European Review for Medical and Pharmacological Sciences 2023; 27: 653-658

Effect of different doses of remifentanil on the cardiovascular response after endotracheal intubation: a randomized double-blind study

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Abstract. – OBJECTIVE: Laryngoscopy and endotracheal intubation (EI) often provoke a marked sympathetic response, which leads to tachycardia and hypertension. The aim of this study was to investigate the effect of different doses of remifentanil on the cardiovascular response to laryngoscopy and EI.

PATIENTS AND METHODS: 100 patients were included in this randomized study. The participants were divided into four groups of 25 patients each. The patients in the control group did not receive remifentanil. The patients from other three groups received remifentanil prior to induction of anesthesia at doses of 0.5 μg/kg, 1 μg/kg, and 1.5 μg/kg. Hemodynamic parameters were measured before and after administration of remifentanil, after induction of anesthesia and one minute after EI.

RESULTS: After administration of remifentanil and induction of anesthesia, a decrease in arterial pressure and heart rate occurred in most patients. After EI, an increase in arterial pressure and heart rate was observed in most patients. The largest increase was recorded in the group of patients who did not receive remifentanil. The best hemodynamic response was observed in patients who received 1 and 1.5 μg/kg of remifentanil.

CONCLUSIONS: Remifentanil at the doses of 1-1.5 μg/kg is absolutely safe for co-induction of anesthesia with thiopental. Such dosing regimen provides optimal conditions for reducing hemodynamic response to laryngoscopy and EI.

Key Words:
Laryngoscopy, Endotracheal intubation, Cardiovascular response, Anesthesia, Remifentanil.

Introduction

Laryngoscopy and endotracheal intubation (EI) have become an integral part of general anesthesia. These procedures result in a marked sympathetic response associated with increased plasma catecholamine concentrations, which lead to tachycardia and hypertension[1]. This response is most pronounced in the first minute after intubation. It is usually insignificant but can lead to severe morbidity in patients with underlying cardiovascular and cerebrovascular diseases as it alters myocardial oxygen demand[2,3]. Commonly, the anesthetic alone is not sufficient to suppress this response. Opioids, α-2 agonists, beta-blockers, lidocaine and magnesium sulfate are most often used as additional pharmacological agents[4,5].

Remifentanil, a 4-anilidopiperidine derivative of fentanyl, is an ultra-short-acting μ-opioid receptor agonist. It has a rapid onset of action (1 minute) and a rapid offset of action following discontinuation (3-10 minutes) irrespective of the duration of infusion[6-8].

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The aim of this study was to examine the effects of different doses of remifentanil on the reduction of hemodynamic response after laryngoscopy and EI in patients younger than 65 years scheduled to undergo surgery under general endotracheal anesthesia.

Patients and Methods

This randomized double-blind clinical study was conducted at the surgery clinics of the Clinical Center of Vojvodina in Novi Sad. Using the method of random selection, the study included 100 patients of both genders, aged 21 to 64 years, who belonged to groups I, II, or III according to the American Society of Anesthesiologists (ASA) classification. The patients were scheduled to undergo various types of elective surgical procedures under general balanced endotracheal anesthesia. The study did not include patients with conditions such as uncontrolled hypertension (diastolic arterial pressure >100 mmHg), hypotension (systolic arterial pressure <80 mmHg), body mass index >35 kg/m^2, hypersensitivity to opioids, patients on chronic therapy with benzodiazepines, opioids, anticonvulsants, α-adrenergic agonists , as well as those who have used the aforementioned drugs within 12 hours before surgery (with the exception of sedation with short-acting benzodiazepines the night before surgery). Patients who had an allergic reaction during the induction of anesthesia and patients in whom endotracheal intubation was difficult, prolonged or impossible were excluded from the study. The procedures were performed after obtaining the informed written consent from the patients. The study was approved by the Ethics Committee of the Clinical Center of Vojvodina in Novi Sad (Serbia). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Depending on the administered intravenous bolus dose of remifentanil for co-induction, the patients were divided into 4 groups of 25 patients each:

Group I (control): 0.9% NaCl 1 ml i.v. + thiopental 3-5 mg/kg i.v;

Group II: remifentanil 0.5 μg/kg i.v. + thiopental 2 mg/kg i.v., followed by 50 mg every 10 seconds until onset of induction;

Group III: remifentanil 1 μg/kg i.v. + thiopental 2 mg/kg i.v., followed by 50 mg every 10 seconds until onset of induction;

Group IV: remifentanil 1.5 μg/kg i.v. + thiopental 2 mg/kg i.v., followed by 50 mg every 10 seconds until onset of induction.

