Evaluation of the effects of esmolol and remifentanil for controlled hypotension application on hemodynamics and oxidative stress parameters

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ABSTRACT

Introduction: Anesthesia induced during a surgical intervention, the duration of the surgical intervention, and the surgical intervention itself tend to affect immune functions, resulting in the formation of free radicals in the metabolism. Free radicals can cause postoperative disorders by targeting biomolecules in the cell, such as lipids, carbohydrates, proteins, and DNA. In the present study, we used remifentanil or esmolol to induce a controlled hypotension in patients who were undergoing septrhinoplasty under general anesthesia, and we planned to compare the effect of these agents on hemodynamics and oxidative stress relative to the control group.

Methodology: A total of 75 patients aged between 18 and 65 y, ASA I-II, planned to undergo elective septrhinoplasty, were included in this study. Patients were randomly divided into the following three groups: Group R (remifentanil group, n = 25); Group E (esmolol group, n = 25); and Group C (control, n = 25). Anesthesia was induced with 2 mg/kg propofol 2 mg/kg, fentanyl 1 µg/kg, and rocuronium 0.6 mg/kg. Immediately after induction, Group R was started loading dose of remifentanil 1 µg/kg/min, followed by infusion at 0.25–0.50 µg/kg/min. In Group E, a loading dose of esmolol 500 µg/kg was given for 1 min, then infusion was continued @ 150–300 µg/kg. A targeted mean arterial pressure (MAP) of 55–65 mmHg was aimed. In Group C, remifentanil was infused at 0.1–0.2 µg/kg/min until a MAP of 70–100 mmHg was reached. During operation; systolic (SAP), diastolic (DAP) and mean arterial pressure (MAP), heart rate (HR), peripheral oxygen saturation (SpO2), EtCO₂ (end tidal CO₂) were recorded before induction, after induction, after intubation, at 5-min intervals during the first 30 min, and then at 10-min intervals during the intervention. The amounts of remifentanil and esmolol consumed by the patients during the operation were calculated and recorded. Blood samples that were taken twice, preoperatively and postoperatively, for malondialdehyde (MDA), superoxide dismutase (SOD), total oxidant level (TOL), total antioxidant level (TAL), and oxidative stress index (OSI).

Results: MAP showed a greater decrease starting from the 25th min and 40th min after intubation in remifentanil group and esmolol group respectively, compared to the control group. In the remifentanil and control groups, there was a statistically significant decrease in the postoperative OSI levels compared to the preoperative levels. One the other hand, in the esmolol group, there was no statistically significant difference between the preoperative and postoperative median OSI levels. There was a significant increase in the postoperative TAL of the remifentanil group compared to the preoperative level.

Conclusion: It was observed that during a hypotensive anesthesia induced by remifentanil or esmolol, remifentanil ensured more stable operating conditions in terms of hemodynamics compared with esmolol, and that remifentanil was also superior to esmolol in reducing oxidative stress.

Key words: Esmolol; Remifentanil; Controlled hypotension; General anesthesia; Oxidative stress

Abbreviations: TOL: Total oxidant level; TAL: Total antioxidant level; SOD: Superoxide dismutase; MDA: Malondialdehyde; OSI: Oxidative stress index

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INTRODUCTION

Antioxidant systems normally work together in unity to protect the cell against toxic effects of free oxygen radicals, which they achieve by keeping the oxidant and antioxidant systems of the organism in balance. Alteration of this balance in favor of oxidants results in the production of inflammatory mediators and free oxygen radicals. The immune system is affected by the anesthesia induced during surgical intervention, the duration of the surgical intervention and the surgical intervention itself, which lead to the formation of free radicals in the metabolism. Free radicals can cause postoperative disorders by targeting biomolecules in the cell, such as lipids, carbohydrates, proteins and DNA. Combined with operative stress, the applied method of anesthesia may induce an imbalance between the antioxidant defense system and reactive oxygen species. Therefore, the oxidant and antioxidant activities of anesthetic agents may be of clinical importance. The effects of intravenous and volatile anesthetics on oxidative stress parameters have been investigated in different studies; however, the effect on oxidative stress of hypotensive anesthesia applied together with different agents has not yet been investigated. The aim of this study was to evaluate the hypotensive anesthesia method, which was applied using two different agents in terms of lipid peroxidation and antioxidant response through a randomized double-blind study.

