Comparison of Remifentanil and Alfentanil Bolus Dose on Extubation Emergence Hemodynamic Profiles, a Randomized Double-blinded Placebo-Controlled Trial

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Abstract

Background: Hemodynamic instability is common during emergence from anesthesia which predisposes patients to development of different side effects. The primary purpose of the present study is to evaluate the effect of Remifentanil and Alfentanil on the hemodynamic profiles during and after extubation.

Methods: Ninety-nine patients aged 20-50 years undergoing minor orthopedic surgery under general anesthesia were randomly allocated into control, Remifentanil and Alfentanil groups. Before extubation patients received Remifentanil (1 µg/kg), or Alfentanil (10 µg/kg) or 5 mL of Saline as a placebo based on their group. Baseline heart rate (HR), mean arterial pressure (MAP) plus systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded and documented again on extubation, and 1, 3 and 5 minutes after extubation. Cough status before and after extubation was recorded.

Results: The basic characteristics of participants in all the three groups were similar. The rise in SBP on extubation in the placebo group was statistically significant compared to the Alfentanil ($p=0.01$) and the Remifentanil ($p<0.001$) groups. Mean arterial pressure decreased during the extubation in group R (97.0±13 mmHg) in contrast to other two groups (A=101.9±13 mmHg, P=101.4±13 mmHg). Heart rate increased in group A and P contrary to group R on extubation.

Conclusion: Remifentanil (1µg/kg) and Alfentanil (10µg/kg) attenuate the rise in SBP on extubation but no significant changes were seen between these two drugs

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Introduction

During emergence of general anesthesia and in the post-extubation period, many adverse reactions such as hemodynamic changes and coughing can be evoked. Some of them may lead to surgical site bleeding and increasing intracranial pressure (1,2). In addition in some groups of patients such as those with ischemic heart disease or hypertension, these hemodynamic changes can lead to irreversible complications. Therefore, it is of great importance to use a technique to prevent these adverse effects and their consequences.

Various techniques such as deep removal of tracheal tube, intravenous administration of opioids, beta blockers or Lidocaine prior to the emergence, and filling the cuff of endotracheal tube with Lidocaine or Sodium bicarbonate have been used to prevent adverse reaction of emergence from anesthesia, however, all of them demonstrated some limitations and the result were not consistent (3-7).

Remifentanil and Alfentanil are ultra-short acting opioid which has a short context sensitive half time. Some previous works have assessed the efficacy of this drug on adverse reaction of emergence of anesthesia (7,8).

The primary purpose of the present study is to evaluate the effect of Remifentanil and Alfentanil on the hemodynamic profile during and after extubation plus study its effect on prevention of post-extubation coughing.

Materials and Methods

The protocol was approved by the Institutional Ethics Committee and informed written form of consent was obtained from all patients. In this randomized, double-blind placebo-controlled clinical trial 99 subjects were randomly selected from patients enrolled for elective orthopedic surgery under general anesthesia

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over a period of 12 months.

Adults of either sex aged between 20 and 50 years compliant with American Society of Anesthesiologist physical status (ASA) I and II, elected for minor orthopedic surgery lasting less than two hours included in the study.

The exclusion criteria consisted of any history of upper respiratory tract hyper reactivity, asthma or any other respiratory related diseases, gastro-esophageal reflux, previous laryngeal or tracheal surgery or pathology, and patients who were under treatment with sedatives, antitussives, or angiotensin converting enzyme inhibitors. Smokers and addicts (including opioids and benzodiazepines), were also excluded from the study.

Prior to general anesthesia all the required drugs were prepared by an anesthetist who was not involved in the administration or observation of the patient; thus, both the anesthesiologist and the patients were blinded to group assignment. Patients were selected using a computer-generated randomization list and were randomly assigned into three groups, control (P group, n=33), Remifentanil (R group, n=33), and Alfentanil group (A group, n=33).

On arrival in operating room, all patients were monitored with an electrocardiogram (ECG), noninvasive blood pressure and pulse oximetry. An 18-gauge cannula was inserted and lactated ringer solution 7 ml.kg-1 was administered. Anesthesia was induced with 5 mg.kg-1 Sodium Thiopental, 0.05 mg.kg-1 Midazolam, and 3 µg.kg-1 Fentanyl; endotracheal intubation was facilitated with 0.5 mg.kg-1 Atracurium. After tracheal intubation, anesthesia was maintained by Isofluran and N2O (50%); 0.2 mg.kg-1 Atracurium and 1µg.kg-1 Fentanyl were administered half hourly. Ventilation was adjusted to maintain normocapnia (end-tidal carbon dioxide partial pressure 4.7-5.3 kPa). At the beginning of the skin sutures, drugs administration was stopped and neuromuscular block was antagonized by intravenous administration of 2.5 mg of Neostigmine along with 1.25 mg Atropine. Then, the patients in group R received Remifentanil (1 µg/kg), patients in group A received Alfentanil (10 µg/kg), and patients in group P received saline as a placebo, all of drugs were prepared into the 5 mL volume.

