Original Article

A Comparative Effect of Intravenous Pethidine vs Sufentanil on Attenuation of Cardiovascular Responses to Laryngoscopy and Tracheal Intubation: a Randomized Double-Blind Placebo Controlled Trial Study

MR Safavi, A Honarmand

Department of Anesthesiology and Intensive Care Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Background: The study was undertaken to compare the effects of small doses of sufentanil or pethidine on cardiovascular changes induced by tracheal intubation.

Patients and Methods: Sixty American Soceity of Anesthesiology (ASA) physical status I-II patients, scheduled for elective abdominal surgery under general anesthesia, randomly allocated in a double- blind fashion to receive an intravenous bolus of either sufentanil 0.1 μg/kg (Group S, n = 30) or pethidine 1.5 mg/kg (Group P, n = 30) for induction of anesthesia. The heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and mean arterial pressure (MAP) were measured before induction of anaesthesia (baseline), at 1-min intervals for 3 min after the induction of anesthesia, at 1, 3, 5, and 7 min after start of laryngoscopy.

Results: No significant differences in SAP, DAP, and MAP were observed between the two groups. Heart rate significantly increased 2 and 3 minutes after induction of anesthesia and 1 minute after intubation in group P compared with group S ($P<0.01$). However, the numbers of patients who developed a heart rate increase more than 20% of basal value were not different between two groups. At the end of the study period, systolic, diastolic, and mean arterial pressure slightly decreased from preinduction values that was transient and did not require treatment.

Conclusions: If adequate timing in opioid administration is warranted according to the time to peak effect of each opioid drug, small doses of sufentanil or pethidine exert similar effect in controlling the inotropic response induced by the laryngoscopy and tracheal intubation.

Keywords: Intubation, Cardiovascular Physiology, Opioids, Meperidine

Introduction

Induction of anesthesia and tracheal intubation may induce profound alteration of the hemodynamic state of the patient according to both the effects of anesthetic drug administered perioperatively, and adrenergic state of the patient.[1] Tracheal intubation induces clinically relevant neurovegetative responses.[2-4] Plasma concentration of cathecolamines is increased[2-4] and there may be associated myocardial ischemia[5] and cerebral hemorrhage.[6] Opioids are widely used to control the neurovegetative response to intubation; a linear relationship exists between increasing opioid dose and cardiovascular response reduction.[7-10] Casati et al.[9] reported that the use of small bolus doses of sufentanil (0.1 μg/kg) effectively blunt the cardiovascular response to intubation. Pethidine or meperidine is a narcotic analgesic similar to morphine. In addition to its strong agonist opioids and anticholinergic effects, it has local anesthetic effects related to its interactions with sodium ion

Correspondence:
Mohammadreza Safavi
Department of Anesthesia and Intensive Care Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
Tel: +98-913-3152416 Fax:+98-311-7751182
E-mail: safavi@med.mui.ac.ir

channels.[11] Van den Berg and colleagues,[12] examined vasomotor responses to tracheal intubation after pethidine given prior to induction of anesthesia, and showed that pethidine reduces the inotropic response to airway instrumentation. Few data are available comparing the efficacy of sufentanil or pethidine in controlling hemodynamic variations during the peri-intubation period. Therefore we conducted a randomized, double- blind study to evaluate any possible blunting of the cardiovascular effects of laryngoscopy and tracheal intubation by the use of small doses of sufentanil or pethidine.

