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How fentanyl and remifentanil affect neuromuscular block, intubation quality and hemodynamic response

Effects of fentanyl and remifentanyl on neuromuscular block

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Abstract
Aim: Opioids suppress noxious autonomic reflexes and affect multiple parameters such as heart rate and blood pressure. The objective of this study was to compare the effects of fentanyl and remifentanil on hemodynamic changes, neuromuscular blockade and the quality of intubation.
Material and Method: Sixty patients were divided into three groups as remifentanil, fentanyl, and a control group. Patients' demographics and hemodynamic parameters were measured before anesthesia induction, immediately after induction, before intubation, immediately after intubation and at 3 minutes and 5 minutes after intubation and compared between the groups. In addition, intubation and side effects were also analyzed.
Results: The mean SBP was remarkably lower in the remifentanil group checked against both fentanyl and control groups after induction and 5 minutes after intubation (for both, $p<0.05$). The mean DBP and MAP and HR values were statistically notably lower in the remifentanil group after induction, before and after intubation and at 3 and 5 minutes (for all $p<0.05$). Excellent-good intubation quality was succeeded in 17 (85%) patients in the remifentanil group and in 16 (80%) patients in the fentanyl group, with no notable difference between them.
Discussion: Opioids increase the quality of intubation and suppress the undesirable hemodynamic response to intubation by blocking the central integration of sensory pathways without affecting neuromuscular conduction. The administration of remifentanil as a 1.5 µg/kg bolus followed by a 0.3 µg/kg/min infusion was more effective in controlling the undesired hemodynamic responses induced by tracheal intubation and laryngoscopy.

Keywords
Fentanyl, General Anesthesia, Intubation, Laryngoscopy, Remifentanil

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Introduction

The vast majority of patients undergoing surgery under general anesthesia require intubation and laryngoscopy as mandatory processes. Physiopathological changes such as reflex increased in blood pressure, heart, rate and serum catecholamine concentration observed following endotracheal intubation are of paramount importance in anesthesia induction [1, 2]. These changes are thought to be due to the stimulation of tracheal and laryngeal tissues during the procedure [3]. Tachycardia and transient hypertension are commonly associated with tracheal intubation and laryngoscopy [4]. Tachycardia and hypertension may be insignificant in healthy persons, but are crucial, especially in patients with increased intracranial pressure and ischemic heart disease. Studies have stated the relationship between post-intubation hypertension and poor outcomes [5]. In addition, in susceptible individuals, these hemodynamic and catecholamine responses may result in morbidity, including myocardial infarction, cerebrovascular events, and acute heart failure [6].

Several approaches have been used to prevent hemodynamic and catecholamine stress responses due to endotracheal intubation and laryngoscopy, including intravenous and topical administration of lidocaine, the use of beta-adrenergic blockers, direct-acting vasodilators, inhalation agents and opioids [2, 7, 8]. Opioids are the most prevalent agents for antinociception during general and have been shown to suppress noxious autonomic reflexes and to affect multiple parameters such as electrocardiogram, respiratory rate, blood pressure and heart rate, [9].

Neuromuscular blockade facilitates endotracheal intubation and provides muscle relaxation required for general anesthesia in certain surgical operations. However, the best intubation conditions should be provided for the quality of muscle relaxation, especially in several conditions, including patients with severe liver, kidney and heart disease, and extreme ages that may lead to pharmacodynamic changes [10]. Peripheral nerve stimulation is commonly used to specify the degree of the neuromuscular blockade through tactile and visual assessment. When peripheral nerve stimulation is used, mortality and morbidity rates have been significantly reduced since the desired degree of neuromuscular blockade can be obtained.

The objective of our study was to compare the effects of fentanyl and remifentanil on neuromuscular blockade provided by cisatracurium, hemodynamic changes induced by intubation and the quality of intubation.

Material and Methods

Study population

The study included 60 patients aged 18-65 years with ASA I-II status who were scheduled for elective operation under general anesthesia in the operating rooms of our hospital. Patients with cardiovascular, pulmonary, hepatic, renal, neuropsychiatric and endocrine diseases, pregnant and breastfeeding patients, substance users, those with atopic structure and difficult intubation and patients with a weight >35% or <20% of the ideal weight were excluded.

Data Collection

Patients' demographic data such as gender, weight and age were recorded. Mean arterial pressure (MAP), oxygen saturation (SpO2), diastolic blood pressure (DBP), systolic blood pressure (SBP), heart rate (HR) values were measured before anesthesia induction (pre-induction), immediately after induction and before administration of cisatracurium (post-induction), before intubation (pre-intubation), immediately after intubation (post-intubation), 3 minutes and 5 minutes after intubation. Drug side effects such as hypotension (SBP<80 mmHg), arrhythmias, bradycardia (HR< 45 bpm), apnea (cessation of breathing for 15 seconds or longer), skin rash and muscle rigidity were also recorded.

