

Comparison of remifentanyl, alfentanil, and fentanyl co-administered with propofol to facilitate laryngeal mask insertion

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Aim: To compare the efficacy of different doses of fentanyl, remifentanyl, and alfentanil co-administered with propofol in patients undergoing minor surgery.

Materials and methods: This double-blind, multi-centered, placebo-controlled study was conducted in 2 medical centers. One hundred forty-one ASA class I and II adult patients aged 18-65 years were included in the study. Patients received i.v. 1 µg kg⁻¹ fentanyl (group F, n = 33), 10 µg kg⁻¹ alfentanil (group A, n = 33), 0.5 µg kg⁻¹ remifentanyl (group R, n = 36), or saline (control group, n = 39) co-administered with propofol 2.5 mg kg⁻¹ without additives over 30 s. An LMA was inserted 90 s later. Conditions for the LMA insertion were assessed. The number of attempts, airway quality, and hemodynamic changes were recorded.

Results: There were no significant differences in the demographic data among the groups. The LMA was more easily placed in the remifentanyl group compared with the other groups. All first attempts for the LMA insertion were successful in the remifentanyl group. When the opiates groups were compared with the control group, easier insertion rates were detected in all the opiate groups. LMA insertion was easiest in the remifentanyl group, followed by the alfentanil, fentanyl, and control groups, in that order. Heart rates and blood pressures were reduced in all groups, but no treatment was required.

Conclusion: Opiates co-administered with propofol improved the LMA insertion conditions compared to propofol alone. Out of the opiates, remifentanyl had the highest success rate.

Key words: Remifentanyl, alfentanil, fentanyl, propofol, laryngeal mask airway

Lareneal mask yerleştirmede propofole eklenen remifentanyl, alfentanil ve fentanilin etkilerinin karşılaştırılması

Amaç: Minör cerrahideki hastalarda propofole eklenen farklı dozlardaki remifentanyl, fentanyl ve alfentanilin etkilerini birbirleriyle ve plasebo kontrollü olarak karşılaştırmayı amaçladık.

Yöntem ve gereç: Bu çalışma çift kör, çok merkezli (GATA-Ankara ve 100. Yıl Üniversitesi-Van), plasebo kontrollü olarak yapıldı. Etik komite onayından sonra ASA I ve II sınıfı, yetişkin, 18-65 yaş arasında çalışmayı kabul eden 141 hasta çalışmaya alındı. İv. olarak hastalardan grup F'ye (n = 33) 1 µg kg⁻¹ fentanyl, grup A'ya (n = 33) 10 µg kg⁻¹ alfentanil, grup R'ye (n = 36) 0,5 µg kg⁻¹ remifentanyl ve kontrol grubu C'ye (n = 39) salin, 2,5 mg kg⁻¹ katkısız propofole ilave olarak 30 sn. üzerindeki sürede verildi. 90 sn. sonra LMA yerleştirildi. LMA yerleştirme kolaylığı değerlendirildi. Girişim sayısı, hava yolu sağlama kolaylığı ve hemodinamik değişiklikler kaydedildi.

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Bulgular: Hastaların demografik verilerinde farklılık yoktu. Diğer gruplarla karşılaştırıldığında remifentanil grubunda LMA daha kolay yerleştirildi. Remifentanil grubunda tüm LMA' lar birinci seferde yerleştirilebildi. Opiat grupları kontrol grupları ile karşılaştırıldığında tümünde kontrol gruplarına göre daha kolay yerleştirme oranları tespit edildi. Grupların daha kolay LMA yerleştirebilme sıralaması remifentanil> alfentanil> fentanil> kontrol grubu olarak bulundu. Kalp hızı ve kan basınçları tüm gruplarda azaldı fakat tedaviye ihtiyaç göstermedi.

Sonuç: Bu çalışma göstermiştir ki propofole eklenen opiatlar LMA yerleştirme koşullarını yalnız kullanılan propofole göre iyileştirmiştir. Opiatlardan en yüksek başarı oranını remifentanil sağlamıştır.

