Evaluation of esmolol and fentanyl in controlling increases in heart rate and blood pressure during endotracheal intubation

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Laryngoscopy and intubation cause an adrenergic response manifested by tachycardia and hypertension. Various pharmacological agents, including fentanyl, have been administered prior to induction in an attempt to attenuate the adrenergic response but they all have limitations. Esmolol, an ultrashort-acting cardioselective beta blocker, has been administered by infusion to successfully protect surgical patients from the stresses of intubation. The objective of our study was to determine if esmolol would be equally effective when administered in a bolus with and without fentanyl.

Forty-four ASA I and II females undergoing elective surgery were randomly divided into four groups and received the following agents prior to intubation:

- **Group 1**—esmolol 1 mg/kg and fentanyl 2 μg/kg,
- **Group 2**—placebo (normal saline),
- **Group 3**—esmolol 1 mg/kg,
- **Group 4**—fentanyl 3.5 μg/kg.

Groups 1 and 4, which received fentanyl, demonstrated significantly less elevation in blood pressure. Esmolol appeared to attenuate increases in heart rate. Esmolol has a tissue distribution time of 2 minutes and an elimination half-life of 9 minutes. The window of its availability to the tissues is narrow, and timing of bolus administration is more critical than in administration by infusion. Doses in excess of 1 mg/kg appear to be necessary for effective control of heart rate. However, when used with fentanyl, esmolol provides effective protection against the adrenergic response to laryngoscopy and intubation.

Laryngoscopy and intubation cause a reflex-mediated adrenergic response, manifested by tachycardia and hypertension. These increases in heart rate (HR) and blood pressure (BP) may be potentially harmful in patients with coronary artery disease. Various agents have been used to attenuate the sympathetic response to intubation. These include anesthetics, analgesics, adrenergic blockers and vasodilators; however, none of these is without limitations. Esmolol hydrochloride, an ultrashort-acting, cardioselective beta blocker, has been successfully used in a number of clinical settings to attenuate the adrenergic response to intubation. In the majority of studies, esmolol was administered by infusion prior to induction. When given by infusion, esmolol was found to protect patients from hypertension and tachycardia.

There are many instances when a rapid-sequence induction (RSI) is required. RSI diminishes the potential for aspiration, but it may heighten cardiac stress and the potential for ischemia. In emergent cases, the preparation and administration of an infusion is time consuming and cumbersome. It would be very helpful if esmolol could be administered as a single bolus rather than by infu-
sion prior to intubation. Ellenbogen and associates administered esmolol in bolus doses to healthy exercising subjects (in whom sympathetic tone may have been relatively high). They found that doses of up to 300 mg could be administered without adverse side effects. They recommended an esmolol bolus dose of about 100-180 mg as an appropriate starting dose for clinical studies.

Two preliminary studies reported in recent literature deal with the administration of esmolol as a single intravenous (IV) bolus prior to intubation. Bernstein et al. administered esmolol in doses of 100 mg or 200 mg approximately 2 minutes prior to RSI and noted that HR and mean arterial pressure (MAP) changes were blunted by esmolol but alpha-adrenergic responses were not diminished. Jacque and associates conducted a study to determine whether single IV doses of esmolol (50 mg, 100 mg or 150 mg) administered 2 minutes prior to intubation prevented tachycardia. Their methods differed from all those reported previously in that esmolol was administered immediately after induction with sodium thiopental. At intubation, which occurred 2 minutes later, a rise in HR was seen in all groups. Jacque and associates found no statistical difference between any group in their study, although the rise in the postintubation heart rate was lowest in the groups receiving 100 mg and 150 mg of esmolol. Based on their results, they suggested that a dose of 150 mg be used within 2 minutes of intubation if one is to expect any protection from tachycardia.

The authors' objective was to study further the effects of a bolus dose of esmolol on hemodynamic variables during induction using commonly accepted anesthetic techniques. The goal was to find the combination of induction agents that would have the most protective effect on hemodynamic variables.

