Original Research Article

Comparison of Cardiovascular Responses between Remifentanil and Fentanyl on Laryngoscopy and Tracheal Intubation in Patients Undergoing Elective Surgery

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Abstract

This was a prospective, randomized, double-blind study comparing the effect of remifentanil and fentanyl on cardiovascular responses from laryngoscopy and tracheal intubation. Forty-four ASA I or II patients aged between 18-65 yrs scheduled for elective surgery under general anaesthesia, were recruited and randomized into two groups. Each patient in Group R received remifentanil of 0.5 mcg/kg bolus over 30 seconds followed by an infusion of 0.25 mcg/kg/min and each patient in Group F received fentanyl of 2 mcg/kg bolus over 30 seconds followed by an infusion of normal saline. Anaesthesia was then induced with propofol, rocuronium and 2% sevoflurane with 100% oxygen. Cardiovascular changes were recorded every minute for 3 minutes after induction and 5 minutes after tracheal intubation. The heart rate remained stable throughout the induction and intubation period in both groups. None of the patients in the remifentanil group develop bradycardia. Systolic blood pressure (SBP) and mean arterial pressure (MAP) were significantly lower in the fentanyl group at the 3rd minute post-induction and 5th minute post-intubation ($p < 0.05$). Diastolic blood pressure (DBP) in the fentanyl group was significantly lower at the 2nd and 3rd minute post-induction and 4th and 5th minute post-intubation ($p < 0.05$). The blood pressure remained stable for the remifentanil group throughout the induction and intubation period. Six patients (27.2%) in the fentanyl group and one patient (4.5%) in the remifentanil group experienced hypertension. Three patients (13.7%) from each group experienced hypotensive episodes. In conclusion, remifentanil 0.5 mcg/kg bolus followed by 0.25 mcg/kg/min infusion resulted in SBP, MAP and DBP remained slightly lower than baseline throughout the whole period but still consider stable, as these changes were not statistically significant.

Keywords: Cardiovascular, remifentanil, fentanyl, laryngoscopy, anaesthesia

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Introduction

The pressor response to laryngoscopy and tracheal intubation, resulting in hypertension and tachycardia, is well described (1). Plasma concentrations of catecholamines are increased and can lead to myocardial ischemia, depression of myocardial contractility and ventricular arrhythmias (2). These responses may be attenuated by several methods, including administration of intravenous opioids (fentanyl, alfentanil, sufentanil, remifentanil) (3,4,5,6), vasodilators (7,8,9), beta blockers (10,11,12,) local anaesthetic agents e.g. lignocaine (13), gabapentin (14) or by increasing the depth of anaesthesia. Currently in our institution, the drug most commonly used is fentanyl of 1 to 3 mcg/kg bolus followed by an induction agent and muscle relaxant for laryngoscopy

and endotracheal intubation in patients undergoing non-cardiac surgeries.

Remifentanil has rapid metabolism by plasma esterase, thus is ultrashort-acting and easy to titrate to achieve desired plasma levels (15,16,17,18). Pharmacokinetic studies demonstrate that remifentanil has a small volume of distribution of 25-30 litres whereas for fentanyl is 334 litres. Remifentanil also has a rapid distribution phase, total clearance of 4.2-5.0 litre/min, a terminal elimination half-life of 10 to 21 minutes, context sensitive half time of 4 minutes and half-time for equilibrium between the plasma and effect of the effect compartment of 1.3 minutes. Clearance of remifentanil is not affected by renal or liver disease, body weight, sex or age. These properties make remifentanil the opioid of choice to obtund noxious cardiovascular reflexes during laryngoscopy and tracheal intubation. An additional advantage is the rapid return of spontaneous respiration and airway reflexes.

Many studies have shown that remifentanil is a safe drug to be administered as an adjuvant to induction (15,16,17,18) as it has minimal adverse cardiovascular effects, meaning mild bradycardia and reduced arterial blood pressure by 15-20% at larger doses. Thompson et al. (1998) investigated the use of remifentanil in normal populations (3), elderly (19), patients with hypertension (20) and patients with ischemic heart disease (21) and found out that remifentanil attenuated the pressor response to laryngoscopy and intubation. However there was associated bradycardia at a standard dosage of 1mcg/kg bolus followed by an infusion of 0.5mcg/kg/min and thus the use of a concurrent vagolytic agent was suggested. Other studies also showed that remifentanil can be used safely as an adjuvant therapy for laryngoscopy and tracheal intubation in children (22), and in rapid sequence induction (23). Remifentanil also acts synergistically with propofol to provide excellent intubation conditions without the use of muscle relaxants (24).