METHODOLOGY

After obtaining approval from the ethics committee of the hospital, our study was performed in patients who had planned elective septorhinoplasty. A total of 75 patients aged between 18 and 65 who complied with the ASA I-II classification were included in this study.

Patients with coronary artery disease and chronic disease; patients who were morbidly obese, pregnant, or lactating; patients with drug and tobacco addiction; and patients with severe anemia were excluded from this study. Patients whose surgeries lasted for less than 120 min and more than 300 min were also excluded from this study. Patients whose surgeries lasted for less than 120 min and more than 300 min were also excluded from this study. Patients were randomly divided into the following three groups: Group R (remifentanil group, n = 25); Group E (esmolol group, n = 25); and Group C (control group [CG], n = 25). A web application was used for randomization (www.randomizer.org).

After obtaining written informed consents from the patients, they were taken to the operating room without applying a premedication, and infusion was initiated with −10 mL/kg 0.9% NaCl solution via vascular access from a peripheral vein. Standard monitoring was performed for the patients using noninvasive blood pressure (NIBP), ECG, and pulse oximetry. Baseline values were measured and recorded. In all patients, the induction of anesthesia was ensured with IV 2 mg/kg propofol and 1 µg/kg fentanyl. After achieving muscle relaxation with 0.6 mg/kg rocuronium, endotracheal intubation was performed. Radial artery cannulation was performed in all patients for invasive arterial pressure monitoring. Anesthesia was maintained through the inhalation of a mixture of 1 MAC sevoflurane and 60% nitrous oxide mixed with 40% oxygen. Immediately after induction, Group R was started on an infusion of 2 mg remifentanil (Ultiva® 2 mg vial, GlaxoSmithKline) diluted with 100 mL isotonic (20 µg/mL), with an initial loading dose of 1 µg/kg/min being followed by a dose range of 0.25–0.50 µg/kg/min. In Group E, an initial loading dose of 500 µg/kg esmolol was applied for 1 min, after which infusion was continued at a dose of 150–300 µg/kg. In both groups, infusion dose adjustment was performed until the targeted mean arterial pressure (MAP) of 55–65 mmHg was reached. In Group C, remifentanil was also diluted with isotonic and infused at 0.1–0.2 µg/kg/min until 70–100 mmHg MAP was reached. During the operation, systolic arterial pressure, diastolic arterial pressure (DAP), MAP, heart rate (HR), peripheral oxygen saturation (SpO₂), and end tidal CO₂ (EtCO₂) values were measured and recorded before induction, after induction, after intubation, at 5-min intervals during the first 30 min, and then at 10-min intervals during the intervention. The amounts of remifentanil and esmolol consumed by the patients during the operation were calculated and recorded. Blood samples were collected in straight tubes from a peripheral vein two times before induction (preoperative) and immediately after extubation (postoperative), and the collected blood samples were centrifuged at 4000 rpm for 10 min in a centrifuge. Malondialdehyde (MDA), superoxide dismutase (SOD), total oxidant level (TOL), total antioxidant level (TAL), and oxidative stress index (OSI) were examined in the blood samples that were taken preoperatively (preop) and postoperatively (postop).

Power analysis:

At least 23 subjects needed to be included in each group for testing, at 80% power and 5% error level, the statistical significance of a difference of at least 0.40 units of a change in postoperative OSI levels compared with preoperative values between at least two of the groups. The difference of 0.40 units was obtained in both the pilot study and the clinical experience. Sample size calculations were performed using the NCSS & PASS 2000 statistical package software.

Statistical Analysis:

Data were analyzed using Statistical Package for
Social Science (SPSS) for Windows 11.5. Normal distribution of the continuous variables was investigated using Kolmogorov–Smirnov test, while homogeneity of the variance was investigated using Levene’s test. Descriptive statistics were shown as mean ± standard deviation or median (minimum–maximum) for continuous measurement variables and as case number for nominal variables.