Methods

The study was a randomized, double-blind clinical trial. Following institutional board approval, informed consent was obtained. Forty-four ASA I and II female patients scheduled for elective gynecological and plastic surgery were randomly divided into four equal groups to receive one of the following regimens:

1. Esmolol 1 mg/kg and fentanyl 2 μg/kg.
2. Control (placebo).
3. Esmolol 1 mg/kg.
4. Fentanyl 3.5 μg/kg.

Exclusion criteria are shown in Table I. Esmolol doses were selected based on the findings of Ellenbogen et al., Bernstein et al. and Jacque et al. Low-dose fentanyl (1.5-3.0 μg/kg) has been shown to attenuate the response to intubation. The doses of fentanyl were chosen with regard to the lowest effective amount that would attenuate responses. These doses approximate the standard induction doses of fentanyl used by practitioners at this institution.

Diazepam 10 mg, metoclopramide 10 mg and ranitidine 150 mg were administered orally 60-90 minutes prior to induction. An intravenous catheter was placed and Ringer's lactate was infused. Leads II and V$_5$ were continually monitored on the ECG, and blood pressure was monitored by an automated blood pressure monitor every minute until 5 minutes postintubation. Baseline hemodynamic readings were recorded upon admission to the operating room and again immediately prior to induction. The latter are reported as baseline vital signs. Oxygen was administered by face mask for 5 minutes prior to induction. Regimen for administration of esmolol and anesthetic agents is illustrated in Table II.

Syringes containing fentanyl, esmolol or placebo (normal saline) were prepared by a separate staff member. The anesthetist and observer were blinded to the contents of the syringes. Syringes labeled "#1" contained either fentanyl 2 μg/kg, fentanyl 3.5 μg/kg or normal saline and were administered 5 minutes prior to intubation (see Table II). Syringes labeled "#2" contained either esmolol 1 mg/kg or normal saline. All syringes contained a total volume of 10 cc. Induction included sodium thiopental 4 mg/kg and succinylcholine 1.5 mg/kg. In all cases, intubation was performed in less than 30 seconds (average time was 8 seconds).

Systolic blood pressure (SBP), diastolic blood pressure (DBP), MAP and HR were recorded by the observer at intubation and each minute thereafter for 5 minutes. Following intubation, patients received nitrous oxide in oxygen (FiO$_2$ = .33) for 5 minutes before adding additional anesthetic agents. If a 40% rise above baseline in SBP occurred, isoflurane 1% was added. Any adverse reactions such as bradycardia (HR < 50 bpm), hypotension (SBP < 90 mmHg), dysrhythmias or bronchospasm were recorded and treated appropriately.

### Table I

<table>
<thead>
<tr>
<th>Exclusion criteria</th>
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<td>Pregnancy</td>
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<td>Age less than 18 years or greater than 60 years</td>
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<td>Preexisting hypertension</td>
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<td>Diabetes mellitus</td>
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<td>Gastroesophageal reflux</td>
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<td>Asthma</td>
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<td>Morbid obesity</td>
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<td>Drug allergy to the agents under study</td>
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<td>Beta-blocker therapy</td>
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<td>Malignant hyperthermia</td>
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The data were analyzed using the SPSSX (Statistical Package for the Social Sciences, Release 10). Analysis of variance (ANOVA) was performed with the factors of esmolol (presence or absence) and fentanyl (presence or absence) for each measurement (at baseline and at each minute following intubation for 5 minutes). P < .05 was accepted as the level of significance.

Results
Patients in the four groups had similar demographic data (Table III). Surgical procedures included mammoplasties, hysterectomies and other gynecological procedures.

The four hemodynamic variables (SBP, DBP, MAP and HR) recorded for each subject were analyzed by ANOVA (between group analysis). The mean and standard deviation of these values are reported in Table IV. Both groups receiving fentanyl (Groups 1 and 4) had significantly less response to intubation as manifested by elevations in SBP, DBP and MAP than did the control group (Group 2) or the subjects receiving esmolol alone (Group 3) p < .001. This is depicted graphically in Figure 1. Esmolol alone in the dosage employed and administered at 3 minutes prior to intubation had no significant effect on blood pressure.

