Low-dose fentanyl-midazolam combination improves sevoflurane induction in adults

La combinaison de fentanyl et midazolam à faible dose améliore l'induction au sévoflurane chez l'adulte

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Received: 27 March 2009 / Accepted: 9 July 2009 / Published online: 30 July 2009
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Abstract

Purpose We investigated the effects of a combination of low-dose fentanyl-midazolam premedication on the speed of inhaled induction with sevoflurane and ProSeal™ laryngeal mask airway (PLMA) insertion conditions.

Methods Eighty adult patients undergoing elective surgery were randomized in a double-blind fashion to receive either a normal saline placebo (Group PLAC) or a fentanyl $0.6 \mu\text{g} \cdot \text{kg}^{-1}$ and midazolam $9 \mu\text{g} \cdot \text{kg}^{-1}$ premedication (Group FM) 5 min before tidal volume sevoflurane 8%/O₂ induction. Anxiety levels, times to loss of eyelash reflex (LER) and PLMA insertion, and cardiorespiratory data were recorded.

Results Times to LER (Group PLAC: 66 ± 34 sec vs Group FM: 47 ± 18 sec, $P = 0.0027$, difference = 19 sec: 95% confidence interval [CI] 7–31 sec) and to PLMA insertion (Group PLAC: 186 ± 80 sec vs Group FM: 119 ± 44 sec, $P < 0.0001$, difference = 68 sec: 95% CI 39–97 sec) were shorter following FM. After PLMA insertion, end-tidal sevoflurane concentration (EtSevo) was lower and end-tidal CO₂ (EtCO₂) was higher following FM. Respiratory rate (RR) was lower with FM, but there was no difference regarding tidal volume. Adverse events, such as movements and apnea, occurred more often in Group PLAC. Systolic blood pressure (SBP) and heart rate (HR) during induction were both lower with FM. Anxiety level after

premedication was lower following FM administration. All participants remembered the face mask being applied in Group PLAC vs 69% in Group FM, $P < 0.0001$.

Conclusion Administration of a low-dose fentanyl-midazolam combination prior to sevoflurane induction decreases time to LER and allows for more rapid and less eventful PLMA insertion. Both SBP and HR were lower when premedication was administered. Patients receiving premedication were less anxious and less likely to remember the face mask. However, premedication was associated with a lower RR and increased EtCO₂ values following PLMA insertion, in spite of lower EtSevo concentrations. (ClinicalTrials.gov ID NCT00723164).

Résumé

Objectif Nous avons examiné les effets d'une combinaison de fentanyl - midazolam à faible dose en prémédication sur la vitesse d'une induction par inhalation de sévoflurane et sur les conditions d'insertion du masque laryngé ProSeal™ (PLMA).

Méthode Quatre-vingts patients adultes subissant une chirurgie non urgente ont été randomisés en double aveugle à recevoir soit un placebo de solution salée (groupe PLAC) ou une prémédication composée de fentanyl $0,6 \mu\text{g} \cdot \text{kg}^{-1}$ et midazolam $9 \mu\text{g} \cdot \text{kg}^{-1}$ (groupe FM) cinq minutes avant l'induction avec du sévoflurane 8 %/O₂ à volume courant. Les niveaux d'anxiété, le temps jusqu'à la perte du réflexe ciliaire (PRC) et l'insertion du PLMA ainsi que les données cardiorespiratoires ont été enregistrées.

Résultats Les temps jusqu'à PRC (groupe PLAC : 66 ± 34 secondes vs groupe FM : 47 ± 18 secondes, $P = 0,0027$, différence = 19 secondes : intervalle de confiance [IC] 95 % 7-31 secondes) et jusqu'à insertion du PLMA (groupe PLAC : 186 ± 80 secondes vs groupe FM : 119 ± 44 secondes, $P < 0,0001$, différence = 68 secondes : IC 95 %

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39–97 secondes) étaient plus courts après l'administration de FM. Après l'insertion du PLMA, la concentration télé-expiratoire de sévoflurane (EtSevo) était plus basse et le CO_2 télé-expiratoire (EtCO_2) plus élevé suite à l'administration de FM. La fréquence respiratoire (FR) était plus basse avec FM, mais aucune différence n'a été observée dans le volume courant. Les effets secondaires, tels que les mouvements et l'apnée, sont survenus plus souvent dans le groupe PLAC. La tension systolique (TS) et la fréquence cardiaque (FC) pendant l'induction étaient toutes deux plus basses lors de l'administration de FM. Le niveau d'anxiété après la prémédication était plus faible suite à l'administration de FM. Tous les participants se sont souvenus de l'application du masque facial dans le groupe PLAC vs 69 % dans le groupe FM, $P < 0,0001$.