All patients fasted from midnight and did not receive pre-medication in order to avoid potential drug interactions. Prior to induction of anesthesia, all patients were administered 5 ml/kg of Ringer's lactate solution. After receiving 3 mins of preoxygenation with 100% oxygen and measuring hemodynamic parameters [systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), and heart rate (HR)], remifentanil ("Ultiva", Glaxo Wellcome) was administered at an intravenous bolus dose of 0.5, 1, or 1.5 μg/kg, over 30-60 seconds. Anesthesia was induced with thiopental at the previously mentioned dose. For neuromuscular relaxation, succinylcholine was administered at a dose of 1 mg/kg i.v. After 1 minute, the anesthesiologist performed direct laryngoscopy and EI. The procedure was performed by the same anesthesiologist, *via* Macintosh laryngoscope (Rudolf Riester GmbH&Co.KG, Jungingen, Germany).

Hemodynamic parameters (SAP, DAP, and MAP) were monitored by a non-invasive method, while HR was monitored via ECG. The following parameters were measured:

- after preoxygenation (basal values);
- after administration of remifentanil;
- after administration of thiopental and succinylcholine (immediately before laryngoscopy and EI);
- 1 minute after EI.

Statistical Analysis

R software (version 3.4.0, Review Manager Web, The Cochrane collaboration, Copenhagen, Denmark) was used for statistical analysis. Mean values and standard deviation were calculated. Statistical significance was tested using Pearson's χ^2 test, Kruskal-Wallis' test, Mann-Whitney test and Fisher's test. The results were considered statistically significant when $p<0.05$.

Results

Hundred patients were included in the study, 43 of which were males (43%) and 57 females (57%). Pearson's χ^2 test revealed no statistically significant difference between the groups with respect to gender (χ^2=3.713, degrees of freedom

Table I. Patient characteristics.

Variables	Group I	Group II	Group III	Group IV
Age (yr), mean (SD)	41.2 (12.9)	43.1 (12.6)	47.3 (12.5)	39.0 (13.1)
Gender (M/F), n	12/13	9/16	14/11	8/17
Weight (kg), mean (SD)	70.6 (13.9)	71.8 (14.6)	77.8 (11.7)	69.6 (13.5)
ASA, n				
1	14	12	12	13
2	8	7	9	7
3	3	6	4	5
Arterial hypertension, n				
Yes	5	v7	v9	4
No	20	18	16	21

There were no statistically significant differences between the four groups.

[df]=3, p=0.2942). Patients were aged 21-64 years (average age 42.7 years). The Kruskal-Walli's test showed that there was no statistically significant difference between the groups in relation to age (Kruskal-Wallis's χ^2=5.997, df=3, p=0.11178). Of the total 100 patients included in the study, 51 were classified as ASA I (51%), 31 as ASA II (31%), and 18 as ASA III (18%). Fisher's test revealed no statistically significant difference between the groups with respect to ASA classification (p=0.95769) (Table I). The above-mentioned results indicated that the groups of respondents were homogeneous, and that the statistical analysis was representative.

The dose of thiopental used for the induction of anesthesia ranged from 2.2 to 6.7 mg/kg (mean value of 4.6 mg/kg). The Kruskal-Wallis' test shows that there is a statistically significant difference between the groups with respect to the dose of thiopental used for the induction of anesthesia and that patients from group I received an averagely higher dose of thiopental (5.3 mg/kg) compared to groups II (4.5 mg/kg), III (4.1 mg/kg) and IV (4.5 mg/kg) (Kruskal-Wallis χ^2=18.997, df=3, p=0.00027).

Systolic Arterial Pressure (SAP)

After administration of remifentanil, there was a drop in SAP in the majority of patients. In group II, the average reduction compared to the basal value was 1.61%, while the values in groups III and IV were 4.28% and 3.74%, respectively (Kruskal-Wallis χ^2=1.094, df=2, p=0.57873). After thiopental administration, significantly greater decrease in SAP was observed in group III (16.02% compared to the basal value) and group IV (10.26% compared to the basal value) (Kruskal-Wallis χ^2=14.359, df=3, p=0.00246). One minute after intubation, an increase in SAP was observed in most patients. The highest increase of 29.28% compared to the basal value was recorded in the control group. A smaller increase was observed in patients who received remifentanil. There was a statistically significant difference between the groups (Kruskal-Wallis χ^2=18.864, df=3, p=0.00029) (Figure 1).

