Sevoflurane with remifentanyl allows rapid tracheal intubation without neuromuscular blocking agents

[Le sévoflurane, additionné de rémifentanyl, permet une intubation endotrachéale rapide sans myorelaxant]

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Purpose: After inhalational induction with sevoflurane, we compared the effects of adding remifentanyl $1 \mu\text{g}\cdot\text{kg}^{-1}$ or remifentanyl $2 \mu\text{g}\cdot\text{kg}^{-1}$ on conditions for tracheal intubation without neuromuscular blocking agents.

Methods: Before anesthetic induction, all patients were given 0.2 mg of glycopyrrolate iv to counteract the bradycardic effects of remifentanyl. Two minutes after inhalational induction with 8% sevoflurane and 50% nitrous oxide, 56 female patients with normal airways scheduled for gynecologic surgery were randomized to receive remifentanyl 1 or $2 \mu\text{g}\cdot\text{kg}^{-1}$ in a double-blind fashion. One minute later, laryngoscopy was initiated for tracheal intubation. Conditions for tracheal intubation and hemodynamic response to tracheal intubation were assessed.

Results: Tracheal intubation was successful in all patients. The incidence of post-intubation coughing was lower in the remifentanyl $2 \mu\text{g}\cdot\text{kg}^{-1}$ group compared to remifentanyl $1 \mu\text{g}\cdot\text{kg}^{-1}$ group (11% vs 39%, $P < 0.02$). Optimal intubation conditions were also higher in the remifentanyl $2 \mu\text{g}\cdot\text{kg}^{-1}$ group at 89% vs 54% ($P < 0.01$). However, the higher dose of remifentanyl also resulted in a greater decrease in mean arterial pressure ($P < 0.05$).

Conclusions: The addition of remifentanyl after sevoflurane induction allows for rapid tracheal intubation without neuromuscular blocking agents. The higher dose of remifentanyl results in improved conditions for tracheal intubation but also caused a greater decrease in mean arterial pressure. Tracheal intubation using sevoflurane and remifentanyl may be an alternative to traditional tracheal intubation with neuromuscular blocking agents.

Objectif: Après l'induction de l'anesthésie par l'inhalation de sévoflurane, nous avons comparé les effets de l'ajout de $1 \text{ mg}\cdot\text{kg}^{-1}$ ou de $2 \text{ mg}\cdot\text{kg}^{-1}$ de rémifentanyl sur les conditions d'intubation endotrachéale sans myorelaxant.

Méthode : Avant l'induction anesthésique, toutes les patientes ont reçu $0,2 \text{ mg}$ de glycopyrrolate iv pour neutraliser la bradycardie associée au rémifentanyl. Deux minutes après l'inhalation de sévoflurane à 8 % et de protoxyde d'azote à 50 %, 56 patientes faciles à intuber et devant subir une intervention gynécologique ont été réparties au hasard et ont reçu 1 ou $2 \text{ mg}\cdot\text{kg}^{-1}$ de rémifentanyl en double insu. Une minute plus tard, on a amorcé la laryngoscopie précédant l'intubation endotrachéale. Les conditions d'intubation et la réponse hémodynamique à l'intubation ont été évaluées.

Résultats : L'intubation endotrachéale a été réussie chez toutes les patientes. L'incidence de toux post-intubation a été plus faible avec la dose de $2 \text{ mg}\cdot\text{kg}^{-1}$ de rémifentanyl comparée à la dose de $1 \text{ mg}\cdot\text{kg}^{-1}$ (11 % vs 39 %, $P < 0,02$). Les meilleures conditions d'intubation ont été observées aussi avec $2 \text{ mg}\cdot\text{kg}^{-1}$ de rémifentanyl, 89 % vs 54 % ($P < 0,01$). Cependant, la plus forte dose de rémifentanyl a entraîné une plus importante baisse de la tension artérielle moyenne ($P < 0,05$).