Patients and Methods

Following institutional approval and obtaining informed consent from all patients, sixty physical status I and II (according to American Society of Anesthesiologists) consecutive patients, aged 18–65 years, scheduled for elective abdominal surgery under general anesthesia, were included in the study. Those taking drugs that could influence hemodynamic and autonomic function were excluded from the study. Further exclusion criteria were patients with predictably difficult airways or obesity (body weight exceeding 100 kg), electrocardiographic abnormalities (a cardiac rhythm other than sinus, premature ventricular contractions, (or if the heart rate was less than 55/min), congestive heart failure, diabetes mellitus, hypertension, and coronary artery, respiratory, renal, or cerebral disease. In a double- blind fashion and using a sealed envelope technique, patients were randomly allocated to one of two groups according to the agents to be used for the induction of anesthesia: sufentanil (Group S, n = 30) or pethidine (Group P, n = 30). Syringes containing sufentanil or pethidine were prepared, in a double- blind fashion, by a collaborator not involved in data recording. The same collaborator administered drugs while other blinded observer collecting data. No premedication was given to the patients. When the patient arrived in the operating room, an intravenous cannula (18 G) was inserted and Ringer's solution was administered, at 10ml/kg/hr throughout the study period. Blood pressure (BP) was checked by an automated BP cuff. Monitoring by electrocardiograph and pulse oximetry was also established. Measurements of pre-induction systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP) and heart rate (HR) were used as baseline values. The induction of anesthesia was carried out by intravenous administration of, sufentanil 0.1 µg/kg (Group S) or pethidine 1.5 mg/kg (Group P), followed 60 second later by thiopental 4 mg/kg. Atracurium 0.6 mg/kg was given as an intravenous bolus to facilitate tracheal intubation performed 5 min after induction. The patients' lungs were manually ventilated for 4 minutes with 100% oxygen before orotracheal intubation was performed. Direct laryngoscopy was carried out using a Macintosh blade at peak effects of iv sufentanil or pethidine (at 6 min after injection), and tracheal intubation was accomplished within 30 seconds. The patients' lungs were then mechanically ventilated with a tidal volume of 10ml/kg and a respiratory rate of 12/min to maintain end-tidal PaCO2 at around 38mmHg. Anesthesia was maintained with isoflurane 1.2 % and 50% nitrous oxide in oxygen. In each patient, BP (SAP, DAP, MAP) and HR. were measured at

three time-points: baseline (3 min before induction of general anesthesia), preintubation (at 1-min intervals for 3 min after the induction of anesthesia), and postintubation (at 1, 3, 5, and 7 min after start of laryngoscopy). Mean blood pressure (MBP) was taken as diastolic blood pressure (DBP) plus 1/3 × [systolic blood pressure (SBP)-DBP]s. Statistical analysis was performed using SPSS version 11.0 and comparisons among the groups were performed using two-way analysis of variance (ANOVA), followed by an unpaired t-test with Bonferroni's correction. Hemodynamic responses to induction and intubation in a given group were analyzed using a repeated-measurements ANOVA (one-way ANOVA) followed by a paired t-test with Bonferroni's correction. The Mann- Whitney test was used to compare continuous variables. Continuous variables were presented as mean ± SD. Ordinal variables were presented as numbers (%). A value of P< 0.05 was considered as the minimum level of statistical significance.

Results

Demographic characteristics, induction time (time from administration of induction drugs to start of laryngoscopy), apnea duration (from removal of mask ventilation to start of mechanical ventilation), and duration of laryngoscopy were comparable among groups (Table 1). There was no significant difference between the two groups in Cormack-Lehane grades (Table 2). The preoperative arterial pressure and HR values were comparable in two groups (Fig. 1). Systolic, diastolic, and mean arterial pressure were not significantly different between the two groups 1-3 min after induction of anesthesia with the administration of either drug and 1-7 min after intubation (Fig. 1). HR significantly increased (P<0.01) 2 and 3 minutes after induction of anesthesia and 1 minute after intubation in group P relative to group S (Fig. 1). Compared with preoperative values, changes in systolic, diastolic, and mean arterial pressure values observed after induction and intubation were not statistically significant in either group. However, at the end of the study period, systolic, diastolic, and mean arterial pressure slightly decreased compared with from preinduction values (Fig. 1). The observed decreases in blood pressure were transient in both groups and did not require treatment for any subject. In comparison with the preoperative values, HR significantly increased 3 minutes after induction and 1-3 minutes after intubation in group P (P< 0.05). In contrast, HR changes

Table 1. Demographic characteristics and peri-intubation data of Patients. (mean ± SD or number)

	Group S (Sufentanil)	Group P (Pethidine)
No. of patients	30	30
Sex (female/male)	9/21	11.19
ASA (I/II)	23/7	21.9
Age (ys)	31.0±4.9	29.97±5.9
Weight (kg)	64.5±6.6	65.4±4.8
Height (cm)	167.6±6.1	165.8±6.3
Induction time (sec)	111.1(3.1)	113.3±(2.8)
Apnea duration (sec)	11.1(2.3)	11.4(1.9)

No significant difference among groups.

Table 2. Cormack-Lehane grades encountered during direct laryngoscopy (number)

	Group S (Sufentanil)	Group P (Pethidine)
No. of patients	30	30
Cormack-Lehane 1	15	13
Cormack-Lehane 2a	12	15
Cormack-Lehane 2b	3	2

No significant difference among the two groups.