Diastolic Arterial Pressure (DAP)

After remifentanil was administered, a decrease in DAP was observed in the majority of patients. In group II, the average reduction compared to the basal value was 1.27%, in group III 5.04% and in group IV 6.52% (Kruskal-Wallis χ^2=5.19, df=2, p=0.07466). Administration of thiopental led to a decrease in DAP in group III (10.48% compared to the basal value) and group IV (7.86% compared to the basal value) (Kruskal-Wallis χ^2=18.92, df=3, p=0.00028). In the first minute after intubation, there was an increase in DAP in most patients. The highest increase of

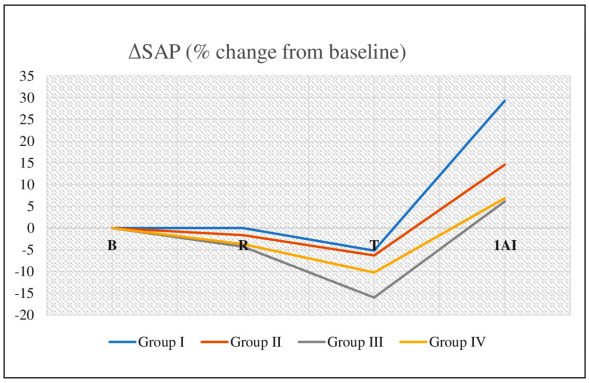

Figure 1. Percent change of systolic arterial pressure (ΔSAP). Values are expressed as mean ± SD. B: basal value, R: after remifentanil, T: after thiopental, 1AI: one minute after intubation.

36.54% compared to the basal value was recorded in the control (I) group. A smaller increase was observed in patients who received remifentanil (groups II, III, IV). The DAP significantly decreased with an increase of remifentanil dose. There was a statistically significant difference between the groups (Kruskal-Wallis χ^2=16.274, df=3, p=0.001) (Figure 2).

Mean Arterial Pressure (MAP)

The administration of remifentanil led to a drop in MAP without a statistically significant difference in relation to the administered dose (Kruskal-Wallis χ^2=2.501, df=2, p=0.28631). Thiopental caused a drop in MAP in group III and IV of 16.05% and 12.67%, respectively. Group I and group II were statistically significantly different from groups III and IV (Kruskal-Wallis χ^2=12.923, df=3, p=0.00481). The average increase in MAP in the first minute after intubation was significantly higher in group I (46.19%) as compared to group II (29.14%), group III (16.14%) and group IV (15.7%) (Kruskal-Wallis χ^2=20.066, df=3, p=0.00016) (Figure 3).

Heart Rate (HR)

Remifentanil caused an increase in HR in some patients and a decrease in others. Regardless of the administered dose of remifentanil, there was no statistically significant difference between the groups (Kruskal-Wallis χ^2=5.612, df=2, p=0.06044, p>0.05). Thiopental caused an increase in HR in most patients. This increase was most pronounced in patients from group I (28.45% compared to the basal value). Group I was significantly different from groups II, III and IV (Kruskal-Wallis χ^2=23.878, df=3, p<0.001). In the first minute after intubation, there was an increase in HR. In the first group, this increase was of the 41.11% compared to the basal value, while significantly lower values were observed in groups II, III and IV (Kruskal-Wallis χ^2=24.002, df=3, p<0.001) (Figure 4).

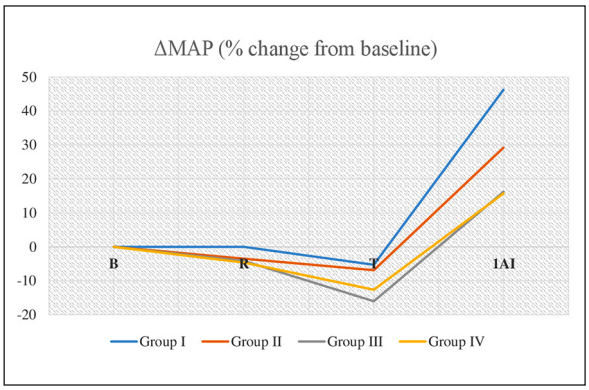

Figure 3. Percent change of mean arterial pressure (ΔMAP). Values are expressed as mean ± SD. B: basal value, R: after remifentanil, T: after thiopental, 1AI: one minute after intubation.

Discussion

Hemodynamic response to airway handling results from reflex sympathetic hyperactivity. Laryngoscopy predominantly affects the increase in blood pressure while EI affects the increase in heart rate[4]. An ideal induction of anesthesia should not be prolonged and should minimize the

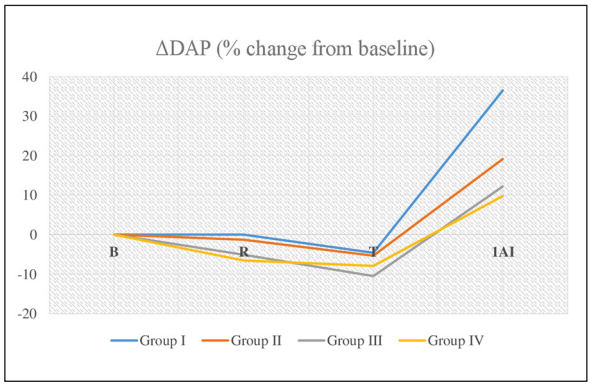

Figure 2. Percent change of diastolic arterial pressure (ΔDAP). Values are expressed as mean ± SD. B: basal value, R: after remifentanil, T: after thiopental, 1AI: one minute after intubation.

