Low-dose fentanyl: hemodynamic response to endotracheal intubation in normotensive patients

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Abstract

Introduction: Endotracheal intubation is one of the most invasive stimuli in anesthesia, often accompanied by a hemodynamic pressor response. The purpose of this study was to investigate the efficacy of a single pre-induction 2 µg/kg bolus injection of fentanyl with a thiopentone/suxamethonium sequence in the attenuation of the hemodynamic response to endotracheal intubation in normotensive patients.

Material and methods: The study consisted of 100 randomly selected ASA physical status I/II male/female adults, aged 18-60 years, scheduled for elective surgery. Group I received a single 2 µg/kg IV bolus of fentanyl diluted to 5 ml with normal saline 5 min prior to laryngoscopy (n=50). Group II received a single 5 ml IV bolus of normal saline (n=50). Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and rate pressure product (RPP) were compared to basal values at pre-induction, induction, intubation and post-intubation, at time increments of 1, 3, 5, 7 and 10 min.

Results: Fentanyl significantly attenuated hemodynamic pressor responses. Attenuation of HR (10.9%), SBP (12.4%), DBP (9.4%), MAP (11.3%) and RPP (23.3%) were observed in the fentanyl group as compared to the equivalent control measured values.

Conclusions: Single pre-induction 2 µg/kg bolus injection of fentanyl in a thiopentone/suxamethonium anesthetic sequence successfully attenuates, but does not suppress, the hemodynamic pressor response in normotensive patients resulting from endotracheal intubation.

Key words: fentanyl, endotracheal intubation, hemodynamic response, attenuation, opioids.

Introduction

Identified as a depth-of-anesthesia-dependent influencing factor [1], endotracheal intubation has been suggested to be one of the most invasive stimuli in anesthesia [2], particularly during induction [3] and after tracheal intubation [3, 4]. It is usually well tolerated by normotensive patients, but even short-lasting stimulation has been associated with increased morbidity and mortality in patients with recent myocardial infarction, hypertension, preeclampsia, and cerebrovascular pathology such as tumors, aneurysms or increased intracranial pressure [2-6]. The exact mechanisms of the pressor response are not known, but have been associated with both sympathetic [2, 4, 7, 8] and parasympathetic responses [4], which may include symptoms such as increased plasma catecholamine

concentrations [7], increased blood pressure and increased heart rate [9].

No pharmaceutical agent to date has been consistently free of complications, in part due to the unique chemical characteristics of each drug and their interaction with the individual biological system of each patient [8]. Traditional inhaled anesthetics have been employed, but may be contradictive in cases of intracranial lesions, hypertension, and hypotension [4]. α-agonists have also been used to block hemodynamic effects; however, few α-agonists are available for intravenous injection [10]. Additionally, α-agonists may cause hypotension and are known to interrupt the baroreflex response, leading to the risk of first dose phenomenon [11]. Vasodilators may also effectively attenuate blood pressure responses to intubation, but have been found to be ineffective in blunting associated heart rate effects, and thus are limited to use in normotensive patients unless a β-blocker is co-administered. However, β-blockers as well have a number of known side effects which include bronchospasm, bradycardia, hypotension, heart failure and cardiac dysrhythmias [4]. Finally, opioids have also been effective in blunting the hemodynamic response, offering a combination of analgesic potency and acceptable profile of adverse effects matched by no other class of drug [12]. Despite this, use of opioids has generally been limited due to a number of well-documented adverse side affects [13], including nausea, vomiting, drowsiness, dry mouth, respiratory depression, histamine release, and neuroexcitatory and gastrointestinal effects [12-14]. Although some of the common and less serious effects have been addressed successfully by dose reductions, symptomatic management, opioid rotations, and changes in administration route [14], the more serious effects still warrant caution.

Fentanyl, a β-opioid receptor agonist [13], is an exception. Characterized by high potency, rapid onset, short duration of action [15] and an apparent absence of the serious side effects normally associated with opioids, it has been particularly effective. However, despite the efficacy demonstrated in previous studies, the ideal dose of fentanyl required to suppress the hemodynamic response to endotracheal intubation has not yet been conclusively determined. It is therefore the purpose of this study to investigate whether a single 2 μg/kg bolus pre-induction injection of fentanyl administered 5 min prior to intubation would significantly attenuate the hemodynamic response to endotracheal intubation in normotensive patients.