Conclusion L'administration d'une combinaison de fentanyl - midazolam à faible dose avant l'induction au sévoflurane réduit le temps jusqu'à la PRC et permet une insertion du PLMA à la fois plus rapide et moins susceptible de provoquer des effets secondaires. La TS et la FC étaient toutes deux plus basses lors de l'administration de prémédication. Les patients recevant une prémédication étaient moins anxieux et moins susceptibles de se souvenir de l'application du masque facial. La prémédication a toutefois été associée à une FR plus basse et à des valeurs d' EtCO_2 plus élevées à la suite de l'insertion du PLMA, en dépit de concentrations plus faibles d'EtSevo. (ClinicalTrials.gov ID NCT00723164).

Owing to its unique non-pungency and low blood-gas partition coefficient, inhalation induction of anesthesia with sevoflurane (IIAS) in adults is an alternative to traditional intravenous induction. Inhaled induction allows for maintenance of spontaneous ventilation,^{1,2} which, in some patients, can facilitate airway management and help to preserve hemodynamic stability.³ Despite such advantages, IIAS is generally lengthier than intravenous induction and can be less satisfactory for patients.^{1–4} Several authors have studied the effect of adding a small dose of either a benzodiazepine or an opioid during IIAS and found that the pre-induction administration of sedative-hypnotics can accelerate induction, facilitate airway management, and increase patient satisfaction.^{5–7} The possible drawbacks of intravenous premedication include respiratory depression and episodes of apnea, thus decreasing speed of induction.^{8,9} Muzi *et al.*¹⁰ demonstrated that combining fentanyl $0.6 \mu\text{g} \cdot \text{kg}^{-1}$ and midazolam $9 \mu\text{g} \cdot \text{kg}^{-1}$ was more advantageous to accelerate and improve tracheal intubation conditions during IIAS than administering a higher dose of either medication alone.

In this randomized controlled trial, our primary hypothesis was that a combination of low doses of

intravenous fentanyl and midazolam would shorten time to loss of consciousness and laryngeal mask airway insertion time. Secondly, each participant's cardiorespiratory status and anxiety and satisfaction levels were also evaluated.

Methods

This trial has been registered at the ClinicalTrials.gov website (ID: NCT00723164). The study protocol was approved by the Research and Ethics Review Board of Maisonneuve-Rosemont Hospital, and written informed consent was obtained from each participant. We recruited adults of both sexes aged 18–75 yr with ASA physical status I–II who were scheduled to undergo minor elective surgery under general anesthesia. Patients were excluded if they had a history of gastroesophageal reflux, if they exhibited a body mass index $>32 \text{ kg} \cdot \text{m}^{-2}$, or if they took sedative or opioid drugs. Although no toxicology screen was conducted, patients with a history of alcohol or drug abuse were also excluded. Prior to IIAS, a computer-generated table was used to randomly divide the subjects into two groups to receive either normal saline 2.5 mL iv (Group PLAC) or a combination of fentanyl $0.6 \mu\text{g} \cdot \text{kg}^{-1}$ and midazolam $9 \mu\text{g} \cdot \text{kg}^{-1}$ to which normal saline was added to obtain a volume of 2.5 mL (Group FM). The information regarding each participant's allocation was placed in a sealed envelope, and an independent anesthesiologist not involved with the patient's anesthesia care prepared the medication in a different room. A single investigator (S.L.) blinded to patients' allocation performed all of the IIAS. Prior to entering the operating room, all subjects, none of whom had received any premedication, were asked by the same investigator performing the IIAS to rate their anxiety level on a verbal numerical scale (VNS) from 0 to 10 (0 being the lowest and 10 being the highest anxiety level). Patients were then transferred into the operating room where standard monitors (non-invasive blood pressure, pulse oximetry, and five-lead EKG) were applied. A lactated Ringer's solution was started through a 20G intravenous catheter. At this stage, the VNS anxiety level was reassessed. At this point, all participants received O_2 through a nasal cannula ($2 \text{ L} \cdot \text{min}^{-1}$), and the study medication was injected. Five minutes after injection, the VNS anxiety level was re-evaluated for a third time, just before beginning the IIAS. Subjects were asked to breathe normally through a face mask connected to a circle system prefilled with 8% sevoflurane in 100% O_2 at a flow rate of $6 \text{ L} \cdot \text{min}^{-1}$ (Dräger Fabius GS, Dräger Medical, Luebeck, Germany). The eyelash reflex was monitored every 15 sec until it disappeared. Jaw relaxation was then assessed every 15 sec until it was judged to be sufficient to allow for the insertion of a ProSeal™ laryngeal mask airway (PLMA) (The Laryngeal