In a later study, Thompson et al. (1996) compared different doses of remifentanil on cardiovascular responses to laryngoscopy and tracheal intubation (15). The same researchers also found out that there were no significant differences in haemodynamic changes in groups given either in a higher dose (1 mcg/kg bolus followed by 0.5 mcg/kg/min infusion) or lower dose (0.5 mcg/kg bolus followed by 0.25 mcgkg/min) of remifentanil, but the incidence of bradycardia was lower in groups which received a lower dose. However, they did not require rescue treatment with any vagolytic agent.

The aim of this study was to compare the effect of remifentanil (0.5 mcg/kg bolus followed by 0.25 mcg/kg/min infusion) and fentanyl (2 mcg/kg bolus followed by normal saline infusion) on cardiovascular responses, i.e. blood pressure and heart rate changes to laryngoscopy and tracheal intubation in patients undergoing elective surgery.

Materials and Methods

This was a prospective, randomized, double-blind control trial conducted after obtaining institutional ethics committee approval where 48 patients aged between 18 to 65 years old with ASA physical status I or II, scheduled for elective surgeries under general anaesthesia with tracheal intubation were recruited into the study. Patients with potential airway difficulties, significant coronary or airway disease, body mass index (BMI) > 30 kg m-2, history of alcohol or drug abuse, history of gastro-oesophageal reflux, those with hypertension on treatment, or known allergies to propofol, opioids or rocuronium, were excluded. Sample size was obtained from calculation using Power and Sample Size Calculation Software. A previous study showed that 20 patients per group would be required to demonstrate a difference in mean arterial pressure (MAP) of 15 mmHg and heart rate of 15 beats per minute. With the power of 0.8 and alpha value of 0.05, and additional drop up rate of 20%, a total of 48 patients were required.

On the day before the scheduled surgery, written informed consent was obtained from all patients. They were fasted overnight and premedication, i.e. midazolam 7.5 mg per patient 7.5mgwas given. They were then randomized into two groups (Group R for remifentanil and Group F for fentanyl) in a double-blind manner by computer generated numbers.

Upon arrival in the operation theatre, each patient received intravenous Hartmann‟s Solution at 5 ml/kg over 5 to 10 minutes before induction of anaesthesia. Standard monitoring of heart rate, blood pressure, oxygen saturation and ECG were established. Blood Pressure was measured non-invasively using Datex CardiocapTM and ECG was monitored in the CM5 position. Heart rate and blood pressure were taken before the start of the study as a baseline.

The study drugs were prepared by an independent anaesthesiologist or a staff nurse not involved in the study and handed to the anaesthesiologist or senior medical officer designated to perform laryngoscopy and tracheal intubation. Each patient in Group R was given 0.5 mcg/kg remifentanil in 10 ml saline over 30 seconds followed by an infusion at a rate of 0.25

mcg/kg/min. Each patient in Group F received 2 mcg/kg fentanyl diluted in 10ml saline over 30 seconds followed by an infusion of saline. Subsequently anaesthesia was induced with propofol at 2.0 mg/kg followed by increments of 10 mg every 10 seconds as needed until anaesthesia was established and rocuronium 0.6 mg/kg was given for neuromuscular blockade. Patients were ventilated manually with 2% sevoflurane and 100% oxygen, to an end-tidal carbon dioxide level of 35-45 mmHg. MAC was not standardized. Laryngoscopy was done by anaesthesiologist or senior medical officer with more than 1 year experience in anaesthesia 3 minutes after loss of verbal contact using a Macintosh laryngoscope, size 3 blade. An endotracheal tube size 7.5 mm was used for female patients and 8.0 mm for male patients respectively. Intubation was considered successful if achieved within 30 seconds in a single attempt. Heart rate (HR), systolic blood pressure (SBP), mean arterial pressure (MAP) and diastolic arterial pressure (DBP) were recorded at 1 minute intervals from induction of anaesthesia until 5 minutes after intubation. Ephedrine at 3 mg increments was administered for hypotension which was defined as a drop of systolic blood pressure of less than 90 mmHg or a decrease of more than 30% from baseline value for more than 60 seconds. For bradycardia which was defined as a drop of heart rate to less than 45 beats per minute, atropine in 0.5 mg increments would be given as needed. Regarding hypertension, defined as SBP of more than 200 mmHg or more than 30% above baseline for more than 60 seconds, and tachycardia defined as heart rate of more than 100 bpm, inspired sevoflurane was increased in increments of 0.5% until control was achieved. Occurrence of these adverse events was recorded. Patients were excluded from the study if there was failed intubation within 30 seconds or if multiple attempts of intubation were necessary.