Anahtar sözcükler: Remifentanil, alfentanil, fentanil, propofol, lareneal mask airway

Introduction

Laryngeal mask airway (LMA) is one of the most popular airway devices in anesthetic practice. The increased speed and reliability of placement, improved hemodynamic stability at induction, reduced anesthetic requirements for airway tolerance, lower frequency of coughing during emergence, and lower incidence of sore throat are the main advantages of LMA over the tracheal tube (1). LMA insertion is not always straightforward and requires suppression of the upper airway reflexes and some degree of skill. LMA may be inserted with propofol alone, and the dose of propofol required for the smooth insertion of the LMA has been reported to range from 2.0 to 2.5 mg kg⁻¹ (2). Higher doses of propofol may cause hemodynamic disturbances. In spite of this, propofol alone may be insufficient to blunt airway responses and not prevent coughing, gagging, breath holding, and patient movement. A number of adjuncts, such as lidocain, low doses of muscle relaxant and opioids have been used to improve the LMA insertion conditions (3-6). Of these, opiates are the most commonly used. Different doses of fentanil, alfentanil, and remifentanil have been proven for this issue and, in general, adjuncts increase the successful insertion rates to over 90% (7). In this prospective, multi-centered, placebo-controlled study, we aimed to compare the LMA insertion conditions and hemodynamic changes with fentanil, alfentanil. and remifentanil added as a bolus to propofol and propofol administered alone during induction of anesthesia.

Materials and methods

The study was conducted in 2 medical centers in Turkey: Gülhane Military Medical Faculty and Yüzüncü Yıl University Medical Faculty. Local Ethical Committee approval for the study was obtained from both centers and written informed consent from all patients. One hundred forty-one ASA class I and II adult patients aged 18-65 years were included in this randomized double-blind study. They were all scheduled for minor surgery in which spontaneous ventilation using a LMA was the most appropriate technique. The patients with an anticipated difficult airway, as determined by a Mallampati score of 3 or more, were excluded.

All patients were fasted for over 6 h and no premedication was given. One of 4 identical 10 mL syringes containing fentanil 1 µg kg⁻¹, alfentanil 10 µg kg⁻¹, remifentanil 0.5 µg kg⁻¹ (made up to 10 mL with normal saline), or 10 mL saline was selected as the study drug. The content of the syringe was decoded after the study. Standard anesthetic monitoring was applied and the patients were pre-oxygenated for 3 min. The study drug, followed by propofol 2.5 mg kg⁻¹, without additives, was injected intravenously over 30 s and flushed with normal saline. The patient was ventilated with oxygen and 90 s later a lubricated LMA, size 3 for females and size 4 and 5 for males, was inserted by one of the authors, who was blinded to the study group, using the technique described by Brain (8).

The study investigator assessed insertion conditions using a 6-variable, 3-point score that graded mouth opening, ease of the LMA insertion, and the patient response, i.e. swallowing, gagging-

coughing, head/limb movement, and laryngospasm. The percentage of the patients exhibiting each response was calculated. The position of the LMA was checked by observing respiratory movements and chest expansion. Any malpositioned or non-functioning LMA was removed, the patient given a further dose of propofol 1 mg kg^{-1} , and, 60 s later, reinsertion attempted. The number of attempts for the successful insertion was noted.

Once the LMA had been successfully inserted, the patient was intermittently ventilated via the LMA to maintain the arterial oxygen saturation above 95% and the end-tidal carbon dioxide concentration between 35 and 45 mmHg until resumption of spontaneous respiration. Anesthesia was then maintained with 2% sevoflurane and 50% nitrous oxide in oxygen.

The patient's blood pressure and heart rate were recorded before induction of anesthesia, 1 min after induction, and again 1 min after successful LMA insertion.

Statistical analysis was performed using SPSS 10.0 for Windows. The number and percentage of the patients with each score for all 6 variables were calculated. Insertion scores were then compared using the chi-square test for trends. Blood pressure and heart rate changes during the insertion were compared using analysis of variance for repeated measures, with Bonferroni correction. Data are presented as mean (SD or range) and $P < 0.05$ was considered significant.

Results

Data were collected from 141 patients, aged 18-65 years. The 4 patient groups were similar with respect to age, gender, ASA physical status, weight, and height (Table 1).