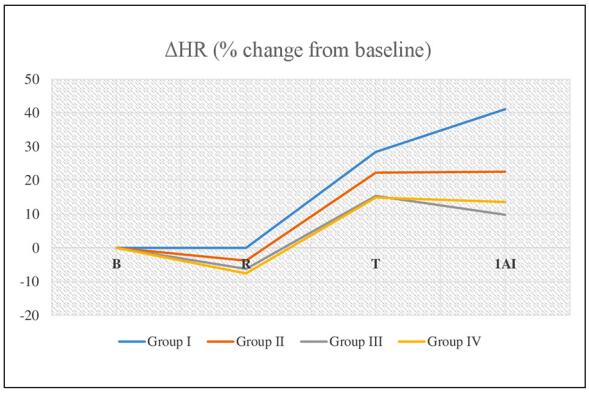

Figure 4. Percent change of heart rate (ΔHR). Values are expressed as mean ± SD. B: basal value, R: after remifentanil, T: after thiopental, 1AI: one minute after intubation.

hemodynamic response. Undoubtedly, the majority of anesthesiologists use opioids to reduce the hemodynamic response. Most opioids act as G-protein coupled μ-receptor agonists and show a dose-dependent decrease in HR and blood pressure[9,10]. In this study, we aimed to identify the effective bolus dose of remifentanil for an acceptable intubation condition when anesthesia was induced with thiopental. The effects of three different doses of remifentanil (0.5, 1 and 1.5 μg/kg) were examined.

Remifentanil can lead to chest wall rigidity and difficulty in ventilation when given in high doses and when administered rapidly[11]. In order to avoid that, we administered the drug over a period of 30-60 s. After receiving remifentanil, the majority of patients experienced a decrease in arterial pressure and heart rate, as expected. In the first minute after intubation, an increase in arterial pressure and heart rate was observed in all groups. The largest increase was in the group that did not receive remifentanil. In the groups that received 1 or 1.5 μg/kg remifentanil, the average increase did not exceed 20%. Ko et al[12], Lee et al[13] and Min et al[14] concluded that a dose of 1 μg/kg remifentanil is optimal for reducing the hemodynamic response to intubation. The authors who investigated the effect of remifentanil on endotracheal intubation in elderly patients showed that the optimal dose of remifentanil for elderly patients is 0.5 μg/kg[15]. These results are certainly logical due to the need to reduce the dosage of remifentanil in elderly patients[16].

Joo et al[17] compared the effects of bolus remifentanil with bolus fentanyl on induction of the anesthesia and EI in patients with cardiovascular disease. They concluded that remifentanil in combination with glycopyrrolate was associated with rapid and predictable clinical anesthetic effects, cardiovascular stability and the ability to control the hemodynamic response to tracheal intubation, and that it is a good alternative to fentanyl for induction in these patients. Remifentanil also has a protective effect on the heart muscle and prevents ischemic lesions of the heart[18]. A study by Ko et al[12] also showed that remifentanil is superior to fentanyl in suppressing the cardiocirculatory response to EI. Compared to sufentanil, remifentanil causes smaller oscillations in blood pressure during induction of anesthesia, as well as smaller increase in blood pressure during intubation[19]. A randomized study[20] comparing the hemodynamic profile of remifentanil and afentanil found that remifentanil was superior.

Limitations

This study is not without limitations. This is a single-center study with a relatively small number of subjects. Hemodynamic parameters were observed based on non-invasive methods. On the other hand, the placement of an arterial catheter for invasive measurement, being a painful procedure, would lead to an increase in the concentration of plasma catecholamines, which would certainly affect the hemodynamic values.

Conclusions

In conclusion, remifentanil at the doses of 1-1.5 μg/kg is completely safe for co-induction of anesthesia with thiopental. Such dosing regimen provides optimal conditions for reducing the hemodynamic response to laryngoscopy and EI.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

None.

Funding

No funding was requested for this study.

Authors' Contribution

All authors had major roles in the conception, design, planning and carrying out the study. All authors contributed to the analysis of the data and the writing and editing of the manuscript.

Ethics Approval

The study was approved by the Ethics Committee of the Clinical Center of Vojvodina in Novi Sad (Serbia). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent

The study was conducted after obtaining the informed written consent from the patients.

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