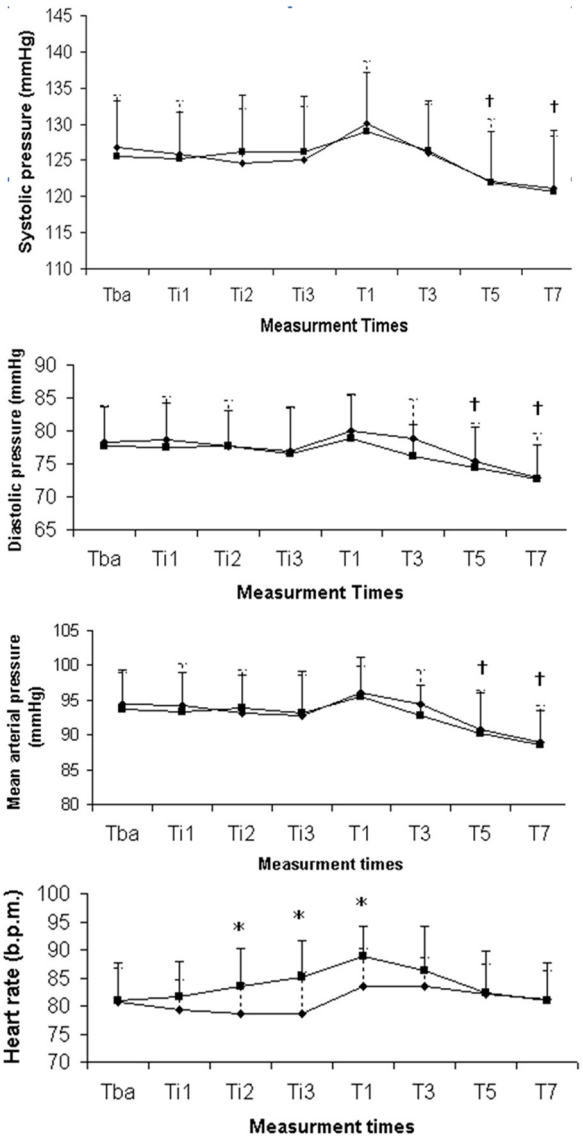

Figure 1: The hemodynamic changes during intubation period in the two groups. Data are mean ± sd. ◦=group S (sufentanil); •=group P (pethidine); Tba = preoperative; Times 1-3= 1-3 min after induction; T1-7= 1-7 min after intubation. † P< 0.05 vs. Tba; * P<0.01= Pethidine vs. Sufentanil.

after induction and intubation were not significant compared with the preoperative values in group S. The numbers of patients who developed a HR increase higher than 20% of preoperative value were not different between two groups 3 minutes after induction, and 1-3 minutes after intubation (Fig. 2). There was no case of arrhythmia or hypotension among groups. There was no ST segment depression in either group.

Discussion

Our study compared the efficacy of intravenous sufentanil 0.1 mg/kg and pethidine 1.5 mg/kg for controlling cardiovascular responses to the laryngoscopy and tracheal intubation. We found that comparable with sufentanil, pethidine attenuated increase in systolic, diastolic, and mean arterial blood pressure after intubation. Direct laryngoscopy and tracheal intubation caused increase in blood pressure and HR.[13] Mechanism of cardiovascular response to intubation is assumed to be a reflex sympathetic reaction to the mechanical stimulation of larynx and trachea. Reflex changes in the cardiovascular system after laryngoscopy and intubation lead to an average increase in blood pressure by 40-50% and 20% increase in HR.[14] Significant elevations in serum levels of norepinephrine and epinephrine following laryngoscopy with and without tracheal intubation have been demonstrated.[2,3] The cardiovascular response to intubation may be attenuated by several methods, including administration of vasodilators,[15] β -blockers,[16] calcium channel blocker,[17] iv lidocaine[18] or by deepening of anaesthesia. However, narcotic administration is the most extensively used strategy. [7,19-21] Opioids, in moderate to high dose, have been suggested as a means of blunting this response.[21] In a study done by Iannuzzi et al,[1] the use of a small dose of sufentanil proved to be an effective strategy to