Material and methods

Following institutional approval by the ethical committee at Mysore Medical College, Rajiv Gandhi University (Mysore, India), informed consent to participate in this study was obtained from 100 patients. The study population consisted of randomly selected ASA physical status I/II male/female adults between the ages of 18 and 60 years, scheduled for elective surgical procedures. There were no statistical demographic differences observed with respect to number of patients in each group (n=50), age or weight (Table I), although the fentanyl group had a disproportionate gender distribution not observed in the control group. Patients having pre-existing systemic disorders, ischemic heart disease, hypertensive heart disease, diabetes mellitus, bronchial asthma, previous myocardial infarction, renal disease, cerebrovascular insufficiency or association with any co-morbid disease were excluded from the study.

Study design

Each patient was randomly assigned to one of two double-blind study groups: the fentanyl group received a single 2 μg/kg IV bolus of fentanyl diluted to 5 ml with normal saline 5 min prior to laryngoscopy and intubation (n=50) and the control group received a single 5 ml IV bolus of normal saline (n=50). Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were recorded via a Siemens SC-7000 multi-channel monitor for each patient prior to administration of the study drug (T-0), pre-induction at 3 min after pre-oxygenation and study drug administration (T-3), induction (T-4), intubation (T-5), and at post-intubation time increments of 1 min (T-6), 3 min (T-8), 5 min (T-10), 7 min (T-12), and 10 min after intubation (T-15). Rate pressure product (RPP) was also calculated and evaluated.

Protocol

One day prior to surgery each patient underwent a thorough pre-anesthetic evaluation with special consideration to a history of hypertension, diabetes

Table I. Study participant demographic data

	Gender ratio* (M/F)	Age** [years]	Weight** [kg]
Control	25/25	40.6±11.9/36.0±11.9	52.4±5.6/59.8±4.1
Fentanyl	39/11	34.2±9.7/26.3±7.7	48.7±6.3/57.1±6.3

**Randomly selected ASA Grade I/II patients (n=50)*
***Values represent means ± SD*

mellitus, chest pain, dyspnea, convulsions, wheezing and myocardial infarction, as well as previous anesthetic history and drug sensitivity. Patients meeting study criteria were advised to fast the night prior to surgery and were pre-medicated with a single oral dose of 150 mg ranitidine and 0.5 mg alprazolam.

On the day of surgery, patients were pre-medicated with a single injection of 0.2 mg glycopyrrolate and 2 mg midazolam given intramuscularly 30 min prior to surgery. After an infusion of dextrose and normal saline, patients were connected to the Siemens multi-channel monitor. After recoding baseline HR, SBP, DBP, and MAP levels (T-0), the study drug (2 µg/kg of fentanyl diluted to 5 ml with normal saline) or the control placebo (5 ml normal saline) was administered and patients were pre-oxygenated for 3 min via a facemask with Bains circuit (T-3). Anesthesia was induced with thiopentone 5 mg/kg as a 2.5% solution and endotracheal intubation was facilitated with 1.5 mg/kg IV succinylcholine one minute prior to laryngoscopy and intubation (T-4). Laryngoscopy and intubation were performed and upon bilateral, equal air entry confirmation, the endotracheal tube was fixed and the patients mechanically ventilated using a Bains system (T-5). HR, SBP, DBP, and MAP levels continued to be recorded up to 10 min post-intubation while anesthesia was maintained using 66% nitrous oxide and 33% oxygen and non-depolarizing muscle relaxant, vecuronium bromide (0.06 mg/kg) and 0.5% halothane. Anesthesia was reversed with 0.05 mg/kg neostigmine IV bolus and 0.02 mg/kg atropine IV bolus.

Statistical analysis

Summary statistics of patient gender, age and weight for both the fentanyl and control groups are reported as means ± standard deviation (Table I). Intra- and inter-group analysis for HR, SBP, DBP, MAP, and RPP were statistically evaluated using one-way ANOVA and paired t-tests using both StatPlus™ v2, and Minitab™, where $P<0.05$ was considered significant, and $P<0.001$ highly significant.

Results

A single pre-induction 2 µg/kg bolus injection of fentanyl in a thiopentone/suxamethonium anesthetic sequence was observed to successfully attenuate the hemodynamic pressor response in normotensive patients resulting from endotracheal intubation.