The significance of difference between the groups in terms of mean values was investigated using one-way analysis of variance (one-way ANOVA), while the significance of difference between the groups in terms of median values was investigated using Kruskal–Wallis test. In cases where the results of one-way ANOVA or Kruskal–Wallis test statistics were found to be significant, Tukey’s post-hoc HSD test or Conover’s nonparametric multiple comparison test was used to determine the conditions causing the difference. Nominal variables were examined using Pearson’s chi-squared test. Wilcoxon Sign Test was used to determine whether there was a statistically significant difference between preoperative and postoperative values of the groups in terms of TOL, TAL, SOD, and MDA.

Repeated measures analysis of variance was used to evaluate hemodynamic measurements. Greenhouse–Geisser test statistics were used to determine whether the group × time interaction was significant. In cases where the group × time interaction was found to be significant, the percentage change observed in the successive monitoring times relative to the baseline was compared between the groups.

For the results, p < 0.05 was considered as statistically significant. However, Bonferroni correction was performed to check Type I error in all possible sub-analyses.

**RESULTS**

In terms of demographic data, no statistically significant difference was noted between the groups, except in terms of remifentanil consumption (p > 0.05). The median value of remifentanil consumption in Group R was 60 mL = 1200 µg, while this value was calculated as 26 mL = 520 µg in Group C (p < 0.05) (Table 1). According to the repeated measures analysis of variance applied to the monitoring of hemodynamic parameters and on the basis of the results of Greenhouse–Geisser test,

### Table 1: Demographic data

| Variables          | Group R | Group E | Group C | P-value |
|--------------------|---------|---------|---------|---------|
| Age (year)         | 31.4 ± 8.8 | 30.0 ± 9.1 | 33.9 ± 9.7 | 0.325   |
| Gender F/M(n)      | 12/13   | 13/12   | 8/17    | 0.321   |
| Height (cm)        | 169.8 ± 10.4 | 171.1 ± 9.3 | 170.9 ± 7.5 | 0.868   |
| Weight (kg)        | 70.0 ± 14.2 | 67.2 ± 13.8 | 71.9 ± 13.0 | 0.480   |
| BMI (kg/m²)        | 24.1 ± 3.6 | 22.8 ± 3.5 | 24.6 ± 4.0 | 0.220   |
| ASA I/II(n)        | 19/6    | 17/8    | 21/4    | 0.416   |
| Duration of Anesthesia (min) | 160 (100–200) | 140 (90–200) | 130 (90–200) | 0.051   |
| Duration of Surgery (min) | 145 (90–190) | 135 (85–180) | 125 (86–185) | 0.071   |
| R Consumption (mL) | 60 (15–180) | –      | 26 (15–32) | p < 0.05 |
| E Consumption (mL) | -      | 90 (30–200) | -      | -      |

Key: F/M: Female/Male. BMI: body mass index, R = remifentanil, E = esmolol, C = control, remifentanil (1 mL = 20 µg). Esmolol (1 mL = 40 µg). Values are shown as mean ±SD, median (minimum–maximum), and number of cases (n).