Anesthesia Management

The routine monitoring was performed with ECG and non-invasive measurement of DBP, SBP, SpO2, HR and MAP. Neuromuscular monitoring was carried out with TOF-Watch® SX device (Organon Ltd.,Ireland). Two surface electrodes were placed on the right wrist for ulnar nerve stimulation. The distal electrode was placed 1 cm proximal to the wrist flexion, and the proximal electrode was placed 2-3 cm adjacent to the distal electrode. The negative output of the monitoring device was connected to the distal, and the positive output to the proximal electrode. An acceleration transducer, which will evaluate the adduction response of the thumb to the ulnar nerve stimulus, was placed on the large surface of the thumb with a plaster. The grade of neuromuscular block at the time of intubation (%), time to T1 90% suppression level (sec), maximum block (effect) onset time (sec) (T1 95%) and time to the maximum (complete) block (T1 100%) were measured and recorded.

The patients were randomly divided into three groups as remifentanil, fentanyl, and control groups. The remifentanil group was administered a bolus dose of 1.5 µg/kg in 30 seconds followed by 0.3 µg/kg/min infusion. The fentanyl group received a bolus dose of 3 µg/kg for 30 seconds, while the control group was given 10 mL of normal saline. After waiting for 20 seconds, thiopental sodium was given to all 3 groups at a dose of 5 mg/kg within 45 seconds until the eyelash reflex disappeared. The peripheral nerve stimulator was calibrated with a single 1 Hz stimulus, and supramaximal stimulus threshold was detected. Cisatracurium at a dose of 0.15 mg/kg was applied within 5-10 seconds, 30 seconds after the administration of thiopental. The timer was then reset and the stimulator was operated in a single stimulus mode with a frequency of 0.1 Hz. After 120 seconds, the level of neuromuscular block was determined as a percentage, and the intubation was performed and evaluated within 10 seconds by another experienced anesthetist who was unaware of the groups. The quality of intubation was evaluated as excellent (easy tube passage without coughing, vocal folds relaxed and in abduction position), good (tube passage with mild coughing and/or resistance, vocal folds relaxed and in abduction position), poor (tube passage with moderate cough and/or resistance, vocal folds in moderate adduction position) or impossible (vocal cords in tight adduction position) as described by Viby-Mogensen et al. [11].

The breathing of the patients was supported with 100% oxygen during the induction phase. Controlled breathing was provided with 50% oxygen + 50% nitrous oxide within the first 5 minutes following intubation. Anesthesia was maintained with appropriate agents and the surgical intervention was started

after 5 minutes.

Ethical Consideration

The study protocol was authorized by our hospital's local committee before the start of the study. We would like to state that our study was carried out in accordance with the ethical principles of the Helsinki Declaration.

Statistical Analysis

We used SPSS version 20.0 (Statistical Package for Social Sciences, USA) to analyze the data collected during the study. To analyze the normality of the variables, the Kolmogorov-Smirnov test was used. One-way ANOVA, Mann-Whitney U test and independent sample t-tests were used for comparing normally distributed continuous variables, and the Kruskal-Wallis test for comparing the non-normally distributed variables between the groups, while Chi-square and Fisher Exact tests were used to compare categorical variables. Mean±standard deviation expression was used to express continuous variables and categorical variables as frequency and percentage, $p<0.05$ values were considered statistically notable.

Results

Sixty patients were randomly assigned to three groups (Remifentanil, Fentanyl, Control) with 20 patients in each. The mean age of the patients was 39.42±10.50 years. The mean age was 43.85±8.97 years in the remifentanil, 38.4±12.33 years in the fentanyl, and 36.00±10.19 years in the control group. The mean weight of the patients was found as 69.15±9.95 kg. The mean weight was 67.30±9.24 kg in the remifentanil, 69.90±9.18 kg in the fentanyl and 70.25±11.42 kg in the control group. No remarkable difference was found between the groups in terms of gender, age and weight (for all $p>0.05$).

No statistically notable difference between the groups when it comes to the levels of neuromuscular block at the time of intubation, time to T1 90% suppression level, maximum block (effect) onset time (T1 95%) and time to the complete block (T1 100%) (for all $p>0.05$). The neuromuscular blockade levels of the groups at different time points are given in Table 1.

