A comparison of fentanyl, esmolol, and their combination for blunting the haemodynamic responses during rapid-sequence induction

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The purpose of this randomized, double-blind study was to compare the ability of a combination of fentanyl and esmolol to blunt the haemodynamic effects of intubation with that of either agent alone. Patients received fentanyl or saline four minutes before, and esmolol or saline two minutes before rapid-sequence induction of anaesthesia. The F_2 group (n = 24) received fentanyl 2 $\mu g \cdot kg^{-1}$, the E_2 group (n = 24) received esmolol 2 $mg \cdot kg^{-1}$, the F_2/E_2 group (n = 25) received a combination of fentanyl 2 $\mu g \cdot kg^{-1}$ and esmolol 2 $mg \cdot kg^{-1}$, and the F_5 group (n = 26) received fentanyl 5 $\mu g \cdot kg^{-1}$. Following tracheal intubation, the maximum percent change from baseline heart rate was less in the F_2/E_2 and F_5 groups (12% and 16% respectively) than in the E_2 group (34%)($P < 0.05$). The maximum percent changes from baseline systolic blood pressure in the F_2/E_2 and F_5 groups (15% and 6% respectively) were less than in the F_2 and E_2 groups (24% and 33% respectively) ($P < 0.05$). The combination of a low dose of fentanyl and esmolol provides an alternative to a higher dose of fentanyl for blunting the haemodynamic responses to laryngoscopy and tracheal intubation during rapid-sequence induction in healthy patients.

Cette étude randomisée, à double insu, compare la capacité de blocage de la réponse hémodynamique à l'intubation de l'association fentanyl/esmolol avec celle des deux agents utilisés séparément. Les patients reçoivent soit du fentanyl ou du soluté physiologique, soit de l'esmolol ou du soluté physiologique, respectivement à quatre minutes et à deux minutes de l'induction d'une anesthésie à séquence rapide. Le groupe F_2 (n = 24) reçoit fentanyl 2 $\mu g \cdot kg^{-1}$, le groupe E_2 (n = 24) reçoit esmolol 2 $mg \cdot kg^{-1}$, le groupe F_2/E_2 (n = 25) reçoit une association de 2 $\mu g \cdot kg^{-1}$ de fentanyl et d'esmolol 2 $mg \cdot kg^{-1}$ et le groupe F_5 (n = 26) reçoit fentanyl 5 $\mu g \cdot kg^{-1}$. Après l'intubation endotrachéale, le pourcentage maximal de variation de la fréquence cardiaque initiale est moindre pour les groupes F_2/E_2 et F_5 (respectivement 15% et 16%) que pour le groupe E_2 (34%) ($P < 0,05$). Le pourcentage maximal de variation de la tension systolique initiale pour les groupes F_2/E_2 et F_5 (respectivement 15% et 6%) est moindre que pour les groupes F_2 et E_2 (respectivement 24% et 33%) ($P < 0,05$). L'association d'une faible dose de fentanyl et d'esmolol constitue une alternative valable aux doses élevées de fentanyl pour atténuer les effets hémodynamiques de la laryngoscopie directe et de l'intubation endotrachéale lors de l'induction à séquence rapide de l'anesthésie chez des sujets en bonne santé.

Key words
ANALGESICS: fentanyl;
INTUBATION, TRACHEAL: complications;
SYMPATHETIC NERVOUS SYSTEM: beta receptor antagonist, esmolol.

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Anaesthetists have employed a multitude of regimens to block the afferent and/or efferent limbs responsible for the haemodynamic responses to intubation of the trachea. Fentanyl in doses greater than or equal to 5 $\mu g \cdot kg^{-1}$ has been reported to be effective.[1,2] However, such doses of fentanyl may lead to excessive sedation, apnoea and chest wall rigidity preoperatively, and to nausea, vomiting and

respiratory depression postoperatively.[3–5] While an agent such as esmolol avoids these complications, it has variable effectiveness in the recommended doses (100–200 mg).[6–9] We postulated that, by both modulating nociceptive input and blunting peripheral adrenergic effects, a combination of fentanyl and esmolol might prove to be more efficacious than either agent alone. The potential benefits of such combination therapy were suggested by previous investigations.[10,11] This randomized, double-blinded study was designed to compare a combination of fentanyl 2 $\mu g \cdot kg^{-1}$ and esmolol 2 $mg \cdot kg^{-1}$ with a regimen of fentanyl 2 $\mu g \cdot kg^{-1}$ alone, fentanyl 5 $\mu g \cdot kg^{-1}$ alone, or esmolol 2 $mg \cdot kg^{-1}$ alone.