Changes in heart rate postintubation are depicted graphically in Figure 2. Patients receiving fentanyl (Groups 1 and 4) had a significantly lower heart rate postintubation compared to baseline (p < .05). However, it should be noted that the variation of heart rate within Group 3 (esmolol) is less than that in Group 1 (esmolol and fentanyl). The group with the least variation in HR was Group 4. When the data were analyzed statistically, a pattern became apparent. Groups receiving fentanyl were significantly less responsive to effects of intubation than groups not receiving fentanyl (p < .001).

Clinically evident changes in bronchomotor tone did not occur in any patient. One patient in Group 1 experienced a junctional rhythm (HR = 67) in the third minute following intubation. One patient in the control group (Group 2) had a transient tachycardia immediately after intubation (T1, HR = 105). One patient in Group 3 had two premature ventricular contractions (PVC) 1 minute after intubation. In Group 4, one patient had a short run of bigeminy 1 minute after intubation, while another had 2 PVCs during the same time frame.

Discussion
Myocardial ischemia is a frequent consequence of intubation, especially in the presence of tachycardia. Patients with known or suspected ischemic heart disease are those who most need to be protected from the stresses of intubation. However, such individuals are least likely to be found in the control group of a prospective study examining hemodynamic control at the time of endotracheal intubation; thus, the efficacy of a pharmacologic agent often can only be extrapolated to this group.

The subjects in this study were ASA I and II females presenting electively for gynecological or plastic procedures. None were perceived to be at risk for myocardial ischemia.

The use of an esmolol infusion to blunt the adrenergic response to intubation is not a new idea. Esmolol has been used in this capacity in a variety of surgical settings. Esmolol has a tissue distribution time of 2 minutes and an elimination half-life of 9 minutes. Therefore, timing the effects of bolus
dose with intubation is more critical than the use of an infusion.

Four recent studies attempting to blunt adrenergic responses are compared with the present study. Two of these studies dealt with the effect of administering bolus doses of esmolol. The technique of Bernstein et al. most closely parallels the present study. Bernstein and associates studied ASA I and II patients presenting for elective surgery; vecuronium was used for defasciculation because they felt it was the agent more commonly used. Their patients received esmolol in single doses of 50, 100 or 200 mg immediately before cricoid pressure and induction with sodium thiopental (STP), and they were given esmolol in doses of 1 mg/kg so that no patient received more than 100 mg.

The patients in Bernstein's group were intubated 1 minute after receiving STP; the patients in the present study were intubated 2 minutes after receiving STP and 3 minutes after receiving esmolol. The tissue distribution time for esmolol is 2.0 ± 0.5 minutes. In Bernstein's study, the maximal changes in the MAP occurred 30 seconds after intubation or 1½-2 minutes after injection of esmolol. At this time, the drug is just beginning to be available to the tissues. In the present study, patients showed a maximal response to intubation at 1 minute postintubation or 4 minutes after injection of esmolol. Patients in Group 3 showed no significant difference from controls with respect to blood pressure. This may be a function of timing as well as dose. Even in these doses, esmolol causes some blunting of chronotropic responses (Table IV).

Jacque and associates published the effects of bolus doses of esmolol, using a different schedule for the administration of induction agents. They administered STP, followed by esmolol (50 mg, 100

<p>| Table IV |</p>
<table>
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<th>Mean (X) and standard deviation of the mean (SD) are shown for four hemodynamic variables: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR).</th>
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B = baseline values
T1 through T5 represents times of 1 to 5 minutes postintubation.
mg or 150 mg) and then succinylcholine. A minimum period of 2 minutes elapsed between esmolol injection and intubation. At intubation, elevated heart rates were seen for all groups with the highest levels occurring 1 minute postintubation or 3 minutes after injection of esmolol. No statistical significance was seen at any time or event between groups; however, in the patients receiving 100 mg or 150 mg of esmolol, the least change in heart rate occurred after intubation. Thus, results for esmolol obtained by Jacque and associates are similar to the present study.

Fentanyl had a significant effect on lowering DBP from baseline postintubation (p < .001). Both groups receiving fentanyl had the greatest decreases in DBP (Figure 1). The group receiving esmolol alone (Group 3) maintained its DBP throughout the study (Figure 1). Decreases in DBP may result in decreases in coronary perfusion pressure; therefore, maintenance of DBP facilitates perfusion. In the present study, there is not a great deal of difference in DBP between Groups 2 and 3 (control and esmolol); however, it should be remembered that the study was limited to a healthy population with a presumably good vasomotor tone.