Conclusion : L'ajout de rémifentanyl après l'induction avec l'inhalation de sévoflurane permet une intubation endotrachéale plus rapide sans recours au myorelaxant. La plus forte dose de rémifentanyl testée a fourni de meilleures conditions d'intubation mais a provoqué une baisse plus marquée de la tension artérielle moyenne. L'intubation réalisée sous anesthésie combinant le sévoflurane et le rémifentanyl peut remplacer l'intubation traditionnelle avec myorelaxant.

SEVOFLURANE, a non-irritating inhalational anesthetic agent with low blood gas solubility, has been used for rapid induction of anesthesia.¹ Proposed advantages of sevoflurane inhalational induction include lack of pain with drug injection, confirmation that the patient can be

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ventilated as anesthesia is induced and the avoidance of neuromuscular blocking agents for tracheal intubation. However, induction time for adequate depth of anesthesia for tracheal intubation with sevoflurane is long when compared to traditional *iv* induction with muscle relaxants. Muzi *et al.* found that time required to reach adequate depth of anesthesia for tracheal intubation, with 95% confidence level (ED_{95}), with sevoflurane was 5.7 min when 66% nitrous oxide was used and 7.7 min when 100% oxygen was used.² It was our hypothesis that remifentanyl,³ an opioid with quick onset and short half-life, used in conjunction with sevoflurane, would provide an adequate depth of anesthesia to allow tracheal intubation at three minutes. The present study was designed to investigate the effects of remifentanyl 1 $\mu\text{g}\cdot\text{kg}^{-1}$ or remifentanyl 2 $\mu\text{g}\cdot\text{kg}^{-1}$ on conditions for tracheal intubation following sevoflurane induction.

Methods

After Institutional Ethics approval and informed consent, 56 ASA class I–II female patients between the ages of 18 to 65 scheduled for gynecologic surgery requiring general anesthesia and tracheal intubation were recruited. Exclusion criteria included allergies to the agents being used, risk of pulmonary aspiration, weight greater than 150% of ideal body weight and ASA classification III or higher.

Sample size calculation was performed on an a priori estimate of a clinically relevant difference of 35% (60% of the patients in Group I (remifentanyl 1 $\mu\text{g}\cdot\text{kg}^{-1}$) and 95% of the patients in Group II (remifentanyl 2 $\mu\text{g}\cdot\text{kg}^{-1}$) in optimal intubating conditions. For a power of 0.80 and an alpha error of 0.05, 28 patients per group were required. Patients were randomized to the different doses of remifentanyl using a computer generated random number assignment. Both the patient and the study investigator were blinded to the dose of remifentanyl. Remifentanyl was prepared by the pharmacy and diluted to 10 mL total volume.

After placement of routine monitors (electrocardiogram, non-invasive blood pressure and pulse oximeter) and an *iv* cannula, all patients received glycopyrrolate 0.2 mg *iv* as an anticholinergic and as prophylaxis against bradycardia. Inhalational anesthetic induction commenced with an anesthetic circuit primed with 8% sevoflurane in 50% nitrous oxide and 50% oxygen (3 lpm N_2O : 3 lpm O_2). Anesthesia was induced using the three breath vital capacity technique² with a two-litre reservoir bag and a Datex AS/3 Anesthetic Delivery Unit. After confirmation of loss of lid lash reflex, ventilation was assisted with positive pressure ventilation to keep end tidal CO_2 at a physiologic level between

30–35 mmHg. Two minutes after induction of anesthesia, the N_2O was discontinued and the patient was placed on 100% O_2 at 3 lpm with 8% sevoflurane. At this point, patients received remifentanyl 1 $\mu\text{g}\cdot\text{kg}^{-1}$ or remifentanyl 2 $\mu\text{g}\cdot\text{kg}^{-1}$. Remifentanyl was administered as a rapid *iv* bolus (less than ten seconds). Laryngoscopy with a #3 Macintosh blade was performed by the primary author (H.J.) one minute later. A 7-mm endotracheal tube with a stylet was used for all patients. Tracheal intubation was categorized as a failure if successful tracheal intubation with end tidal CO_2 confirmation was not achieved within two minutes after initiation of laryngoscopy. If conditions for tracheal intubation were poor due to patient movement, inadequate jaw relaxation or inadequate opening of the vocal cords, rocuronium 0.3 $\text{mg}\cdot\text{kg}^{-1}$ *iv* was administered. If the patient coughed for more than 20 sec after tracheal intubation, rocuronium 0.3 $\text{mg}\cdot\text{kg}^{-1}$ was administered. After confirmation of successful tracheal intubation, anesthesia was continued using sevoflurane with 1 lpm of N_2O and 1 lpm of O_2 .