Mouth opening was ideal (full) in all the patients in the remifentanyl group compared to the others (100% in the remifentanyl group, 94% in the alfentanil group, 78% in the fentanyl group, and 71% in the control group; $P < 0.05$). Median score of mouth opening was lowest in the remifentanyl group, while it was highest in the control group (remifentanyl $<$ alfentanil $<$ fentanyl $<$ control; $P < 0.05$, Table 2).

The LMA insertion was graded as easy in all the patients in the remifentanyl group. The ratio of easy LMA insertion was similar between the fentanyl and alfentanil groups (84% vs. 87%; $P > 0.05$) and higher than the control group (71%, $P < 0.05$) (Figure).

The LMA insertion resulted in swallowing, gagging-coughing, and head-limb movement responses in all study groups. Out of them, the remifentanyl group had the lowest score, while the control group had the highest ($P < 0.05$). Scores of the alfentanil group were lower than those of the fentanyl group ($P < 0.05$). Laryngospasm occurred in all groups except the remifentanyl group, but this difference was not statistically significant ($P > 0.05$). When comparing the total score of the LMA insertion conditions, the total score of the remifentanyl group was lower than that of the other groups (remifentanyl $<$ alfentanil $<$ fentanyl $<$ control; $P < 0.05$).

Table 1. Patient demographics and ASA status for the study groups. No significant difference between the groups.

	Fentanyl n = 33	Alfentanil n = 33	Remifentanyl n = 36	Control n = 39	P value
Gender (f/m)	11: 22	8 : 25	10 : 26	12 : 27	0.862
ASA grade (I/II)	27 : 6	24 : 9	26 : 10	35 : 4	0.130
Age (years)	31.54 \pm 11.29	34.45 \pm 14.11	33.88 \pm 16.12	31.07 \pm 9.74	0.106
Weight (kg)	72.51 \pm 12.55	73.39 \pm 12.14	76.86 \pm 14.17	73.84 \pm 11.59	0.866
Height (cm)	169.84 \pm 7.29	170.78 \pm 8.27	170.30 \pm 8.83	169.97 \pm 18.18	0.506

Results presented as mean (SD) or ratios. $P < 0.05$ considered statistically significant.

Table 2. The LMA insertion conditions of the study groups. Assessments used 6 variables/3 grade score.

Assessment	Grades	Fentanyl	Alfentanil	Remifentanyl	Control	P value
Mouth opening	full (1) / partial (2) / nil (3) Median Score	26 / 7 / 0 1.2 ± 0.4	31 / 2 / 0 1.06 ± 0.2	36 / 0 / 0 1.0 ± 0	28 / 10 / 1 1.30 ± 0.5	0.01
Overall ease	easy (1) / difficult (2) / impossible (3) Median Score	28 / 5 / 0 1.15 ± 0.3	29 / 4 / 0 1.12 ± 0.3	36 / 0 / 0 1.0 ± 0	25 / 12 / 2 1.41 ± 0.5	0.00
Swallowing	nil (1) / slight (2) / gross (3) Median Score	27 / 4 / 2 1.27 ± 0.5	29 / 2 / 2 1.18 ± 0.5	34 / 2 / 0 1.12 ± 0.3	20 / 12 / 7 1.66 ± 0.7	0.01
Gagging & coughing	nil (1) / slight (2) / gross (3) Median Score	28 / 3 / 2 1.24 ± 0.5	29 / 2 / 2 1.18 ± 0.5	32 / 3 / 1 1.13 ± 0.4	25 / 7 / 7 1.53 ± 0.7	0.025
Head & limb movement	nil (1) / slight (2) / gross (3) Median Score	21 / 8 / 4 1.48 ± 0.7	26 / 4 / 3 1.30 ± 0.6	31 / 4 / 1 1.16 ± 0.4	12 / 17 / 10 1.97 ± 0.77	0.00
Laryngospasm	nil (1) / partial (2) / total (3) Median Score	31 / 1 / 1 1.09 ± 0.3	32 / 0 / 1 1.06 ± 0.3	36 / 0 / 0 1.0 ± 0	34 / 2 / 3 1.20 ± 0.5	0.14
Total Score of the LMA insertion conditions		7.39 ± 2.2	6.93 ± 2.0	6.27 ± 0.94	9.1 ± 2.8	0.00

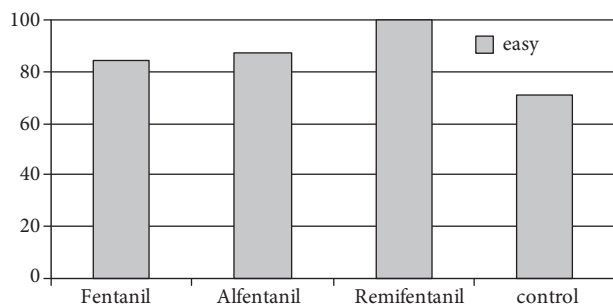


Figure. Comparison of ease of the LMA insertion between the groups. Values are expressed as percentages (%).