Heart rate (HR)

Attenuation of heart rate related hemodynamic response to tracheal intubation by a single 2 µg/kg bolus of fentanyl was observed at all measured time points – 10.9% greater than the control group (Figure 1A) and 12% from fentanyl basal levels (Figure 1B). At pre-induction (T-3), the fentanyl group was observed to have a 5% decrease in heart rate as compared to the control group, although not statistically significant ($t=1.74$ $P=0.08$). Likewise, induction values for the fentanyl group were 13% below those of the control group (T-4), but were still not statistically different ($t=1.32$, $P=0.194$). At intubation (T-5), however, the fentanyl group had a highly significant mean heart rate at 16% below the control ($t=7.75$, $P\leq0.001$). Further, significant attenuation was also observed 1 min after intubation (T-6) ($t=7.47$, $P\leq0.001$), which was lower than the control value by 15%, 3 min after intubation by 18% (T-8) ($t=8.94$, $P\leq0.001$), 5 min after intubation by 17% (T-10) ($t=7.89$, $P\leq0.001$), 7 min after intubation by 14% (T-12) ($t=6.35$, $P\leq0.000$), and again at 10 min post-intubation the fentanyl group was 12% lower than that of the control (T-15) ($t=5.55$, $P\leq0.001$).

Systolic blood pressure (SBP)

Highly significant attenuation of systolic blood pressure was observed in the fentanyl group with a 12.4% average lower value than the control over all measured points (Figure 2A) and a 12% lower value than the fentanyl basal value (T-0) ($n=50$, $P<0.001$) (Figure 2B). The greatest difference between

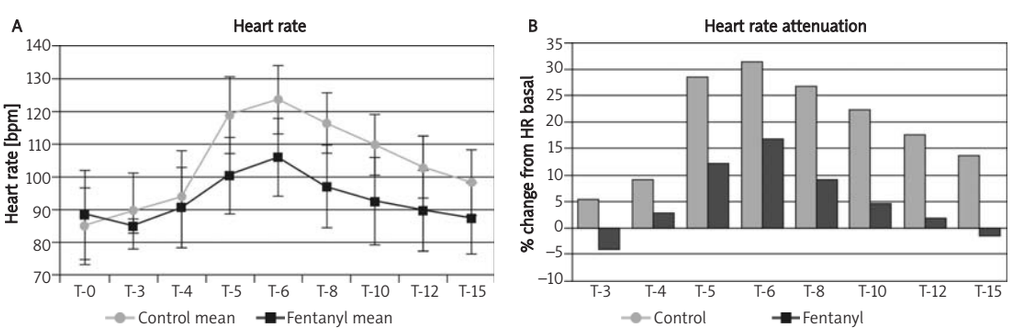

Figure 1. A – mean HR values for control and fentanyl groups ± SD and **B** – percent difference between measured HR levels and basal values

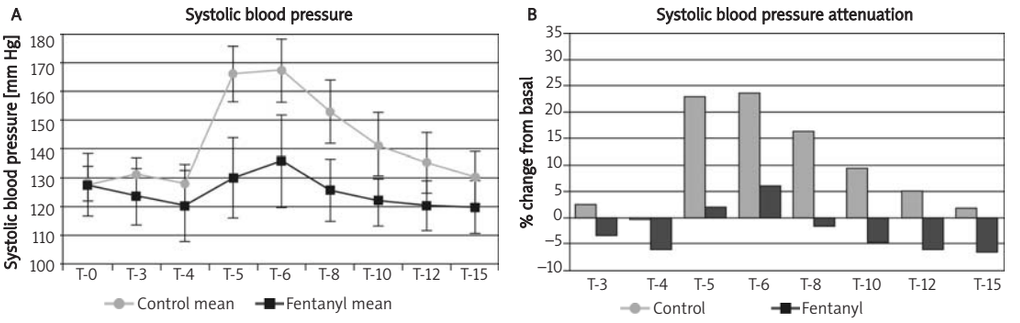

Figure 2. A – mean SBP values for control and fentanyl groups ± SD and **B –** percent difference between measured SBP levels and basal values

measured points was at intubation (T-5), where a 24% decrease from control levels was observed in the fentanyl group (t=13.95, P≤0.001), followed by a 21% difference at 1 min post-intubation (T-6) (t=12.16, P≤0.001), 20% at 3 min (T-8) (t=11.74, P≤0.001), 15% at 5 min (T-10) (t=8.83, P≤0.001), 12% at 7 min (T-12) (t=7.01, P≤0.001), and an 8% difference at 10 min post-intubation (T-15) (t=5.62, P≤0.001).