Mask Company, Henley-on-Thames, UK), #4 for women and #5 for men, using the manufacturer's recommended technique.¹¹ If PLMA insertion failed (inability to correctly position the PLMA for oxygenation and ventilation), the facemask was applied again and another attempt was made as soon as it was deemed possible. If participants exhibited upper airway obstruction during IAS prior to PLMA insertion, a nasopharyngeal cannula could be inserted, but positive pressure ventilation was avoided.

Following PLMA insertion, the inspired sevoflurane concentration was decreased to 4% and the fresh gas flow rate was reduced to 3 L · min⁻¹. For the first spontaneous three breaths following PLMA insertion, the end-tidal CO₂ (EtCO₂) and sevoflurane (EtSevo) concentrations were recorded (GE Solar® 8000 & 9500 monitoring system, GE Healthcare, Chalfont St. Giles, UK) and averaged. Adverse events (movements, cough, stridor, and episodes of apnea lasting longer than 15 sec) were recorded during IAS and PLMA insertion. Spontaneous respiratory rate and tidal volume were then registered for the next 3 min. Starting with the beginning of the IAS, systolic blood pressure and heart rate were recorded every minute during a 10-min period. Spontaneous breathing was maintained during the entire observation period. Surgical stimulation was not allowed before data collection was completed, and the remainder of the anesthetic management was at the discretion of the attending anesthesiologist.

All patients were contacted 24 hr postoperatively by the principal investigator who had performed all IAS, and they were asked the following questions: "Do you remember having a mask applied to your face before sleeping?" (Yes, no); "What is your appreciation level of the anesthesia induction technique?" (Very pleasant, pleasant, unpleasant, or very unpleasant); and "Would you choose the same technique for a future surgery?"

The primary outcome measurement was the time interval between the start of inhaled sevoflurane application until insertion of the laryngeal mask airway. Previous

studies have shown that this time interval averaged around 135 sec with a SD of 40 sec.^{3,4} We decided that a difference of 30 sec in insertion time would be deemed clinically significant. Sample size calculation, accepting alpha and beta errors of 0.05 and 0.2, respectively, suggested that 35 patients per group would be required. We enrolled 40 patients per group to account for potential dropouts. Statistical analyses were performed using Prism® 3.0 (GraphPad Software, La Jolla, CA, USA). Continuous data were analyzed using Student's *t* test. Ordinal data and proportions were compared with Mann-Whitney *U*-test and Fisher's exact test, respectively. Two-way ANOVA was used to compare heart rate, systolic blood pressure, respiratory rate, and tidal volume between groups. If a significant difference was found, it was followed by Bonferroni's post hoc test. Unless stated otherwise, data are expressed as mean ± SD. A *P* < 0.05 was considered to indicate statistically significant differences.