The primary variables measured were conditions for tracheal intubation. Secondary variables measured included: 1) heart rate, blood pressure, end tidal CO_2 , end tidal sevoflurane concentration and oxygen saturation, measured every minute; 2) time to loss of consciousness; 3) degree of muscle rigidity after administration of remifentanyl; and 4) time to successful tracheal intubation.

Degree of muscle rigidity after administration of remifentanyl was graded as: 0) completely relaxed if no resistance to mask ventilation was felt; 1) mildly rigid if rigidity was felt by the operator but did not affect manual ventilation; 2) moderately rigid if ventilation was affected but ventilation was still possible; and 3) fully rigid if muscle rigidity made positive pressure ventilation difficult. Conditions for tracheal intubation were assessed using vocal cord opening, jaw relaxation, coughing and patient movement. Vocal cord opening was graded as: 0) open; 1) partially open if they were less than 30° open; and 2) fully closed. Jaw relaxation was graded as: 0) fully relaxed if no jaw stiffness was felt; 1) mildly stiff if stiffness was felt but did not affect mouth opening; 2) moderately stiff if there was difficulty in mouth opening but it could be overcome with manual force; 3) severely stiff if there was difficulty with mouth opening. Coughing was graded as: 0) no cough; 1) mild cough, less than ten seconds; 2) moderate cough; ten to 20 sec; and 3) severe cough >20 sec. Patient movement was defined as any movement of the arms, legs or thorax.

Time to successful tracheal intubation was defined as the interval between removal of the facemask and

TABLE I Patient demographics

	<i>Sevoflurane with remifentanyl 1 $\mu\text{g}\cdot\text{kg}^{-1}$ n=28</i>	<i>Sevoflurane with remifentanyl 2 $\mu\text{g}\cdot\text{kg}^{-1}$ n=28</i>
ASA physical status	1 (1–1)	1 (1–1)
Age (yr)	37.6 $\pm$ 8.3	41.2 $\pm$ 11.6
Weight (kg)	71.1 $\pm$ 18.3	65.2 $\pm$ 10.4
Height (cm)	160.8 $\pm$ 7.1	161.1 $\pm$ 6.0
Smoker	6 (21%)	11 (39%)
End tidal CO ₂ 1 min before intubation (mmHg)	30 (27.5–33.5)	29 (26–32)
End tidal sevoflurane (%) 1 min before intubation	4.3 $\pm$ 0.7	4.2 $\pm$ 0.6
End tidal sevoflurane (%) 1 min after intubation	4.5 (4.2–5.2)	4.5 (4.3–4.8)

Data expressed as mean $\pm$ standard deviation or median (25–75th percentile) where appropriate.

detection of CO₂. Optimal intubating conditions were defined as conditions where the jaw was fully relaxed with partially to fully open vocal cords and no coughing at tracheal intubation. Good intubating conditions were defined as conditions where either the jaw was partially relaxed and/or there was mild coughing after tracheal intubation. Marginal intubating conditions were defined as conditions as above but when there was moderate coughing after tracheal intubation, or if the jaw was moderately stiff. Poor intubating conditions were defined as conditions where the jaw was severely stiff, the vocal cords were closed or where there was severe coughing after tracheal intubation. Hypotension was defined as systolic blood pressure <80 mmHg and hypoxemia was defined as SpO₂ <90%.