Diastolic blood pressure (DBP)

As with SBP, high attenuation of the DBP pressor response to intubation in the fentanyl group was observed at all measured times – on average 9.4% greater attenuation than the control group (Figure 3A) and 10% lower than fentanyl basal values (Figure 3B). The greatest attenuation was observed at 1 min post-intubation with a 16% difference (T-6) (t=8.06, P<0.001). This was preceded by a 7% difference at pre-induction (T-3) (t=2.612, P=0.012), 6% at induction (T-4) (t=2.38, P=0.021) and a 14% reduction at intubation (T-5) (t=7.49, P≤0.001), and then followed by a fentanyl reduction of 14% at 3 min (T-8) (t=8.06, P≤0.001) and 5 min post-intubation (T-10) (t=6.12, P≤0.001), 8% at 7 min (T-12) (t=3.38, P=0.001), and 7% at 10 min post-intubation (T-15) (t=0.24, P=0.002).

Mean arterial pressure (MAP)

Inter-group MAP values yielded significant attenuation in the fentanyl group for all recorded time periods – 11.3% greater attenuation than the control group (Figure 4A) and 12% than fentanyl basal values (T-0) (P≤0.001) (Figure 4B). The greatest degree of attenuation, as was seen with SBP, was observed at intubation, with a 22% lower mean value in the fentanyl group (T-5) as compared to the control group (t=7.94, P≤0.001). Pre-induction fentanyl mean was 7% less than the control (T-3) (t=3.62, P=0.001), followed by an induction difference of 5% (t=2.64, P=0.01). At 1 min post-intubation there was an 18% difference (T-6) (t=10.71, P≤0.001), at 3 min 16% (T-8) (t=9.58, P≤0.001), at 5 min a 14% difference (T-10) (t=7.66, P≤0.001), at 7 min 10% lower (T-12) (n=50, t=5.93, P≤0.001), and finally an 8% lower mean in the fentanyl group at 10 min post-intubation (T-15) (t=5.11, P≤0.001).

Rate pressure product (RPP)

Rate pressure product, as expected, was observed to follow similar results as observed for HR and SBP with regards to percent difference between control and fentanyl groups. 23.3% greater attenuation was observed in the fentanyl group

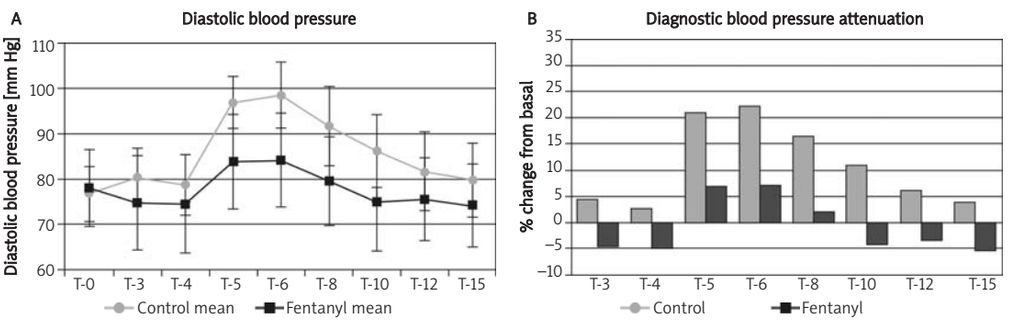

Figure 3. A – mean DBP values for control and fentanyl groups ± SD, **B –** percent difference between measured DBP levels and basal values