Results

This study took place at Hôpital Maisonneuve-Rosemont and patients were recruited during the period from October 11 to December 14, 2005. During this three-month period, 80 eligible patients accepted to enter the study, and they all completed the protocol without deviation, except for one patient belonging to Group FM who received 100 mg of propofol because the attending anesthesiologist felt that her agitation and persistent cough prevented her from inhaling enough sevoflurane to deepen the anesthesia. She maintained spontaneous breathing and, except for postoperative measurements, her data were included in the statistical analysis. Demographic and surgical data of the participants are listed in Table 1. Mean times for loss of eyelash reflex (Group PLAC: 66 ± 34 sec vs Group FM: 47 ± 18 sec, *P* = 0.0027, difference = 19 sec; 95% confidence interval (CI) 7–31 sec), and to PLMA insertion (Group PLAC:

Table 1 Demographic and surgical data

	PLAC (<i>n</i> = 40)	FM (<i>n</i> = 40)
Age (yr)	48.2 ± 12.8 (25–73)	44.4 ± 13.0 (23–74)
Gender (M/F)	11/29	9/31
Height (m)	1.66 ± 0.08 (1.50–1.85)	1.64 ± 0.08 (1.52–1.80)
Weight (kg)	67.9 ± 12.3 (47–95)	67.9 ± 11.0 (45–90)
Smokers	12	6
Surgeries		
Mastectomy	13	11
Gynecologic	11	11
Plastic	5	7
Ophthalmological	3	4
Others	8	7

Data are presented as mean ± SD (range) when applicable. PLAC placebo group; FM fentanyl-midazolam group

Table 2 Induction time and PLMA insertion characteristics

	PLAC (n = 40)	FM (n = 40)	P
Time to loss of eyelash reflex (sec)	66 ± 34	47 ± 18	0.0027 ^a
Time to PLMA insertion (sec)	186 ± 80	119 ± 44	<0.0001 ^a
Attempts (1/2)	33/7	39/1	0.057 ^b
EtCO ₂ (mmHg)	37 ± 6	43 ± 7	<0.0001 ^a
EtSevo (%)	4.3 ± 1.0	3.7 ± 0.9	0.0057 ^a

Data are presented as mean ± SD when applicable

PLMA ProSeal™ laryngeal mask airway; PLAC normal saline group; FM fentanyl-midazolam group; EtCO₂ end-tidal CO₂ partial pressure after PLMA insertion; EtSevo end-tidal sevoflurane concentration after PLMA insertion

^a Unpaired Student's *t* test

^b Fisher's exact test

Table 3 Adverse events during induction and PLMA insertion

	PLAC (n = 40)	FM (n = 40)	P
At least one adverse event	34	23	0.0126
Movements	28	18	0.04
Cough	9	3	0.11
Apnea (>15 sec)	23	13	0.04
Stridor	13	6	0.11

All data were analyzed with Fisher's exact test

PLAC normal saline group; FM fentanyl-midazolam group

186 ± 80 sec vs Group FM: 119 ± 44 sec, $P < 0.0001$, difference = 68 sec: 95% CI 39–97 sec) were shorter in the premedicated FM group (Table 2). All PLMA insertions were achieved with either one or two attempts. In Group FM, 97.5% of the PLMA were inserted on the first attempt compared with 82.5% in Group PLAC. End-tidal sevoflurane concentration values were lower and EtCO₂ concentrations were higher in Group FM. Patients from Group PLAC experienced more adverse events (Table 3). More movements and apnea episodes were observed in Group PLAC, but no participant required positive pressure ventilation, and they all kept O₂ saturation levels above 95%. The incidence of cough and stridor was similar in the two groups. Two patients belonging to Group PLAC required insertion of a nasopharyngeal device to relieve airway obstruction during IAS.

No differences were observed between groups regarding tidal volume during the first three minutes following PLMA insertion, although respiratory rates were lower in Group FM (Fig. 1). Following PLMA insertion, systolic blood pressure and heart rate values were significantly greater in Group PLAC compared with Group FM (Fig. 2).

Fig. 1 Tidal volume (top) and respiratory rate (bottom) during the 3 min following PLMA insertion. PLAC placebo group; FM fentanyl-midazolam group. Two-way analysis of variance (ANOVA): $P = 0.8$ for tidal volume. Two-way ANOVA: $P < 0.0001$ for respiratory rate followed by Bonferroni post-test: * $P < 0.01$, ** $P < 0.001$. Data are expressed as mean ± SD

Anxiety levels were similar between the two groups before and immediately after the subjects entered the operating room. Five minutes after the administration of the study medication and prior to IAS, median anxiety levels were less in Group FM compared with Group PLAC (Fig. 3). Each participant of Group PLAC recalled the mask being applied to his/her face, compared with 27 of the 39 patients in Group FM ($P < 0.0001$). The satisfaction level was high in both groups. Ninety-five and 100% of participants in the PLAC and FM groups, respectively, stated that they would choose the same induction technique again. Only two patients in Group PLAC and one patient in Group FM rated the inhaled induction with sevoflurane as being either unpleasant or very unpleasant.