Baseline heart rate (HR), mean arterial pressure (MAP) plus systolic blood pressure (SBP) and diastolic blood pressure (DBP) were recorded. The neuromuscular blockade was checked using a nerve stimulator for adequacy of reversing of Atracurium effect when second or third responses to train of four stimulation was observed. Patients were considered awake when they opened their eyes on demand or after gentle tactile stimulation. When patients were found awake and tactile double burst stimulation monitoring demonstrated ratio higher than 50%, tracheal tube was removed. Variables recorded at the baseline were noted again on extubation, and 1, 3, and 5 minutes after extubation.

Cough was defined as an abrupt noisily expulsion of air from the lungs plus a strong contraction of the abdomen. A trained investigator recorded the incidence of coughing before and after extubation. Grading of response of patients during extubation was assessed by a 3 point scale (mild cough=1-2 coughs, moderate coughs=3-5 coughs, severe coughs=sustained (>5)).

Statistical analysis were performed using SPSS for windows (version 13.5; SPSS Inc., Chicago, IL, USA). Normal distribution of data was evaluated and confirmed by Kolmogorov-Smirnov test. For statistical analysis of demographic data and comparison of different groups one way ANOVA was used. Fischer's exact or Chi-square tests were used for analysis of categorical data. HR and MAP, DBP, SBP were analyzed by repeated measures analysis of variances. Two tailed p-value<0.05 was considered statistically significant.

Results

Ninety nine patients met the inclusion criteria for this study. Thirty three patients were in the control group (C group, male (M)=16, female (F)=17) who received placebo and 33 in each of the other two groups who received Remifentanil (R group, M=19, F=14) or Alfentanil (A group, M=15, F=18) prior to extubation. The basic characteristics of the participants were similar in all three groups (Table 1).

Table 1. Basic characteristics and baseline parameters of the participants.

Variables	Remifentanil Group	Alfentanil Group	Control Group
Age (years)	39.2±6.7	39.8±7.3	39.7±6.1
Weight (Kg)	69.3±12.2	70.4±9.8	69.4±9.7
Duration of the surgery (minutes)	110.9±34	101.1±40	103.3±35
Duration of anesthesia (minutes)	137.1±34	131.9±43	127.3±38
Baseline Systolic blood pressure	126.4±19	125.3±17	128.0±14
Baseline Diastolic blood Pressure	84.2±16	85.4±14	84.2±12
Baseline Mean arterial pressure	98.3±17	98.7±14	98.8±12
Baseline Heart rate	77.9±14	82.6±12	81.3±12

* Data presented as mean ±SD

Table 2. Hemodynamic changes during extubation in patients receiving a bolus dose of Remifentanil or Alfentanil or placebo.

Variables	Groups	Baseline	On Extubation	1st minute	3rd Minute	5th Minute
Heart rate (b/min)	Remifentanil	7.9±14	83.9±12	85.0±11	82.7±12	81.8±12
	Alfentanil	82.6±12	94.2±14	92.5±13	89.1±12	88.0±12
	Placebo	81.3±12	90.4±14	91.0±16	90.1±17	86.3±14
	p-value	0.319	0.010	0.059	0.060	0.122
Systolic Blood Pressure (mmHg)	Remifentanil	126.4±19	126.2±13	127.3±14	127.7±15	127.1±15
	Alfentanil	125.3±17	130.4±16	130.3±16	129.2±16	129.4±16
	Placebo	128.0±14	140.1±14	139.4±13	135.8±11	131.7±14
	p-value	0.804	0.001	0.003	0.047	0.462
Diastolic Blood Pressure (mmHg)	Remifentanil	84.2±16	82.5±13	84.0±15	82.2±5.0	81.9±14
	Alfentanil	85.4±14	87.6±13	86.9±12	85.8±11	84.7±10
	Placebo	84.2±12	93.7±14	89.4±13	84.4±10	83.5±11
	p-value	0.918	0.004	0.268	0.488	0.613
Mean Arterial Pressure (mmHg)	Remifentanil	98.3±17	97.0±13	98.5±14	97.4±14	96.9±14
	Alfentanil	98.7±14	101.9±13	101.4±12	100.3±11	99.6±10
	Placebo	98.8±12	101.4±13	106.0±12	101.6±10	99.6±11
	p-value	0.987	0.001	0.050	0.351	0.593

Systolic and diastolic blood pressure

In the placebo group, systolic blood pressure "on extubation" (140.1±14 mmHg) was significantly higher compared to the Alfentanil (130.4±16 mmHg, p=0.01) and the Remifentanil group (126.2±13 mmHg, p<0.001). Post-hoc Tukey test showed that there was no significant difference between groups A and R.