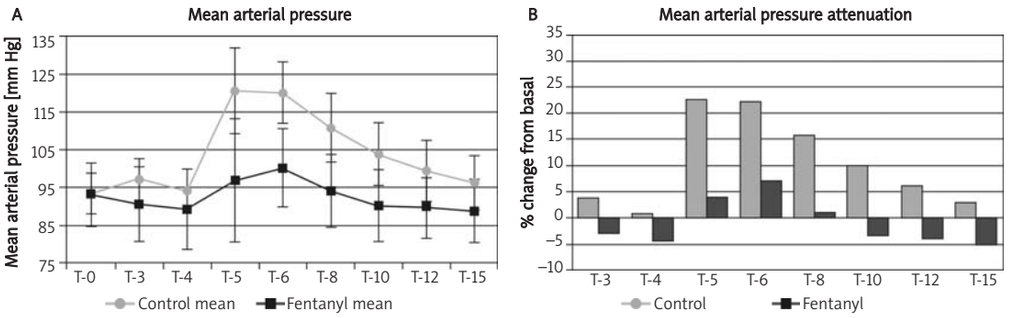

Figure 4. A – mean MAP values for control and fentanyl groups ± SD, **B** – percent difference between measured MAP levels and basal values

(Figure 5A) and 24% to fentanyl basal values (Figure 5B). As with SBP, the greatest attenuation was observed at intubation, with the fentanyl group a mean of 41% below that of the control group (T-5) (t=13.01, P≤0.001). Pre-induction fentanyl mean was 11% below (T-3) (t=2.99, P=0.004) and induction 10% below (T-4) (t=2.688, P=0.01) control values. One-minute post-intubation was still significantly different at a 36% lower value with fentanyl (T-6) (t=11.63, P≤0.001), 37% lower at 3 min (T-8) (t=13.205, P≤0.001), 32% lower at 5 min (T-10) (t=10.532, P≤0.001), 25% at 7 min (T-12) (t=8.34, P≤0.001), and 21% lower with fentanyl at 10 min post-intubation than observed with the control (T-15) (t=6.88, P≤0.001).

Discussion

Since as early as 1940 [16], the occurrence of the hemodynamic pressor response associated with laryngoscopy during endotracheal intubation and the mechanisms responsible have been extensively investigated. Numerous studies have also concentrated on methods to modify the magnitude of the observed pressor response, which has been associated with factors including depth of anesthesia, the duration of laryngoscopy and intubation and the anesthetic agents used. The pharmacodynamic properties of an anesthetic agent remain the number one priority for induction of anesthesia for most developed countries [17], where practitioners are not overwhelmingly burdened by concerns of cost or required advanced techniques. However, the cost and relative advantage of using a particular anesthetic drug is of great importance in any area where patients depend on public hospitals for health problems, as is the case in many developing nations. These public hospitals are severely handicapped by their poor support from the government and therefore need to depend on an economically beneficial drug like fentanyl. As a consequence, fentanyl remains a commonly administered opioid for attenuation of hemodynamic responses in various surgical procedures as well as endotracheal intubation procedures. In this study, fentanyl was chosen not only because of its continued economic advantage but because of the unique pharmacodynamic benefits it offers as compared to those of later generation opioids. The most significant advantages are its rapid onset of action, absence of histamine release and its cardio-stable anesthetic properties. Many opioids, including morphine, are known to produce histamine release in humans [18] which, like endogenous histamine release, may be associated with a number of negative chronotropic

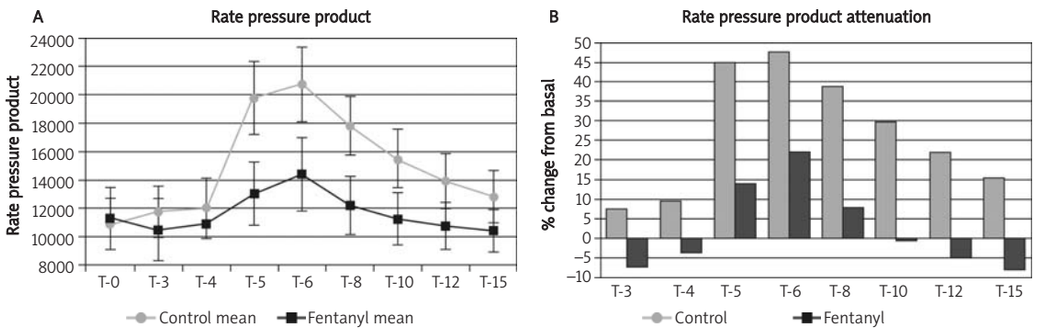

Figure 5. A – mean RPP values for control and fentanyl groups ± SD, **B –** percent difference between measured RPP levels and basal values

and inotropic cardiovascular effects [19, 20] including dilatation of terminal arterioles, leading to a profound decrease in systemic blood pressure, bronchoconstriction [21] and even cardiovascular collapse [22]. Studies like that of Philbin et al. have observed a remarkable lack of cardiovascular changes with high doses of fentanyl and no histamine release [18], which may account for the hemodynamic stability associated with this drug.