Discussion

The results of this study show that IAS and PLMA insertion are facilitated by the administration of a combination of low doses of fentanyl ($0.6 \mu\text{g} \cdot \text{kg}^{-1}$) and midazolam ($9 \mu\text{g} \cdot \text{kg}^{-1}$). The mean time to loss of consciousness was reduced by nearly 20 sec and the time required for PLMA insertion was reduced by >60 sec. Fewer side effects, such as movement or apnea, were

Fig. 2 Systolic blood pressure (top) and heart rate (bottom) during inhalation induction of anesthesia with sevoflurane (IIAS). Time zero is the beginning of the IIAS. PLAC placebo group; FM fentanyl-midazolam group. Two-way analysis of variance: $P < 0.0001$ for both systolic blood pressure and heart rate, followed by Bonferroni post-test: * $P < 0.01$, ** $P < 0.001$. Data are expressed as mean $\pm$ SD

Fig. 3 Anxiety levels between groups before induction. PLAC placebo group; FM fentanyl-midazolam group. Data were analyzed with the Mann-Whitney test. * A significant difference was observed 5 min post-medication: $P = 0.0016$. The P values in the waiting room and before the administration of the medication are 0.24 and 0.10, respectively. Data are expressed as median, quartiles, and range

observed in the premedicated patients. Furthermore, fentanyl-midazolam was associated with decreased anxiety levels and absence of recall of the induction procedure in nearly one-third of patients.

Fentanyl-midazolam premedication also allowed PLMA insertion at lower EtSevo values. The MAC-sparing effect of both fentanyl¹² and midazolam^{13,14} can probably explain these results. Still, authors who have studied the administration of opioids or midazolam alone prior to IIAS have

found conflicting results. Some showed increased^{7–15} time to loss of consciousness or time needed before laryngeal mask insertion, while others showed a decrease.^{5–10} The choice of drugs and doses in this study was influenced by Muzi *et al.*¹⁰ who showed that this particular combination accelerated and improved conditions for endotracheal intubation. Muzi's dosages were selected because of a previous study by Ben-Shlomo *et al.*¹⁴ showing that fentanyl and midazolam act synergistically and that 25% of the ED50 of fentanyl was required in combination with 23% of the ED50 for midazolam to achieve the ED50 of the combination. Still, contrary to Muzi *et al.*, we opted for PLMA use instead of tracheal intubation. Therefore, maybe even lower dosages could have been appropriate, since PLMA insertion is far less stimulating than direct laryngoscopy and endotracheal intubation. We also examined patients' anxiety and satisfaction with the technique. Our study also included a placebo group, which Muzi *et al.* did not deem necessary, electing to refer to another study, also by his group, for comparison.¹⁶

In this study, the time to loss of eyelash reflex during IIAS without premedication, approximately 60 sec, is consistent with previous publications^{5,6,15–19} showing times ranging from 35 to 90 sec.^{2,4,7,20,21} These differences can be explained by the different ways IIAS can be performed. Basically, anesthesiologists may ask their patients to breathe normally or they may choose to rely on the single-breath inhalation technique.^{4,6} Although the latter is praised by some,²² its real efficacy is controversial^{20,21} and requires patient cooperation, which may be altered by premedication. For these reasons, we opted for the normal breathing approach. The use of N₂O during IIAS has produced mixed results, most authors finding either little or no clinical benefit in adults.^{17,18} That, and the fact that it is customary in our institution to avoid N₂O in most circumstances, prompted us to proceed without N₂O in this study. The time needed before laryngeal mask insertion varies from 127 to 184 sec amongst published works.^{4,7,17,18} The time observed in our study in unpremedicated subjects (186 sec) is somewhat longer than what has been reported. Again, these differences can be explained by the various manners in which IIAS is conducted and by the subjectivity of evaluating jaw relaxation.