On the "first minute after extubation" the same trend was observed (139.4±13 in placebo group, 130.3±16 in Alfentanil group and 127.3±14 in Remifentanil group, p=0.003). Systolic blood pressure three minutes following extubation in group R (127.7±15 mmHg) was less than group P (135.8±1 mmHg) which was statistically significant (p=0.02). SBP in group A (129.2±16 mmHg) was not statistically different (p=0.058) compared to placebo group on the same period of time.

Five minutes after extubation, there was no statistically significant differences observed in the SBP of the patients in the three groups (A=129.4±16, R=127.1±15, P=131.7±14 mmHg). Although no statistically significant differences was observed in DBP in groups P (93.7±14 mmHg) and A (87.6±13 mmHg) during the extubation period, DBP recorded during the extubation time in group R (82.5±13 mmHg) was significantly lower compared to group P (p=0.004). Almost the same tendency as SBP was observed in the diastolic blood pressure throughout the study.

Mean arterial pressure and heart rate

Mean arterial pressure decreased on extubation in Group R (97.0±13 mmHg) in contrast to the other two groups (A=101.9±13 mmHg, P=101.4±13 mmHg). There was no statistically difference in between the three groups 1, 3, and 5 minutes after extubation.

On extubation heart rate increased significantly in groups A and P (A=94.2±14 b/min, P=90.4±14 b/min), in contrast to group R (83.9±12 b/min, p=0.007). After extubation alterations in the heart rate were not statistically different in between the three groups.

Cough

The incidence of coughing before extubation for all the patients was 33% (Group A=7%, Group R=14%, Group P=12%) and after extubation the number decreased to %15 (Group A=5%, Group R=4%, Group P=6%) but there was no statistically difference in between the groups before or after the extubation. According to the 3-point grading scale of the cough, 21 patients had a decrease and 3 patients had an increase in cough's grading after extubation. In Group R, 30.3% of the patients had a decrease in cough grades after extubation.

Discussion

In this study extubation hemodynamic profiles of the patients receiving a bolus dose of either Remifentanil, Alfentanil or placebo prior to post-extubation were observed. This study demonstrated that administration of a bolus dose of Remifentanil (1μg/kg) or Alfentanil (10μg/kg) does attenuate the rise in SBP during the extubation period but no significant changes were seen between these two drugs. We also showed that a bolus dose of Remifentanil (1μg/kg) could make the hemodynamic response to extubation smooth, by decreasing the heart rate and decreasing the rise in MAP during extubation compared to Alfentanil and placebo, but these effects did not persist after extubation. The incidence of coughing during and after extubation was quite the same in all the three groups, although patients whom received Alfentanil had the lowest frequency of coughing before extubation and patients with a pre-extubation bolus dose of Remifentanil had the lowest incidence of coughing after the extubation.

Rapid emergence from extubation with reliable return of airway reflexes is of great importance but

conducting not only a rapid but smooth emergence with the least hemodynamic changes is always a great challenge to anesthesiologist.

Remifentanil, is a short-acting μ-receptor opioid agonist which undergoes widespread extrahepatic metabolism by blood and tissue nonspecific esterases, resulting in an extremely rapid clearance of approximately 3 L/min (180 L/h) (8).

It has been shown that a bolus dose of Alfentanil can be helpful in modifying the response to intubation (10). In one study, it has been demonstrated that Remifentanil treated patients have more stable hemodynamic profiles intra-operatively compared to Fentanyl treated patients but questioned this constancy during the extubation period (11). Maguire et al also studied the effect of Remifentanil and Alfentanil on intubation and concluded that both of these drugs attenuate the intubation profiles similarly (12). In studies mentioned above less attention is paid to the extubation profiles which is the main goal of the present study.

The study of intravenous Alfentanil on airway circulatory reflexes during extubation has shown a decrease resulting an enhanced extubation (13,15). Earlier studies show that maintaining an infusion of Remifentanil throughout the operation could help smooth the emergence from extubation by reducing cough (14,16).

Although previously Remifentanil's effect on hemodynamic changes intra operatively and on extubation profiles has been studied but there is a lack of data on comparison of this opioid with other opioids on cardiovascular parameters (17).

The question that whether a bolus dose of Remifentanil is as effective as the infusion of this drug and adjustment of the dosage of the drug for the best result is still unanswered. Remifentanil's effects on extubation profiles in comparison to other opioids such as Alfentanil need more attention because achieving a smoothly controlled extubation should be in the interest of every anesthesiologist.

Conclusion

This study showed that Remifentanil and Alfentanil not decreases the cough incidence after extubation and on the whole a greater stability in the hemodynamic profiles was observed with Remifentanil compared to Alfentanil.

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