All first attempts for the LMA insertion were successful in the remifentanyl group. Three patients in the alfentanil group and 5 patients in the fentanyl group required a second attempt, which was lower than the control group (14 patients; $P < 0.05$). The LMA insertion was impossible in 1 patient in the fentanyl group and 5 patients in the control group and these patients were intubated with ETT (Table 3).

Heart rates, and systolic and diastolic blood pressures decreased in all groups following induction compared with the baseline ($P < 0.05$; Table 4). The

decreases in blood pressure were greater in the patients receiving remifentanyl and heart rate decreases were greater in the alfentanil group ($P < 0.05$); they were well within clinically acceptable limits. After the insertion of the LMA, blood pressures were elevated in all groups except the remifentanyl group. The difference was not statistically significant ($P > 0.05$). After the insertion of the LMA, heart rates remained stable in all groups.

Discussion

We showed that propofol (2.5 mg kg^{-1}) co-administered with alfentanil ($10 \text{ } \mu\text{g kg}^{-1}$), fentanyl ($1 \text{ } \mu\text{g kg}^{-1}$), or remifentanyl ($0.5 \text{ } \mu\text{g kg}^{-1}$), compared with propofol alone (2.5 mg kg^{-1}) reduced the number of the patients who responded adversely to the LMA insertion from 35% to 7.8%.

We used a 6-variable/3-grade scoring system described by Chui et al. and further modified by Hui et al. to assess the LMA insertion conditions (Table 2) (6,9,10). The studies to facilitate the LMA insertion with opiates added to propofol can be divided into 2 main categories. The first category included studies comparing different doses of same opiate co-

Table 3. Number of attempts and endotracheal intubation.

	Fentanil	Alfentanil	Remifentanil	Control	P value
Second attempt of the LMA insertion	5 (15%)	3 (9%)	0 (0%)	14 (35%)	0.022
Endotracheal Intubation	1 (3%)	0 (0%)	0 (0%)	5 (12.8%)	0.031

Table 4. Hemodynamic changes.

		Fentanil	Alfentanil	Remifentanil	Control	P value
Preinduction	SAP	128 ± 14	132 ± 20	133 ± 19	130 ± 16	0.653
	DAP	74 ± 12	76 ± 10	72 ± 11	76 ± 9	0.378
	MAP	94 ± 10	96 ± 13	94 ± 14	93 ± 11	0.812
	HR	83 ± 13	80 ± 12	77 ± 18	79 ± 13	0.383
Postinduction	SAP	100 ± 14	100 ± 18	101 ± 15	105 ± 17	0.468
	DAP	56 ± 9	56 ± 14	53 ± 9	60 ± 13	0.089
	MAP	73 ± 9	71 ± 14	72 ± 11	76 ± 13	0.395
	HR	76 ± 13	70 ± 11	73 ± 16	76 ± 16	0.219
1 min after the LMA insertion	SAP	105 ± 15	107 ± 24	100 ± 15	116 ± 22	0.010
	DAP	59 ± 13	61 ± 14	53 ± 11	68 ± 15	0.00
	MAP	77 ± 14	78 ± 16	73 ± 12	86 ± 17	0.03
	HR	72 ± 15	69 ± 12	70 ± 15	74 ± 12	0.405