Parametric data were analyzed using the Student's *t* test. Non-parametric data were analyzed using the Mann-Whitney rank sum test. Proportions were analyzed using Fisher's exact test. Hemodynamic

TABLE II Induction and tracheal intubation

	<i>Sevoflurane with remifentanyl 1 $\mu\text{g}\cdot\text{kg}^{-1}$ n=28</i>	<i>Sevoflurane with remifentanyl 2 $\mu\text{g}\cdot\text{kg}^{-1}$ n=28</i>
Time to loss of consciousness (sec)	44.6 $\pm$ 9.2	43.7 $\pm$ 7.9
<i>Muscle rigidity</i>		
- none	13 (46%)	17 (60%)
- mild	12 (43%)	8 (29%)
- moderate	3 (11%)	1 (4%)
- severe	0 (0%)	2 (7%)
<i>Jaw relaxation</i>		
- complete	24 (86%)	26 (93%)
- mild stiffness	4 (14%)	2 (7%)
- moderate stiffness	0	0
- severe stiffness	0	0
<i>Vocal cords</i>		
- fully open	21 (75%)	22 (79%)
- partially open	7 (25%)	6 (21%)
- closed	0	0
Successful tracheal intubation	28 (100%)	28 (100%)
Time to successful tracheal intubation (sec)	33.9 $\pm$ 9.6	34.7 $\pm$ 11.0
<i>Coughing after intubation</i>		
None (<i>P</i> =0.02)	17 (61%)*	25 (89%)*
Mild	8 (29%)	3 (11%)
Moderate	3 (11%)	0
Severe	0	0
<i>Patient movement</i>		
Before intubation	0	0
After intubation	1 (4%)	0
Optimal intubating conditions (<i>P</i> < 0.01) (no cough, jaw relaxed, no movement)	15 (54%)*	25 (89%)*
Good intubating conditions (coughing for <10 sec or mild jaw stiffness)	10 (35%)	3 (11%)
Marginal intubating conditions (coughing for >10 sec or moderate jaw stiffness)	2 (7%)	0 (0%)
Poor intubating conditions (coughing >20 sec, severe jaw stiffness, and/or body movement)	1 (4%)	0 (0%)
Hypotension during induction (<i>P</i> =0.11)	3 (11%)	8 (29%)
Lasting for 2–3 min	1 (4%)	2 (7%)
Lasting for 1 min	2 (7%)	6 (22%)
Hypoxemia during induction (SpO ₂ <90%)	1 (4%)	0 (0%)

Data expressed as mean $\pm$ standard deviation where appropriate.

FIGURE 1 Mean arterial blood pressure with standard deviation during the first six minutes of anesthetic induction. Remifentanyl was given at two minutes and laryngoscopy was initiated at three minutes.

responses were analyzed using repeated measures ANOVA. SigmaStat 2.0. (SPSS, Chicago, IL, USA) was used for statistical analysis. P value <0.05 was considered statistically significant.

Results

Patient demographics (ASA status, age, weight, height and history of smoking) were similar for both groups (Table I). Induction of anesthesia with sevoflurane/nitrous oxide was successful in all patients in both groups without any complications. Mean time to loss of consciousness was 45 sec in Group I and 44 sec in Group II (Table II). Following the administration of remifentanyl 1 or 2 $\mu\text{g}\cdot\text{kg}^{-1}$, the incidence of muscle rigidity or jaw stiffness was similar between the two groups. No patient in either group coughed or moved during laryngoscopy. Mean time to successful tracheal intubation was similar at 34 sec for Group I and 35 sec for Group II. The incidence of post-intubation coughing was higher in Group I at 39% *vs* 11% in Group II ($P < 0.02$). Optimal intubation conditions were achieved more often in Group II at 89% *vs* 54% in Group I ($P < 0.01$). However, both groups had a high incidence of good to optimal intubating conditions, with Group I at 89% and Group II at 100%. The incidence of post-intubation hypotension was 11% for Group I and 29% for Group II ($P=0.11$). The decrease in mean arterial pressure (MAP) was significant compared to baseline ($P < 0.05$; Figure 1). However, the decrease in MAP was greater in Group II ($P < 0.05$). Heart rate increased after administration of glycopyrrolate (Figure 2). There