The protection of coronary perfusion by esmolol was also reported by Ebert and associates who compared the effects of fentanyl, esmolol and a placebo on the hemodynamic responses to intubation. In this study, subjects received both esmolol and fentanyl by infusion. Fentanyl was infused at the rate of 0.8 μg/kg/minute x 10 minutes with the infusion terminating 1 minute before intubation. It was found that fentanyl produced significant decreases in HR, SBP and DBP. Although fentanyl effectively blocked responses to laryngoscopy and intubation, depression of DBP might detrimentally affect myocardial blood flow in some patients. When Splinter and Cervenko administered fentanyl (3 μg/kg) to geriatric patients 1 minute prior to induction with STP, DBP was lowered in 55% of these patients to 20% less than ward baseline values.

The use of fentanyl in the present study appears to attenuate the adrenergic response to intubation. Esmolol given as a bolus dose blunts the response, but an optimal time frame for its administration has not yet been determined. Ebert and associates feel that administration by infusion is necessitated by its short elimination half-life and duration of action. We would suggest, like Bernstein et al., that doses should probably be in excess of

![Figure 1](image1.png)

**Figure 1**

Systolic blood pressure (SBP) and diastolic blood pressure (DBP)

- **Time (minutes) at baseline and postintubation**
  - SBP: Group 1, Group 2, Group 3, Group 4
  - DBP: Group 1, Group 2, Group 3, Group 4

Blood pressure recorded in mmHg
Baseline values recorded at 5 minutes preintubation

![Figure 2](image2.png)

**Figure 2**

Heart rate (beats per minute)

- **Time (minutes) at baseline and postintubation**
  - Group 1, Group 2, Group 3, Group 4

Baseline values recorded at 5 minutes preintubation
100 mg. One is also led to question the convenience of a drug whose window of effectiveness must be so tightly controlled when using bolus doses.

Conclusion

The effects of tachycardia are generally considered more deleterious to the compromised myocardium than those of hypertension. Groups 1 and 4 had significantly lower heart rates after intubation than Groups 2 and 3 (p < .05), although Group 3 exhibited some blocking of chronotropic response. Ebert and associates postulated at the conclusion of their study that "a combination of a smaller dose of fentanyl with esmolol should provide a stable HR in the presence of a modestly reduced or unchanged DBP, thus optimizing the myocardial O2 supply-demand relationship." The authors' data support this. Fentanyl alone, or in combination with esmolol, affords protection against changes in blood pressure and heart rate caused by the stress of intubation. Esmolol alone, or in combination with fentanyl, modulates increases in heart rate after intubation. Bolus doses of esmolol in excess of 1 mg/kg may be necessary to provide the desired protective effect. The authors suggest that the combination of low-dose fentanyl (1.5 to 3.0 mcg/kg) and a bolus dose of esmolol administered 2 to 3 minutes prior to intubation offer synergistic protection against hypertension and tachycardia while minimizing the adrenergic response to intubation.

REFERENCES


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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting views of the Department of the Army or the Department of Defense.
CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzo diazepines are contraindicated in patients with acute narcolepsy or narcolepsy type 1.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose and in the management of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation.

Continuous monitor for early signs of underventilation or apnea, which can lead to respiratory depression. The use of the ventilator should be anticipated and prepared for. The volume of 

intravenous VERSED has been associated with respiratory depression and apnea and should be anticipated and prepared for. The volume of 

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for elderly patients and for patients with possible increased intracranial pressure (e.g., head trauma, subarachnoid hemorrhage) or who are premedicated with narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus. Administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

OVERDOSAGE: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased systolic and/or diastolic blood pressure, tachycardia, tachypnea, bradycardia, flushing, flushing, flushing (5.6%), pain or agitation, prolonged emergence from anesthesia, dreaming during emergence, retching, retching, retching.

Other effects (- 1%) mainly IV administration. Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachycardia, tachycardia, tachycardia, tachycardia, tachycardia.

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