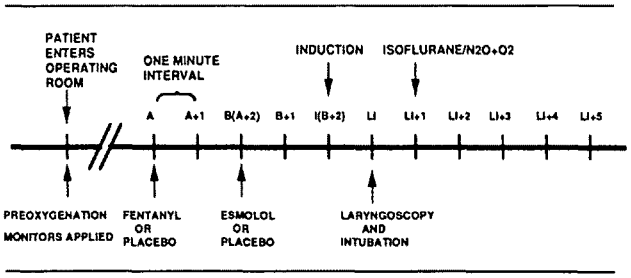

FIGURE 1 Time line of events and data collection points. Interval between successive vertical lines is one minute. A and B indicate times of injection for syringes A and B, respectively. I = induction; LI = laryngoscopy and intubation.

Methods

Following approval of the institutional Human Investigation Committee, informed written consent was obtained from 102 patients scheduled for elective surgery of longer than one hour in duration. Exclusion criteria were ASA physical status III–V, age <21 or >65 yr, weight <50 or >100 kg, atrial or ventricular arrhythmias, second or third degree A-V conduction block, hypertension, congestive heart failure, bronchial asthma, chronic narcotic use, or beta-adrenergic antagonist therapy. Patients were randomly allocated to one of four treatment groups in a double-blind fashion: the F_2 group received fentanyl 2 $\mu g \cdot kg^{-1}$, the E_2 group received esmolol 2 $mg \cdot kg^{-1}$, the F_2/E_2 group received a combination of fentanyl 2 $\mu g \cdot kg^{-1}$ and esmolol 2 $mg \cdot kg^{-1}$, and the F_5 group received fentanyl 5 $\mu g \cdot kg^{-1}$. Each regimen consisted of two syringes which were prepared by an investigational pharmacist. Syringe A contained 10 ml of either saline, fentanyl 2 $\mu g \cdot kg^{-1}$ or fentanyl 5 $\mu g^{-1} \cdot kg^{-1}$; syringe B contained 20 ml of saline or esmolol 2 $mg \cdot kg^{-1}$. A benzodiazepine premedication (midazolam 0.02–0.04 $mg \cdot kg^{-1}$ *im* or diazepam 0.15 $mg \cdot kg^{-1}$ *po*) was administered at the discretion of the patient's anaesthesia care provider; the dose was not dictated by the study protocol so as to enable us to assess the four study groups in the context of routine care at our institution.

In the OR, baseline heart rate (HR) and blood pressure (BP) were obtained by automatic noninvasive brachial oscillometry and ECG (Lead II) after the patient was placed on the OR table. Such measurements were obtained at each event of the study protocol (Figure 1), and repeated at one-minute intervals until five minutes after tracheal intubation. At two-minute intervals during preoxygenation, the patient received the contents of syringe A, syringe B, and then an induction dose of thiopentone (4 $mg \cdot kg^{-1}$) which was followed immediately by succinylcholine (1.5 $mg \cdot kg^{-1}$). One minute after the beginning of administration of the induction agent, laryngoscopy and intubation were performed. Then, mechanical ventilation with 100% oxygen was commenced to maintain end-tidal CO_2 at 30–35 mmHg. One minute after intubation, 1% isoflurane and 70% N_2O were added and maintained during the remainder of the study period. Post-intubation hypertension (systolic BP >160 mmHg or >20% above baseline) and tachycardia (HR >100 bpm) were treated with incremental doses (25 mg) of thiopentone.

Demographic data, the duration of laryngoscopy and intubation, and maximum percent changes in HR and BP during the five minutes following intubation were analyzed using analysis of variance (ANOVA). The HR and BP at each time and changes in HR and BP from baseline were analyzed using ANOVA, repeated measures ANOVA, and Student-Newman-Keuls for multiple comparisons. Fisher's exact and chi-squared tests were used to compare the groups with respect to the proportion of patients with "pre-defined" extreme changes in HR and BP. When a difference in proportions was found among the groups, pairwise comparisons were done, and a Bonferroni adjustment was made for multiple comparisons. An alpha level of 5% ($P < 0.05$) was used to establish statistical significance.