Various studies have indicated that an intravenous single bolus of fentanyl before laryngoscopy and endotracheal intubation is sufficient to attenuate unwanted increases in pressor response [23]. However, the conclusion as to whether a high or low dose of fentanyl is best varies considerably. High or anesthetic doses of fentanyl ranging from 25 to 75 µg/kg have been shown to effectively block sympathetic responses, but were often accompanied by hypotension, respiratory depression and truncal rigidity [24, 25]. Not all high-dose studies, though, observed significant occurrences of these adverse side effects [9, 26, 27]. Alternately, low doses of fentanyl, at times in conjunction with various IV induction drugs, have also been observed to attenuate the hemodynamic response to endotracheal intubation [3-5, 28-31]. These dosages and conclusions vary widely as well, but many have focused on doses of 10 µg/kg of fentanyl or less. For example, Iyer and Russel concluded that 10 µg/kg of fentanyl was required to blunt the blood pressure but not heart rate response [4, 24]. Similar, however, to the independent studies of Dahlgren et al. [32] and Kautto [33], this study found that 2 µg/kg of fentanyl significantly attenuated the heart rate and blood pressure effects. At pre-induction (T-3), when fentanyl or the saline placebo was administered, a significant difference between fentanyl and the control group HR was not observed, but at intubation (T-5) a 16.9% lower HR value was recorded for the fentanyl group (Figure 1A). Over all measured points, the fentanyl group HR was 10.9% lower than the control. SBP, DBP, MAP and RPP values, unlike HR, were significantly different at both pre-induction and intubation. Systolic blood pressure was observed to be 12.4% lower overall, 6.1% lower at pre-induction and an impressive 24.4% at intubation (Figure 2A). Diastolic blood pressure resulted in a slightly lower overall average of 9.4% between the fentanyl and control values, but still a significant 7.1% at pre-induction and 14.5% at intubation (Figure 3A). Mean arterial pressure was also found to have a lower overall average value of 11.3% for fentanyl, 7.0% at pre-induction and a significant 21.8% at intubation (Figure 4A). Based on these observations, it was not unexpected that the calculated rate pressure product value was also statistically lower for the fentanyl group, 23.3% overall. At pre-induction RPP was 11.2% lower with fentanyl and a notable 40.9% at intubation (Figure 5A). As with other studies, a general decline in hemodynamic changes occurred after intubation, with only slightly significant differences observed 10 min after intubation for all measured values.

Study limitations

Further complicating the predictive power of the clinician is the administration of drugs under non-steady state conditions, such as found with a single IV bolus administration, which must accommodate the time between changes in plasma concentrations and the observed effects [8]. These discrepancies, combined with the confounding variables introduced by other interventions such as intubation, have been suggested to explain, in part, the inconsistent results between studies [8]. It has also been suggested that the lack of high frequency measurements provides gaps where peak pharmacodynamic effects may be missed [8]. In our study pre-anesthetic medication consisted of 0.2 mg glycopyrrolate and 2 mg midazolam IM 30 to 60 min before anesthetic induction. As far as use of glycopyrrolate is concerned, we believe the administration of an anti-cholinergic before general anesthesia and tracheal intubation so increases safety that it would be inappropriate to omit it for the sake of increasing the pharmacological priority of our study. We also chose midazolam as a pre-medication agent for its sedative anxiolytic properties and short duration of action, but acknowledge that this too may have impacted the results.

In conclusion, the results from this study are in agreement with the common properties of many opioids such as high potency, rapid onset and short duration of action and support the conclusion that a pre-anesthetic 2 µg/kg bolus injection of fentanyl given 5 min prior to intubation is effective in reducing the response to endotracheal intubation in ASA physical status I/II adults aged 18-60 years without any significant side effects. Fentanyl's low economic cost and unique pharmacodynamic properties make it still one of the best opioids at present to attenuate hemodynamic responses to endotracheal intubation with minimal side effects. This study then provides further evidence of the safety and efficacy of lower-dose fentanyl adjuncts prior to laryngoscopy during endotracheal intubation.

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