Statistical analysis was performed using the Chi-Square test for baseline characteristics and Wilcoxon Signed Rank Test in SPSS Version 18 for cardiovascular variables for intra-group and inter-group comparison. A p value of <0.05 was considered to be statistically significant.

Results

Forty-eight patients were recruited. Three patients were withdrawn due to unsuccessful first attempt intubation and one patient was dropped out due hypertension on beta-blocker discovered subsequently. The baseline characteristics including age, weight, BMI (body mass index), gender and ASA status were comparable (Table 1).

Table 1: Patients' characteristics. Values expressed as mean (SD) and number where appropriate.

	Group F (n=22)	**Group (n=22)**
Age (Year)	37.1(11.4)	38.9(10.9)
Weight (kg)	66.7(11.4)	64.5(12.3)
Height (cm)	168.91(7.4)	165.8(8.0)
BMI (Body Mass Index)	23.2(2.7)	23.3(3.1)
Race		
Malay	20	13
Chinese	1	5
Indian	1	3
Others	0	1
Gender		
Male	14	13
Female	8	9
ASA status		
I	17	19
II	5	3

Table 2 showed changes in haemodynamic parameters with time. There were no significant changes over time in both groups compared to baseline. There were also no significant changes in between groups. There was no incidence of bradycardia seen in the remifentanil group, thus no vagolytic treatment needed for any of the patients in that group. Two patients in the fentanyl group experienced tachycardia for about 1 minute after intubation and needed deepening of anaesthesia using the volatile agent.

In the Fentanyl group, the SBP and MAP were significantly lower after induction at the 3rd minute ($p < 0.05$), and again after intubation at the 5th minute ($p < 0.05$). DBP were lower than baseline significantly after induction at the 2nd and 3rd minutes and after intubation at the 4th to 5th minute. Throughout the entire study period, the SBP, MAP and DBP remained lower compared to baseline but not statistically significant. In the Remifentanil group, the SBP, MAP and DBP remained slightly lower than baseline throughout the whole study period. However, these changes were not statistically significant.

Three patients in the fentanyl group and three patients in the remifentanil group experienced hypotension post induction and all patients needed only one bolus of ephedrine 3mg (13.6% each group) as treatment. Six patients (27.2%) in the fentanyl group and one patient (4.5%) in the remifentanil group experienced

Table 2: Mean (SD) HR, SBP, MAP and DBP at baseline, after induction of anaesthesia (Ind) and after tracheal intubation (Int) in Group F and Group R. P<0.05 compared to baseline.

	Baseline	Ind+ 1min	Ind+ 2min	Ind+ 3min	Int + 1min	Int + 2min	Int + 3min	Int + 4min	Int + 5min
Group F (n=22)									
HR	77 (10)	74 (8)	72(10)	69 (9)	82(17)	84 (19)	79 (17)	76 (15)	73 (13)
SBP	130 (13)	118 (16)	112 (14)	106(16)*	122 (19)	124 (19)	116 (18)	110 (16)	109(12)*
MAP	94 (11)	84 (12)	80 (10)	76 (10)*	88 (13)	90 (12)	84 (11)	79 (9)	78 (7)*
DBP	76 (9)	67 (11)	64 (9)*	60 (9)*	71 (12)	74 (10)	68 (10)	65 (8)*	63 (7)*
Group R (n=22)									
HR	80 (11)	81 (11)	79 (10)	74 (9)	82 (11)	80 (12)	76 (10)	76 (10)	72 (10)
SBP	119 (10)	113 (11)	107 (13)	105 (11)	116 (12)	113 (11)	110 (11)	108 (12)	107 (14)
MAP	86 (6)	82 (6)	78 (8)	76 (6)	85 (8)	83 (8)	80 (9)	79 (8)	77 (10)
DBP	71 (6)	66 (5)	63 (5)	62 (5)	70 (7)	68 (8)	66 (8)	65 (7)	63 (8)

hypertension and required an increase in sevoflurane concentration to increase the depth of anaesthesia.