Results

Of the 102 patients enrolled, three did not complete the study: one in the F_2 group required multiple attempts at intubation, one in the E_2 group required awake tracheal intubation and a third withdrew from the study after consent was signed. Demographic data for the 99 remaining patients are presented in Table I. There were no differences among the groups with respect to sex, age, weight, height, ASA physical status, or premedication; nor were there differences among the groups with respect to the baseline HR and BP or duration of laryngoscopy and intubation (which averaged 27 sec overall). Except for one case of apnoea requiring assisted ventilation before induction in the F_5 group, there were no other adverse events, i.e., severe bradycardia, hypotension, chest wall rigidity, or post-surgical respiratory depression.

TABLE I Patient demographics data

	F_2 group (n = 24)	E_2 group (n = 24)	F_2/E_2 group (n = 25)	F_5 group (n = 26)
Sex				
– Male (n)	3	3	4	8
– Female (n)	21	21	21	18
Age (yr)[a]	41 ± 2	42 ± 2	40 ± 2	39 ± 2
Weight (kg)[a]	70 ± 2	65 ± 2	70 ± 2	69 ± 2
Height (cm)[a]	165 ± 2	164 ± 1	163 ± 2	166 ± 2
ASA Physical Status				
– I (n)	12	12	15	14
– II (n)	12	12	10	12
Premedication				
– Yes (n)	19	20	22	21
– No (n)	5	4	3	5

[a]Mean ± SD.

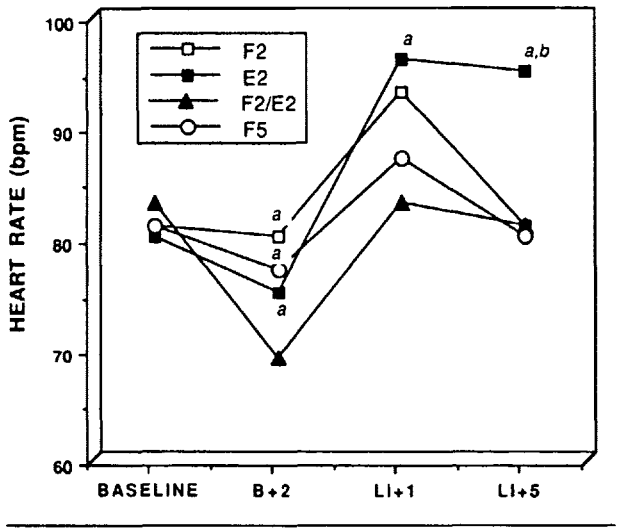

FIGURE 2 Heart rate (HR) responses at selected time points. The mean HR for each of the four groups is provided for the first assessment in operating room (baseline), two minutes after syringe B (B+2), one minute after the onset of laryngoscopy (LI+1) and five minutes after the onset of laryngoscopy (LI+5). $a = P < 0.05$ vs F_2/E_2 group; $b = P < 0.05$ vs F_5 group.

Heart rate

Patients in each group demonstrated a transient preinduction decrease in mean HR from baseline following the administration of fentanyl and/or esmolol (Figure 2). The greatest reduction was noted in the F_2/E_2 group ($P < 0.05$ between F_2/E_2 and each of the other groups). One patient in the E_2 group and three in the F_2/E_2 group experienced a decrease in heart rate to less than 50 bpm prior to induction; in all four patients, however, the HR increased to above baseline immediately after induction of general anaesthesia.

Following tracheal intubation, an increase in HR was noted in each group. The maximum percent change from baseline HR was less in the F_2/E_2 and F_5 groups (12% and 16% respectively) than in the E_2 group (34%) ($P < 0.05$), and also less than that in the F_2 group (22%) (P = NS). A HR >100 bpm was noted in 13 of 24 patients in the E_2 group, nine of 23 patients in F_2, three of 25 patients in F_2/E_2, and five of 26 patients in the F_5 group (Table II, $P < 0.01$ for E_2 vs F_2/E_2).

Blood pressure

Following administration of fentanyl and/or esmolol, systolic blood pressure (SBP) tended to decline in each group (P = NS). Following intubation, however, SBP increased in all groups. The maximum percent change from baseline SBP in the F_2/E_2 and F_5 groups (15% and 6% respectively) was less than that in the F_2 and E_2 groups (24% and 33% respectively) ($P < 0.05$). It also was less in the F_5 group than in the F_2/E_2 group ($P < 0.05$) (Figure 3). The proportion of patients with maximum SBP >160 mmHg in the F_2/E_2 and F_5 groups was less than one third of that noted in the F_2 and E_2 groups ($P < 0.01$, Table II). The F_5 group also experienced the highest incidence (16/26) of a 20% or greater decrease in SBP ($P < 0.01$ for F_5 vs F_2 and E_2). However, when only data obtained prior to the addition of isoflurane were analyzed, 5/26 F_5 patients and 5/25 F_2/E_2 patients evidenced such a decrease. In general, diastolic blood pressure paralleled changes in SBP throughout the study period (Figure 4). A greater number of patients in the F_2 and E_2 groups required supplemental thiopentone for post-intubation hypertension and tachycardia (six in the F_2, six in the E_2, three in the F_2/E_2 and one in the F_5 group); however, such intergroup differences were not statistically significant.