Values are expressed as mean ± SD. P < 0.05 considered statistically significant. SAP = Systolic Arterial Pressure (mmHg), DAP = Diastolic Arterial pressure (mmHg), MAP = Mean Arterial Pressure (mmHg), HR = Heart Rate (beats/min)

administered with propofol to find out the standard dose of the opiate for the LMA insertion. Kodaka et al. compared 0.5, 1, and 2 $\mu\text{g kg}^{-1}$ fentanil co-administered with propofol using target-controlled infusion to determine the effective concentration for 50% of the attempts (EC 50 LMA) to secure the LMA insertion and reported that a fentanil dose of 0.5 $\mu\text{g kg}^{-1}$ is sufficient to decrease EC 50 LMA of propofol with minimum respiratory depression (11). Wong et al. compared 4 different doses of fentanil (0.5, 1.0, 1.5, and 2.0 $\mu\text{g kg}^{-1}$) co-administered with propofol 2.5 mg kg^{-1} and reported a standard dose of that 1.0 $\mu\text{g kg}^{-1}$ fentanil provided optimal conditions in 65% of the cases and stated that a 90 s period for the LMA insertion may have been insufficient for fentanil to reach its peak effect (12).

In our study, 1 $\mu\text{g kg}^{-1}$ fentanil enabled easy insertion of the LMA in 28 out of 33 patients (85%). The difference between our study and Wong's study may be attributed to their patients being mainly

ethnic Chinese with smaller jaws. Yu et al. compared 5, 10, 15, and 20 $\mu\text{g kg}^{-1}$ doses of alfentanil co-administered with 2.5 mg kg^{-1} propofol to determine an optimum dose of alfentanil to facilitate LMA insertion and found that the optimum dose for alfentanil was 10 $\mu\text{g kg}^{-1}$ and the duration of apnea increased with increasing dosage of alfentanil to over 5 min (13). The laryngeal mask insertion was unsuccessful only in 1 out of 60 alfentanil patients (98%). In contrast, Ang et al. compared 2 different doses of alfentanil (5 and 10 $\mu\text{g kg}^{-1}$) added to propofol 2.5 mg kg^{-1} and concluded that 5 $\mu\text{g kg}^{-1}$ prior to propofol provides excellent conditions for the insertion of laryngeal mask with minimal adverse hemodynamic changes (14). The success rate during the first attempt was similar in the 5 and 10 $\mu\text{g kg}^{-1}$ alfentanil groups (96% and 94%, respectively). However, the use of alfentanil 10 $\mu\text{g kg}^{-1}$ with propofol led to a significant decrease in the mean arterial pressure and the heart rate.

In another study, Lee et al. compared 2 different doses of remifentanyl ($0.25 \mu\text{g kg}^{-1}$ and $0.5 \mu\text{g kg}^{-1}$) added to 2.5 mg kg^{-1} propofol or 2.5 mg kg^{-1} propofol administered alone and found that $0.25 \mu\text{g kg}^{-1}$ remifentanyl provides excellent conditions for the insertion of the LMA with minimal hemodynamic disturbances (15). Furthermore, 82.5% of the patients in the $0.25 \mu\text{g kg}^{-1}$ remifentanyl group and 85.0% of the patients in the $0.5 \mu\text{g kg}^{-1}$ remifentanyl group had excellent insertion conditions as compared with the control group, 32.5%.

In a similar study, Yazicioglu et al. found that both doses of remifentanyl combined with propofol provided good and excellent conditions for the LMA insertion with minimal hemodynamic disturbances and propofol given alone is not a good agent for the LMA insertion (16). Ease of the LMA insertion was assessed as grade 1 in 100% of the patients in the $0.5 \mu\text{g kg}^{-1}$ remifentanyl group, 65% in the $0.25 \mu\text{g kg}^{-1}$ remifentanyl group, and 30% in the saline group. Undesirable responses following the LMA insertion were observed in 54% of the patients in the control group. Kwak et al. reported that the bolus dose of remifentanyl to facilitate the LMA insertion with propofol 2.5 mg kg^{-1} at which there was a 50% probability of successful laryngeal mask insertion (ED_{50}) during induction with 2.5 mg kg^{-1} propofol was $0.56 (0.07) \mu\text{g kg}^{-1}$ in children without a neuromuscular blocking agent (17). Grewal and Samsoon reported that remifentanyl $0.3 \mu\text{g kg}^{-1}$ combined with propofol target-controlled infusion compared to propofol alone facilitates the LMA insertion with minimal adverse hemodynamic changes (18). Remifentanyl significantly increased the ease and success of laryngeal mask insertion, with grade 1 (no coughing/gagging) conditions observed in 29 (68%) of the remifentanyl group and 21 (49%) of the control group ($P < 0.01$). The doses of remifentanyl and propofol used were not associated with any significant cardiorespiratory instability.

