cough incidence from 74% to 63 and 31%, respectively but higher Ce was associated to prolonged PACU stay. In a small study, Cho et al. found that effects of maintaining remifentanil at different Ce for this purpose were not significantly different with sevoflurane vs. Desflurane.[12] This study confirms that maintaining remifentanil Ce at 2.0-2.5 ng.ml^{-1} during TE is effective and safe, but sevoflurane emergence profile seems to be more affected when compared with desflurane. We believe that this difference is due to implicit PK/PD characteristics of desflurane that secondarily impact on times to awakening and a lesser compromise by concomitant use of remifentanil.

We believe our work has some limitations. We did not measure remifentanil plasma concentrations, as we based our predictions of Ce on Minto's model which is well known as predictable with an acceptable risk of bias.[32,33] Secondarily, we only included ASAI-II

adult subjects undergoing elective procedures so we do not know if our observations apply to other subpopulations. This study tried to include a great variety of surgical procedures that involved multiple clinical situations and type of patients so we think our results may be generalized and extrapolated.

Patients undergoing head and neck surgeries are more likely to suffer from cough as the neural pathways involved in this reflex are closely related to the structures being operated on. In this study, similar strategies to prevent cough were used in such patients as in subjects who underwent other types of procedures. The inclusion of head and neck surgery patients had the purpose of avoiding possible overestimation of results.

Conclusion

In conclusion, maintaining a remifentanil Ce at 2.0-2.5 $ng.ml^{-1}$ is effective to reduce the risk of cough but not hemodynamic responses during TE, when compared with 1.0 $ng.ml^{-1}$ in ASA I-II adult patients undergoing elective procedures under BGA with sevoflurane or desflurane. Antitussive effect of remifentanil at these Ce is not affected by the type of halogenate used but there is a significant compromise in TE and awakening times when sevoflurane is used. While both remifentanil Ce have similar clinical effects, we think there is no reason to exceed a Ce of 2.5 $ng.ml^{-1}$ given that additional benefits are poor at higher Ce values.

Financial disclosures

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Conflicts of interest

Fredy Ariza: This author has previously received honoraria for lectures related to OCTAPLEX (Octapharma AG, Switzerland); the company was not involved in the planning or analysis of the present study.

Gustavo Cruz: This author has no conflicts of interest to declare.

Darío Castaño: This author has no conflicts of interest to declare.

Iván Quintero: This author has no conflicts of interest to declare.

Laura Suárez: This author has no conflicts of interest to declare.

Mauricio Burbano: This author has previously received honoraria for lectures related to DESFLURANE (BAXTER Laboratories, Colombia); the company was not involved in the planning or analysis of the present study.

Einar Billefals: This author has no conflicts of interest to declare.

Clinical trial number

NCT03132519. www.ClinicalTrials.gov

Highlights

1. Remifentanil Ce at 2.0-2.5 $ng.ml^{-1}$ significantly reduces cough after balanced inhaled anesthesia
2. Remifentanil does not suppress hemodynamic response to extubation
3. Time to awakening is significantly prolonged when remifentanil is maintained after sevoflurane

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