Discussion

Results obtained from the present investigation suggest

TABLE II Incidence of extreme changes in HR and BP

	F_2 group (n = 24)	E_2 group (n = 24)	F_2/E_2 group (n = 25)	F_5 group (n = 26)
Minimum HR < 50 bpm	0	1	3	0
Maximum HR > 100 bpm	9	13[a]	3	5
Maximum SBP > 160 mmHg	14[a,b]	15[a,b]	4	2

HR = heart rate; BP = blood pressure; SBP = systolic blood pressure.
[a] $P < 0.01$ vs F_2/E_2 group.
[b] $P < 0.01$ vs F_5 group.

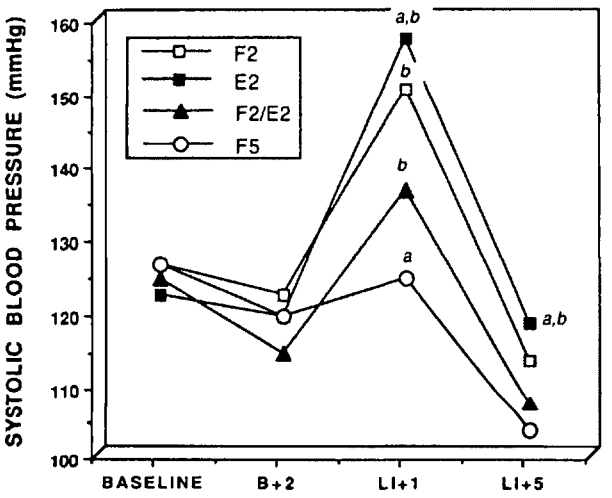

FIGURE 3 Systolic blood pressure (SBP) responses at selected time points. The mean SBP for each of the four groups is provided at baseline, two minutes after the syringe B (B+2), one minute after the onset of laryngoscopy (LI+1) and five minutes after the onset of laryngoscopy (LI+5). *a* = $P < 0.05$ vs F_2/E_2 group; *b* = $P < 0.05$ vs F_5 group.

that pretreatment with a combination of low-dose fentanyl and esmolol provides safe and effective suppression of the HR and BP responses to laryngoscopy and intubation in healthy patients. This combination may prove to be a suitable alternative when one seeks to avoid higher doses of opioids or esmolol. Only three patients receiving this combination experienced a peak HR above 100 bpm following laryngoscopy and tracheal intubation. This group also evidenced a smaller change from baseline SBP and fewer patients with SBP >160 mmHg than did the groups receiving esmolol alone or low-dose fentanyl.

Esmolol 2 mg · kg^{-1} administered alone did not consistently provide haemodynamic stability during laryngoscopy and intubation. Patients receiving esmolol alone experienced the highest degree of haemodynamic response to intubation. These findings are in general agreement with other investigators,[6–9] who likewise noted that esmolol in doses of 100–200 mg was only partially effective in blunting the haemodynamic responses. Furthermore, they were not markedly different from patients who received saline placebo in a similar setting.[12] Although higher doses of esmolol might blunt both the HR and BP responses, they may be associated with myocardial depression. In this regard, Ebert *et al.*[8] and Miller *et al.*[10] reported reductions in cardiac index and ejection fraction following intubation when esmolol was administered in doses of 2.5–3 mg · kg^{-1}.