The studies in the second category were conducted to compare the effects of different opiates co-administered with propofol on the LMA insertion conditions. Hui et al. compared the insertion conditions following co-administration of $10 \mu\text{g kg}^{-1}$ alfentanil with $1 \mu\text{g kg}^{-1}$ fentanyl added to 2.5 mg kg^{-1} propofol and reported that co-administration of

alfentanil-propofol provided better insertion conditions than fentanyl-propofol, although apnea was prolonged by 72 s (10). Mouth opening and ease of the insertion were not improved with alfentanil co-administration. Alfentanil-propofol reduced the incidence of swallowing, gagging, movement, and laryngospasm ($P < 0.05$), with 29% (alfentanil) compared to 45% (fentanyl) of the patients responding ($P = 0.05$) to the LMA insertion. Qattan et al. compared the insertion conditions following co-administration of $0.5 \mu\text{g kg}^{-1}$ remifentanyl with $5 \mu\text{g kg}^{-1}$ alfentanil added to 2.5 mg kg^{-1} propofol and found excellent conditions in 85% of the patients in the remifentanyl group and in 80% of the patients in the alfentanil group compared to 55% in the control group (19). Mean arterial pressure decreased significantly in all groups and the mean heart rate was significantly lower in the remifentanyl and alfentanil groups compared to baseline values, which were well within clinically acceptable limits. They concluded that both drugs provided similar conditions for the LMA insertion. In our study, we found that remifentanyl is superior when compared to alfentanil by means of mouth opening, ease of the LMA insertion, and head and limb movement (100% vs. 93%, 100% vs. 88%, and 86% vs. 78%, $P < 0.05$).

In the present study, the categories of "head-limb movement" and "swallowing" had the highest number of non-ideal patients (36% and 25%, respectively). These results conflict with the study by Hui et al., which reported that mouth opening and the insertion of the LMA were non-ideal in 47%-49% and 32%-42% of their patients (10). This difference is surprising because they did not have a control group, which was greatly responsible for the unfavorable conditions. In our study, the majority of these non-ideal patients were included (69%). When the control group is excluded, the ratio of the non-ideal patients is reduced to 23.5%. In our study, ease of the LMA insertion and mouth opening were assessed as grade 1 in 100% of the patients in the remifentanyl group. This result is supported by the study by Yazicioglu et al. (16). Once again, these 2 categories had lowest number of non-ideal patients with the category of "laryngospasm" in all study groups (14%, 16%, and 5.6%, respectively). In addition, the major role of propofol for the LMA insertion should not be forgotten. Propofol continues

to be the drug of choice by means of hypnotic for the LMA insertion. In a recent study, Uzun et al. compared propofol (2.5 mg kg^{-1}) with etomidate (0.3 mg kg^{-1}) co-administered with a remifentanil bolus of $0.5 \mu\text{g kg}^{-1}$, followed by a 2-min remifentanil infusion of $0.05 \mu\text{g kg}^{-1}$ per min (20). Only 13 LMAs of 25 were inserted at the first attempt in the etomidate-remifentanil group compared with 23 of 25 in the propofol-remifentanil group. Gagging, chest rigidity, and myoclonus occurred significantly more frequently in the etomidate-remifentanil group.

The decreases in heart rates and blood pressure following induction were statistically significant, but these hemodynamic changes did not require any treatment. No patient in the study groups developed significant hypotension, bradycardia, or desaturation. Many authors reported that drug doses in our study resulted in clinically insignificant hemodynamic disturbances (14-19). Despite co-administration of

opiates, in 8 patients (7.8%) a second attempt of the LMA insertion was required and one of them (fentanil group; 1%) was intubated. However; all the first attempts were successful in the remifentanil group compared to the other opiates groups ($P < 0.05$). Once again, these results are lower than the control group. The success rate of the LMA insertion in our study is higher than that of the study of Hui et al. when the control group of our study is excluded (1% vs. 3.5%) (10).

In conclusion, co-administration of remifentanil-propofol provides better insertion conditions than alfentanil-propofol, fentanil-propofol, and propofol alone.

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