No statistically notable difference was found in mean pre-induction SBP values between the three groups (for all $p>0.05$). The mean SBP was notably lower in the remifentanil group compared to both fentanyl and control groups post-induction and at 5 minutes after the intubation (for both, $p<0.05$). The lowest SBP values were found in the remifentanil group immediately post-induction, pre-intubation, immediately post-intubation, and at 3 and 5 minutes.

The mean DBP was statistically remarkably lower in the remifentanil group in comparison with both fentanyl and control groups immediately post-induction, pre-intubation, right after post-intubation, and at 3 and 5 minutes after intubation (for all $p<0.05$). The mean DBP values were remarkably lower in the fentanyl group compared to the controls in the measurements made at 3 and 5 minutes (both $p<0.05$). Systolic and diastolic blood pressure values over time according to the groups are expressed in Figure 1.

Statistically speaking, no significant difference was found between the three groups in terms of mean HR (for all, $p>0.05$). The mean HR was notably lower in the remifentanil group compared to other groups post-intubation ($p<0.001$), compared to the fentanyl group post-induction ($p<0.05$), and pre-intubation and compared to the control group at 3

Table 1. Neuromuscular blockade levels of the groups at different time points

	Remifentanil		Fentanyl		Control	
	Mean	± SD	Mean	± SD	Mean	± SD
Neuromuscular blockade level at the time of intubation (%)	57.95	17.22	53.65	20.22	56.00	25.03
Time to T1 90% suppression (sec)	198.58	51.14	193.74	49.49	185.49	60.75
Time to T1 95% suppression (sec)	219.00	62.03	218.07	52.69	216.51	71.66
Time to complete block (T1 100%) (sec)	251.91	68.93	242.12	61.10	252.45	79.55

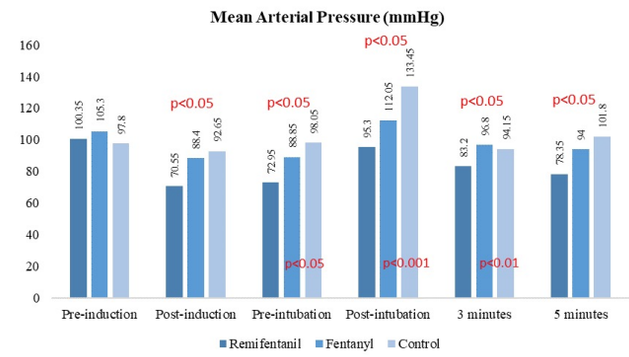

Figure 1. Mean arterial pressure values of the groups at different time intervals

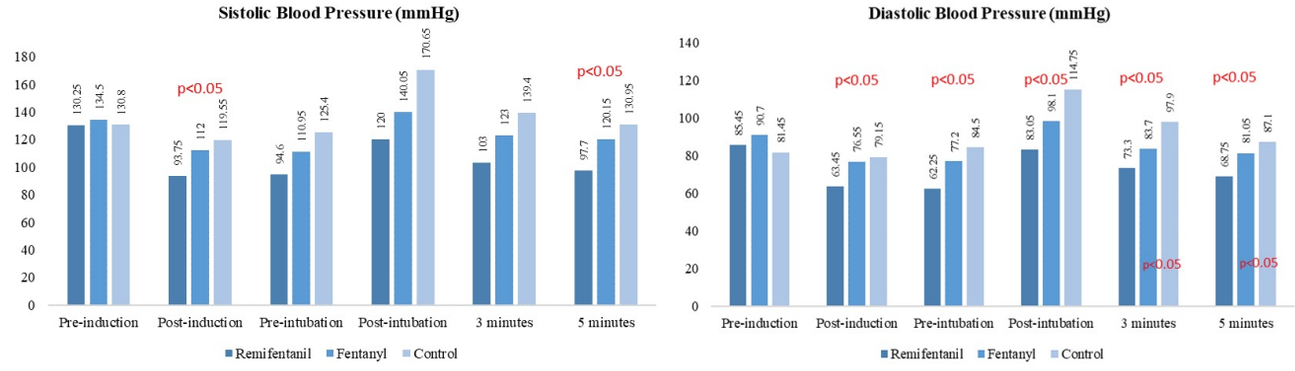

Figure 1. Diastolic and systolic blood pressure values of the groups at different time intervals

(p<0.001) and 5 minutes (p<0.01). The mean HR value was notably lower in the fentanyl group compared to the controls at 3 and 5 minutes (both p<0.05) (Figure 3). The measurements of the SpO2 were similar in all groups at all time intervals (for all, p>0.05).