In this study, there were fewer episodes of apnea in the fentanyl-midazolam group. Kelly *et al.*²³ reported similar results while studying desflurane inhalation induction with or without fentanyl-midazolam premedication. All the episodes of apnea they observed occurred in the placebo group. Aside from the pungency of desflurane that might have caused some of the participants in the Kelly *et al.* study to hold their breath, we can speculate that unpremedicated patients may have been hyperventilating when IIAS was started, thus lowering their arterial pCO₂ below

respiratory threshold. As a result, the combined effect of sevoflurane and hypocarbia could have provoked apnea when the patients lost consciousness. This hypothesis could explain why no patient in this study needed ventilatory assistance, their breathing resuming spontaneously when their arterial $p\text{CO}_2$ increased sufficiently. It is also possible that the unpremedicated patients who exhibited increased minute ventilation were quicker to reach high EtSevo concentrations. The faster sevoflurane is administered the higher the chance the patient will become apneic.²⁴ Respiratory irregularities can also contribute to the prolongation of IIAS. The deepening of inhalation anesthesia is obviously hampered by apnea, and this may have contributed to the longer intervals observed in our placebo group before loss of eyelash reflex and PLMA insertion. However, it is important to be careful before concluding that intravenous premedication during IIAS is always beneficial from a respiratory standpoint. It has been shown that administration of opioids alone, in doses higher than those used in this study, can provoke apnea during IIAS,^{8,10} and even though we observed fewer episodes of apnea in the premedicated group, the administration of fentanyl-midazolam was associated with lower respiratory rate and higher EtCO₂ values following PLMA insertion. Both were likely caused by the premedication, since they occurred despite lower EtSevo concentrations in Group FM. Respiratory depression during IIAS may be a major concern, especially for patients with a difficult airway where it may be strongly advisable to maintain spontaneous breathing. Since none of the participants in this study had any obvious medical problem that could have exacerbated ventilatory depression, we suggest caution before concluding that premedication is safe in patients with respiratory compromise or in those exhibiting a potentially difficult airway.

The intravenous fentanyl-midazolam combination seems to have dampened the hemodynamic response to PLMA insertion. Other studies have shown that the use of a premedication during IIAS could lower systolic blood pressure and heart rate, but generally they remain within normal limits.^{7,8,15,25} The opioid part of the mixture is likely to be responsible for this effect.¹⁰ However, caution is warranted since adding opioids to IIAS, particularly sufentanil²⁶ and remifentanil,^{27,28} has been linked to asystolic episodes.

This study suggests that premedication may be an attractive solution for reducing anxiety. A significant number of patients who received premedication did not remember breathing through a mask. The hypnotic properties of midazolam⁶ may well explain these findings. The high satisfaction level found in both groups is in line with those previously published.^{5,6} Still, data pertaining to satisfaction evaluation have to be considered with caution, since they can be easily influenced by factors such as the desirability bias.^{1,29}

This study has several limitations. Amongst them, the fact that all inductions were performed by a single investigator may prompt some debate. Although a single operator facilitates standardization of the process, one cannot be certain that the results would have been reproducible with different anesthesiologists with different levels of experience with inhaled induction using sevoflurane. Furthermore, several endpoints, including the assessment of jaw relaxation and grading of PLMA insertion, are somewhat subjective. It is also possible that some of the effect of the premedication could have been detected by the investigator conducting the anxiety questionnaire, thus hinting at the group to which participants belonged. Finally, we chose to evaluate a fixed combination of drugs and doses that were recommended by Muzi *et al.*¹⁰ Dose-response data would be desirable, but the complexity of conducting dose response evaluations in the non-steady-state clinical setting of anesthetic induction makes such evaluations very difficult from a methodological perspective.

In conclusion, a low-dose combination of intravenous fentanyl-midazolam premedication administered 5 min before IIAS accelerates loss of consciousness and facilitates PLMA insertion. This drug combination is associated with fewer hemodynamic changes and helps to reduce patients' anxiety. This premedication combination is also associated with fewer episodes of apnea, although lower respiratory rates and higher EtCO₂ values suggest that spontaneous ventilation is somewhat depressed.

Competing interests None declared.

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