FIGURE 2 Mean heart rate with standard deviation during the first six minutes. Glycopyrrolate was given before initiation of induction. Remifentanyl was given at two minutes and tracheal laryngoscopy was initiated at three minutes.

was a significant drop in heart rate following remifentanyl administration in both groups ($P < 0.05$). However, no patient developed a heart rate of less than 45 $\text{beats}\cdot\text{min}^{-1}$. There were no complications during tracheal intubation. One patient in Group I developed mild hypoxemia (88% O_2 saturation) due to post-intubation coughing but this quickly resolved with increased FiO_2 .

Discussion

The results of this study show that tracheal intubation can be achieved within three minutes of anesthetic induction with sevoflurane and remifentanyl. When used with sevoflurane, remifentanyl 2 $\mu\text{g}\cdot\text{kg}^{-1}$ was associated with better intubating conditions than remifentanyl 1 $\mu\text{g}\cdot\text{kg}^{-1}$. Both groups, however, had a high proportion of good to optimal conditions for tracheal intubation at 89% with 1 $\mu\text{g}\cdot\text{kg}^{-1}$ and 100% with 2 $\mu\text{g}\cdot\text{kg}^{-1}$ of remifentanyl. These results compare favourably to reported results of propofol/remifentanyl tracheal intubation without neuromuscular blocking agents at 35–100%.⁴⁻⁷

Potential problems with the use of remifentanyl during anesthetic induction include hypoventilation, muscle rigidity and bradycardia.³ Muzi *et al.* studied methods to decrease the time to adequate depth of anesthesia with sevoflurane for tracheal intubation and found that when fentanyl was given before sevoflurane induction, it actually increased time to successful tracheal intubation due to hypoventilation and muscle rigidity.⁸ We administered remifentanyl two minutes

after sevoflurane induction and did not encounter problems with hypoventilation or muscle rigidity. This may be due to the intrinsic muscle relaxant properties of sevoflurane.⁹ Spontaneous ventilation ceased after the administration of remifentanyl but positive pressure ventilation with a facemask was possible in all patients. The administration of remifentanyl following sevoflurane induction has been associated with severe bradycardia and even asystole.¹⁰ In the present study, glycopyrrolate was administered as prophylaxis against bradycardia and bradycardia was not encountered.¹¹

An advantage of the sevoflurane/remifentanyl induction technique is the avoidance of neuromuscular blocking agents. Spontaneous ventilation is preserved until remifentanyl is administered. Should airway obstruction arise during induction of anesthesia, induction may be aborted and the patient allowed to awaken. If ventilation difficulties arise after remifentanyl is given, its effects may be reversed with naloxone.

Although a sevoflurane/remifentanyl induction allows tracheal intubation within three minutes after induction, there may be drawbacks. There was an 11% incidence of hypotension in the 1 $\mu\text{g}\cdot\text{kg}^{-1}$ group and 29% in the 2 $\mu\text{g}\cdot\text{kg}^{-1}$ group. However, hypotension was transient and was easily treated by decreasing the depth of anesthesia. Previously, we have shown that a sevoflurane inhalational induction is associated with a higher incidence of post-operative nausea and vomiting (PONV) when compared to induction with *iv* propofol.¹² The induction method in the present study may, possibly, be associated with a similar, high incidence of PONV.

In conclusion, good to optimal conditions for tracheal intubation can be achieved with the use of remifentanyl and three minutes of sevoflurane induction. The optimal dose of remifentanyl for tracheal intubation in this study was 2 $\mu\text{g}\cdot\text{kg}^{-1}$. Sevoflurane/remifentanyl induction and tracheal intubation may be an alternative to tracheal intubation with sevoflurane alone or traditional *iv* induction agents with neuromuscular blocking agents.

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