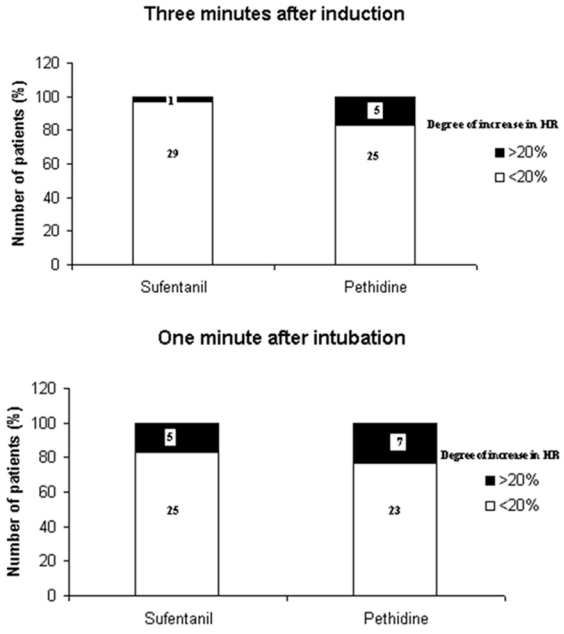

Figure 2: The number of patients who developed a heart rate increase more than 20% of the value before the induction of anesthesia for each group. There was no significant difference between two groups at any time. HR = Heart rate.

blunt the cardiovascular response to intubation in healthy normotensive patients. These effects of sufentanil were also documented in Casati et al.[9] study. Currently pethidine is used for pre-anesthesia and the relief of moderate to severe pain, particularly in obstetrics and post-operative situations. Pethidine exerts its analgesic effects by the same mechanism as morphine, by acting as an agonist at the μ-opioid receptor. Van den Berg A, and colleagues compared the efficacy of equipotent doses of tramadol, nalbuphine, pethidine (3.0, 0.3 mg/kg, 1.5 mg/kg, respectively) and placebo given prior to induction of anesthesia on the pressor responses after tracheal intubation and showed that pethidine and nalbuphine blunted the inotropic response to intubation.[12]

In another study conducted by Flacke JW and colleagues,[22] it was shown that intraoperative plasma epinephrine levels were lowest in patients receiving sufentanil and pethidine . It has been demonstrated that, when small doses of opioids are used before tracheal intubation, physician must accurately consider the time to peak effect in order to maximize the advantages of opioid administration.[23] Sufentanil is a synthetic opioid analgesic drug has an immediate onset of action (1-3 min), with a distribution of 0.72 minutes, time to peak effect of 5-6 min and redistribution of 13.7 minutes.[24] When pethidine was given intravenously, the onset of analgesia was noted within 1 minute and the time to peak effects was 5–7 minutes.[11] This strategy (similar time to peak effect) could account for the efficacy of such small doses of opioids.[25] Although arterial pressure significantly decreased from baseline values at the end of the study period, a small proportion of patients experienced a decrease in systolic pressure to < 90 mmHg after induction of general anesthesia. The observed decreases in arterial pressure values were transient in both groups and did not require treatment for any subject. Moreover, the small doses of opioid used in this study were not associated with opioid-related side effects such as bradycardia or chest wall rigidity. In our study, heart rate significantly increased 3 minutes after induction and 1-3 minutes after intubation in patients receiving pethidine. However, incidence of increases in HR to greater than 20% above basal values was not significantly different between two groups. The rise in HR during peri-intubation period was most likely due to anticholinergic

effect of pethidine.[26]

In conclusion, results of this prospective, randomized, double-blind study demonstrated that, if adequate timing in opioid administration is warranted according to the time to peak effect of each opioid drug, small doses of sufentanil or pethidine provide similar effect in controlling the inotropic response induced by the laryngoscopy and tracheal intubation.

Acknowledgements

The authors gratefully acknowledge the assistance of Dr. Danesh for data collection. No sources of funding were used to assist in the preparation of this study. Financial support for this study was obtained from department of anesthesia and critical care medicine, Isfahan University of Medical Sciences, Isfahan Iran. The authors declare that they have no Conflicts of Interest.

References

1 Iannuzzi E, Iannuzzi M, Cirillo V, et al. Peri-intubation cardiovascular response during low dose remifentanil or sufentanil administration in association with propofol TCI. A double blind comparison. *Minerva Anestesiol* 2004; **70**:109-15.

2 Russell WJ, Morris RG, Frewin DB, et al. Changesin plasma catecholamine concentration during endotracheal intubation. *Br J Anaesth* 1981; **53**:837-9.

3 Shribman AJ, Smith G, Achola KJ. Cardiovascular andcatecholamine response to laryngoscopy with and without endotracheal intubation. *Br J Anaesth* 1987; **59**:295-9.

4 Derbyshire DC, Chmielewski A, Fell D, et al. Plasma catecholamine responses to tracheal intubation. *Br J Anaesth* 1983; **55**:855-60.