Accordingly, excellent-good intubation quality was achieved in 17 (85%) patients in the remifentanil group and in 16 (80%) patients in the fentanyl group. The disparity between these two groups was not statistically significant (p=0.904). Whereas impossible intubation was not observed in the remifentanil and fentanyl groups, 25% (n=5) of the intubations were assessed as impossible in the control group, and the disparity was significant compared to both the remifentanil (p=0.026) and control (p=0.047) groups.

When the side effects of the drugs were evaluated; three (15%) of the patients in the remifentanil group developed hypotension, while neither of the patients in this group developed bradycardia. Three (15%) patients in the remifentanil group and one (15%) patient in the fentanyl group developed apnea. Skin rash was observed in one (5%) patient in the control group, while muscle rigidity was seen in two (10%) patients in the fentanyl group.

Discussion

The use of intravenous opioids for anesthetic induction and neuromuscular monitoring has been reported to alleviate hemodynamic stress responses, including hypertension and tachycardia during general anesthesia [9, 12-14]. In our study, we compared the effects of remifentanil and fentanyl on the neuromuscular block induced by cisatracurium via peripheral nerve stimulation, hemodynamic changes and the quality of intubation.

De Kort et al. performed intubation using propofol 1-2 mg/kg as premedication and obtained good intubation in 85% and inadequate intubation in 15% of patients [15]. Karaman et al., provided excellent intubation in 19/20 (95%) of patients with fentanyl using the Viby-Mogensen score as in our study [16]. Abdelhalim et al. reported that 2 µg/kg fentanyl followed by 3 mg/kg propofol provided a higher rate of excellent intubation compared with 2 µg/kg fentanyl followed by 2 mg/kg propofol [17]. In our study, we used cisatracurium as a neuromuscular relaxation agent. Svalingam et al., obtained excellent intubation in 64%, good intubation in 32% and poor intubation in 4% of the patients with alfentanil 10 µg/Kg and suxamethonium 1 mg/Kg, without using muscle relaxant [18]. Although studies have been reported different rates of intubation quality,, high rates of excellent-good intubation indicate the benefits of using opioids for improving the quality of intubation.

Barclay et al. compared bolus doses of 1 µg/kg, 2 µg/kg and 4 µg/kg of remifentanil in a placebo-controlled study in preventing hemodynamic response to intubation [19]. They used propofol as a hypnotic agent and cisatracurium at a dose of 0.15 mg/kg as a muscle relaxant during induction. They found that the 2 µg/kg dose of remifentanil completely suppressed the hemodynamic response to intubation, while the increased dose of 4 µg/kg did not provide any additional benefit, and node of the patients developed complications such as bradycardia, tachycardia, hypotension or hypertension [19]. The results of this study are in parallel with our findings.

Lee et al. reported significant decreases in SBP post-intubation compared to pre-induction with the use of remifentanil (p<0.001) [20]. A number of studies published in peer-reviewed journals have compared the effects of remifentanil and other agents on hemodynamic responses induced during general anesthesia. Habib et al. compared remifentanil bolus (0.5 over 30 seconds) followed by an infusion (0.1 µg//Kg/min) with alfentanil bolus (10 µg/kg over 30 seconds), and both regimens effectively suppressed the hemodynamic response to laryngoscopy and intubation [21]. Sezen et al. lowered blood pressure and heart rate through administration of remifentanil plus desflurane [22]. Tuncel et al. compared remifentanil and alfentanil infusions in abdominal surgery and reported that remifentanil better controlled intraoperative hemodynamic responses [23]. On the other hand, Farzi et al. found no notable difference between remifentanil and fentanyl in terms of hemodynamic parameters [24]. Although results of studies can significantly differ due to several factors, such as the opioids to be compared, other agents used for premedication and presence of neuromuscular relaxation. However, the results of our study and other studies usually indicate a marked superiority of remifentanil in terms of hemodynamic responses, including HR and blood pressure values.

Study Limitations

The main limitations of this study are that the study was carried out in a single center and the number of participants was relatively low. Nevertheless, we feel that the results we acquired will contribute to the existing literature on the effects of using opioids on hemodynamic responses induced by anesthesia induction.

Conclusion

The findings of our study showed that opioids increase the quality of intubation and suppress the undesirable hemodynamic response to intubation by blocking the central integration of sensory pathways without affecting neuromuscular conduction. The administration of remifentanyl as a 1.5 µg/kg bolus followed by a 0.3 µg/kg/min infusion did not provide a significant advantage in improving the quality of intubation compared to a 3 µg/kg bolus dose of fentanyl, but remifentanyl was more effective in controlling undesirable hemodynamic responses to laryngoscopy and tracheal intubation and therefore, it is worthy of promotion in clinical practice.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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