Discussion

Laryngoscopy and endotracheal intubation are rapid, simple and safe airway management techniques which are routinely performed. However, both procedures produce noxious stimuli to the cardiovascular system in the practice of general anaesthesia (2). These adverse physiological responses pose major concerns for Anaesthesiologists as it can lead to traumatic complications. The cardiovascular response arises from sympathoadrenal reflexes (1). Coughing and 'barking' also add to increased venous, intracranial and intraocular pressures. These haemodynamic changes, even though short-lived, can cause serious problems in patients with cardiovascular and cerebral status. In this study, we used opioids as an adjuvant therapy to reduce the hemodynamic responses during both procedures. In terms of induction agents, Edelist (1987) showed that propofol provided excellent intubation conditions in 97% of patients as compared to 80% in the thiopentone group (25). In addition, Martin et al. also showed that propofol reduces the remifentanil requirements in a synergistic manner (26). The use of the muscle relaxant, rocuronium at 0.6 mg/kg, was to provide excellent quality of anaesthesia and suppression of laryngeal reflexes. Rocuronium does not affect the haemodynamic parameters as it is free of clinically significant cardiovascular side effects (27).

From the present study, it was found that remifentanil of 0.5 mcg/kg bolus followed by 0.25 mcg/kg/min can be used safely as an adjuvant to attenuate cardiovascular responses during laryngoscopy and tracheal intubation for routine cases. Patients who may benefit from the use of remifentanil are those who can only tolerate minimal haemodynamic changes during laryngoscopy and tracheal intubation, e.g. patients with aneurysms, penetrating eye injury or cardiovascular disease with compromised function. However, further studies are needed to confirm the benefits of the use of remifentanil in these groups of patients.

In this study, the incidence of hypotension requiring rescue medications were 13.6%, which was comparable to the study done by Hall et al. (28) Hogue et al. (29) and Kautto (30) which reported incidence of hypotension of 10%, 10% and 17% respectively. In the remifentanil group, only one patient (4.5%) experienced hypertension. Hogue et al. reported 25% incidence of hypertension associated with the use of remifentanil.

Most of the multicentre studies reported the occurrence of bradycardia in patients receiving higher dosages of remifentanil (3). Hogue et al. (1996) reported an incidence of bradycardia in 7% of patients receiving 1 mcg/kg bolus followed by 0.5 mcg/kg/min; and 19% in patients receiving a bolus dose of 1 mcg/kg followed by 1mcg/kg/min infusion (29). However, our results were comparable to the study done by Thompson and Rowbotham (1996) (15) who reported a lower incidence of bradycardia (5%) in patients who received a lower dosage of 0.5 mcg/kg bolus followed by 0.25 mcg/kg/min infusion. These patients did not require any vagolytic treatment. For studies using a higher dosage of 1mcg/kg bolus and 0.5 mcg/kg/min infusion, most authors would give intravenous glycopyrrolate as a vagolytic agent as it was known that the incidence of bradycardia may be as high as 50% (3). In another study for patients, ASA II-III and in the elderly, an even lower dose of

remifentanil 0.5 mcg/kg bolus followed by 0.1 mcg/kg/min was used, no incidence of bradycardia was reported and haemodynamic changes during laryngoscopy and endoctracheal intubation were successfully attenuated (19).

Fentanyl is commonly used for attenuation of cardiovascular responses in which the dose used is 1-3 mcg/kg bolus given prior to administration of induction agents. In this study, 2 mcg/kg bolus was used. Xue et al. (2008) concluded that 2 mcg/kg fentanyl suppresses the haemodynamic response to endotracheal intubation more than laryngoscopy (5). Kautto (1982) showed that induction with 2 mcg/kg fentanyl significantly prevented the undesirable increase in heart rate, arterial blood pressure and rate pressure product after laryngoscopy and intubation, and fentanyl 6 mcg/kg completely prevent adverse haemodynamic responses (30). However, unnecessarily large doses of fentanyl may lead to muscle rigidity, bradycardia, nausea, vomiting and may also cause prolonged respiratory depression postoperatively especially if the surgery duration is short.

A limitation to this study would include this being a multi-operator study whereby the skill and experience of the Anaesthetist could have influenced the process of laryngoscopy and intubation. In conclusion, remifentanil 0.5 mcg/kg bolus followed by 0.25 mcg/kg/min infusion resulted in SBP, MAP and DBP remained slightly lower than baseline throughout the entire period but still considered stable, as these changes were not statistically significant.

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