5 Edwards DN, Alford AM, Dobson PMS, et al. Myocardial ischaemia during tracheal intubation and extubation. *Br J Anaesth* 1994; **7**:537-9.

6 Fox EJ, Sklar GS, Hill CH, et al. Complications related to the pressor response to endotracheal intubation. *Anesthesiology* 1977; **47**:524-5.

7 Chung KS, Sinatra RS, Halevy JD, et al. A comparison of fentanyl, esmolol and their combination for blunting the haemodynamic responsesduring rapid-sequence induction. *Can J Anaesth*1992; **39**:774-9.

8 Maguire AM, Kumar N, Parker JL, et al. Comparison of effects of remifentanil and alfentanil on cardiovascular response to tracheal intubation in hypertensive patients. *Br J Anaesth* 2001; **86**:90-3.

9 Casati A, Fanelli G, Albertin A, et al. Small doses of remifentanil or sufentanil for blunting cardiovascular changes induced by tracheal intubation: a double-blind comparison. *Eur J Anaesthesiol* 2001; **18**:102-12.

10 Barclay K, Kluger MT. Effect of bolus dose of remifentanil on haemodynamic response to tracheal intubation. *Anaesth Intensive Care* 2000; **28**:403-7.

11 Roerig DL, Kotrly KJ, Vucins EJ, et al. First pass uptake of fentanil, meperidine, and morphine in human lung. *Anesthesiology* 1987; **67**:466-72.

12 van den Berg AA, Halliday EM, Soomro NA, et al. Reducing cardiovascular responses to laryngoscopy and tracheal intubation: a comparison of equipotent doses of tramadol, nalbuphine and pethidine, with placebo. *Middle East J Anesthesiol* 2004; **17**:1023-36.

13 Stoelting RK. Circulatory changes during direct laryngoscopy and tracheal intubation: Influence of duration of laryngoscopy with or without prior lidocaine. *Anesthesiology* 1997; **47**:381-4.

14 Bruder N, Granthil C, Ortega D. Consequences and prevention methods of hemodynamic changes during laryngoscopy and intubation. *Ann Fr Anaesth Reanim* 1992; **11(1)**:57-71.

15 Stoelting RK. Attenuation of blood pressure response to laryngoscopy and tracheal intubation with sodium nitroprusside. *Anesth Analg*1979; *58*:116-9.

16 Vucevic M, Purdy GM, Ellis FR. Esmolol hydrochloride for management of the cardiovascular stress responses to laryngoscopy and tracheal intubation. *Br J Anaesth* 1992; **68**:529-30.

17 Mikawa K, Obara H, Kusunoki M. Effect of nicardipine on the cardiovascular response to tracheal intubation.*Br J Anaesth* 1990; **64**:240-2.

18 Hamill JF, Bedford RF, Weaver DC, et al. Lidocaine before endotracheal intubation: intravenousor laryngotracheal? *Anesthesiology* 1981; **55**:578-81.

19 Weiss-Bloom LJ, Reich DL. Haemodynamic responses to tracheal intubation following etomidate and fentanyl for anaesthetic induction. *Can J Anaesth* 1992; **39**:780-5.

20 Miller DR, Martineau RJ, O'Brien H, et al. Effects of alfentanil on the hemodynamic and catecholamine response to tracheal intubation. *Anesth Analg* 1993; **76**:1040-6.

21 Sareen J, Hudson RJ, Rosenbloom M, et al. Dose-response to anaesthetic induction with sufentanil: haemodynamic and electroencephalographic effects. *Can J Anaesth* 1997; **44**:19-25.

22 Flacke JW, Bloor BC, Kripke BJ, et al. Comparison of morphine, meperidine, fentanyl, and sufentanil in balanced anesthesia: a double-blind study. *Anesth Analg* 1985; 64(9):897-910.

23 Ko SH, Kim DC, Han YJ, et al. Small-dose fentanyl: optimal time of injection for blunting the circulatory responses to tracheal intubation. Anesth Analg 1998; **86**:658-61.

24 Thomson IR, Henderson BT, Singh K, et al. Concentration-response relationships for fentanil and sufentanil in patients undergoing coronary artery bypass grafting. *Anesthesiology* 1998; **89**:852-861.

25 Driver I, Wilson C, Wiltshire S, et al. Co-induction and laryngeal mask insertion. A comparison of thiopentone versus propofol. *Anaesthesia* 1997; **52**:698-700.

26 http://en.wikipedia.org/wiki/Pethidine. (20 may 2008)