Although fentanyl has been used to blunt the haemodynamic responses to intubation,[1,2] moderate-to-high doses of fentanyl often are not given in a full-stomach rapid-sequence setting for the fear of being unable to ventilate the lungs prior to induction or following a failed attempt at intubation. In the present study, one patient became apnoeic after receiving 5 μg · kg^{-1} of fentanyl and required assisted ventilation before laryngoscopy. McClain *et al.* also reported apnoeic episodes in 4/7 patients who received 3.2–6.5 μg · kg^{-1} fentanyl.[13] In addition, such

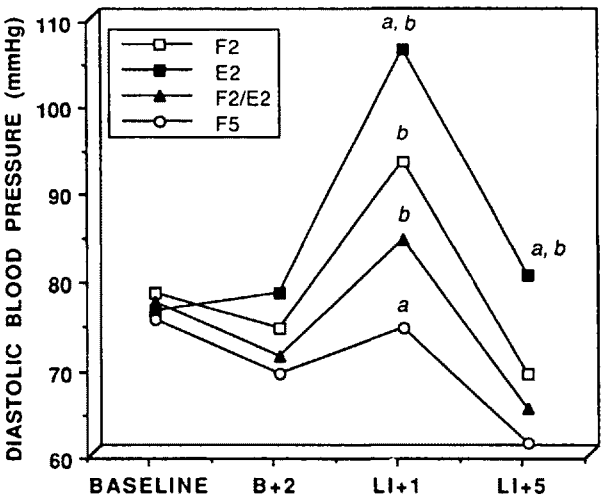

FIGURE 4 Diastolic blood pressure (DBP) responses at selected time points. The mean DBP for each of the four groups is provided at baseline, two minutes after syringe B (B+2), one minute after the onset of laryngoscopy (LI+1) and five minutes after the onset of laryngoscopy (LI+5). *a* = $P < 0.05$ vs F_2/E_2 group; *b* = $P < 0.05$ vs F_5 group.

doses of fentanyl may lead to prolonged and recurrent ventilatory depression after relatively short surgical procedures lasting less than two hours.[4,5,13] While this can be managed effectively with assisted ventilation, the present data suggest that the addition of esmolol allows the use of lower doses of respiratory depressants such as fentanyl and reduces the potential morbidity and costs associated with prolonged ventilatory assistance.

We postulated that fentanyl's modulation of nociceptive input and esmolol's blockade of adrenergic receptors should enable their combination to provide effective blunting of the response to intubation while minimizing the undesirable effects of larger doses of each agent alone. The potential benefit and safety of combination therapy were suggested by previous investigations;[10,11] however, none of these was randomized with respect to whether or not patients received fentanyl. Cole[11] reported that the addition of esmolol (100 or 200 mg) to the 5 $\mu g \cdot kg^{-1}$ dose of fentanyl that they administered to high-risk patients prior to induction did not affect the HR and BP responses to intubation (which already were blunted by the fentanyl). Their findings suggest the relative safety of combination therapy in that the incidence of bradycardia and hypotension associated with fentanyl/esmolol combination was similar to that observed following administration of fentanyl alone.

While we noted a decreased HR prior to induction of anaesthesia in the esmolol alone and combination groups, such changes were clinically insignificant; in each case, the HR increased to above baseline immediately after induction. Nevertheless, the central vagomimetic effect of fentanyl[14] combined with the negative chronotropic effect of esmolol theoretically could result in severe bradycardia. Therefore, HR should be carefully monitored and appropriate treatments considered if severe, albeit typically transient, bradycardia is observed.

This study had some limitations. Although it recently has been reported that multiple regression analysis of pooled data from several institutions indicated that benzodiazepine premedication can have a moderating effect on the pressor response,[15] we did not dictate the indications for, or the dose of, benzodiazepine. This was done so as to enable the assessment of the four study groups in the context of routine care at our institution. Of note, the number of patients who received premedication was similar in all four treatment groups. With respect to our study population, we did not randomize according to gender; this resulted in over-representation of females. Although the power of the present study was adequate to identify significant differences with respect to blood pressure, the power to identify a significant difference in maximum heart rate between F_2 and E_2/F_2 or F_2 and F_5 groups was low (30%).

In summary, the combination of low-dose fentanyl (2 $\mu g \cdot kg^{-1}$) and esmolol (2 $mg \cdot kg^{-1}$) is more effective than the same dose of either agent alone in blunting tachycardic and hypertensive responses to laryngoscopy and intubation following rapid-sequence induction. It is more effective in blunting the HR but was less effective in blunting the BP response than fentanyl 5 $\mu g \cdot kg^{-1}$. It was associated with less hypotension than fentanyl 5 $\mu g \cdot kg^{-1}$. The combination thus provides an alternative to a higher dose of fentanyl for blunting the haemodynamic responses to laryngoscopy and intubation during rapid-sequence induction in healthy patients. Follow-up studies evaluating the safety and efficacy in higher risk patients are warranted.

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