### Table 2: Mean arterial pressure levels readings to monitoring times (mmHg)

| Monitoring Time | Group R     | Group E   | Group C     |
|-----------------|-------------|-----------|-------------|
| Baseline        | 96.9 ± 9.7  | 100.1 ± 8.2 | 100.7 ± 10.1 |
| Before induction| 81.6 ± 14.2 | 85.1 ± 11.2 | 83.5 ± 10.7  |
| Intubation      | 85.7 ± 16.6 | 98.3 ± 13.6 | 96.0 ± 17.8  |
| 5th min         | 76.3 ± 10.2 | 85.2 ± 10.3 | 89.9 ± 14.8  |
| 10th min        | 70.3 ± 9.1  | 77.3 ± 9.3  | 83.8 ± 15.1  |
| 15th min        | 66.8 ± 7.8  | 70.9 ± 10.0 | 79.2 ± 11.6  |
| 20th min        | 63.3 ± 7.8  | 67.5 ± 9.6  | 76.4 ± 9.6   |
| 25th min        | 60.7 ± 3.9  | 65.5 ± 7.8  | 74.4 ± 6.6   |
| 30th min        | 59.1 ± 4.5  | 64.5 ± 7.3  | 71.3 ± 6.6   |
| 40th min        | 59.1 ± 4.2  | 61.5 ± 5.7  | 71.0 ± 5.8   |
| 50th min        | 59.0 ± 3.2  | 60.8 ± 5.0  | 71.6 ± 5.6   |
| 60th min        | 59.4 ± 3.9  | 60.8 ± 4.1  | 72.7 ± 7.3   |
| 70th min        | 59.8 ± 3.9  | 59.2 ± 4.1  | 72.0 ± 5.9   |
| 80th min        | 59.7 ± 2.9  | 59.0 ± 4.3  | 73.0 ± 6.7   |
| 90th min        | 58.7 ± 3.4  | 59.4 ± 3.8  | 76.0 ± 8.8   |
| 100th min       | 59.3 ± 4.0  | 60.0 ± 3.3  | 74.2 ± 8.5   |
Geisser test statistics, statistically significant differences were noted between the groups in terms of changes in MAP (F = 3.925 and p < 0.001). As these types of analyses only tolerate a maximum of 20% data loss, the hemodynamic parameters were evaluated up to the 100th minute. In the remifentanil group, MAP showed a greater decrease starting from the 25th minute after intubation compared with the CG (p < 0.0001). In the esmolol group, MAP showed a greater decrease starting from 40th minute after intubation compared to the CG (p < 0.0001). According to the Bonferroni Correction, there was no statistically significant difference between the remifentanil and esmolol groups in terms of the percentage change in the mean blood pressures (p > 0.0004) (Table 2).

According to the Bonferroni correction, no statistically significant difference was noted between the postoperative and preoperative TOL and TAL median values in both the remifentanil and esmolol groups (p > 0.017), while in the CG, a significant decrease was noted in postoperative TOL and a significant increase in the TOL level compared with the preoperative levels (p = 0.003 vs. p < 0.001, respectively). According to the Bonferroni correction, no statistically significant difference was noted between the postoperative and preoperative TAL median scores in both the remifentanil and esmolol groups (p > 0.017); however, a significant increase was noted in postoperative TAL in the remifentanil group compared with the preoperative level (p = 0.003). No statistically significant change was observed between postoperative and preoperative MDA median values in any of the groups (p > 0.017). (Table 3: Figure 1)

In the remifentanil and control groups, a statistically significant decrease was noted in the postoperative OSI levels compared with the preoperative levels (p = 0.003 and p = 0.007). On the contrary, no statistically significant difference was noted in the esmolol group between preoperative and postoperative median OSI levels (p = 0.577) (Table 3: Figure 1).

**DISCUSSION**

In surgical interventions, controlled hypotension during general anesthesia, or hypotensive anesthesia minimizes bleeding and ensures a higher quality of surgical field of view, and thereby shortens the duration of the operation.8,9 Antihypertensives or opioid receptor agonists are widely used to this end. All studies conducted on controlled hypotension tend to evaluate intraoperative hemodynamic stability, postoperative recovery, and cognitive functions.7,8,9 However, there appear to be no studies in the literature on the oxidative changes in the metabolism caused by hypotension. In the present study, we used remifentanil or esmolol to induce a controlled hypotension in patients who were undergoing septorhinoplasty under general anesthesia, and we planned to compare the effects of these agents on hemodynamics and oxidative stress relative to the CG (low-dose remifentanil). In our study, when we evaluated each of the three groups in terms of hemodynamics, we observed that the targeted MAP was achieved within a shorter period in the remifentanil group compared with the esmolol group, and we also noted that the remifentanil group was associated with more stable hemodynamics during the operation (Table 2). We also observed greater surgical satisfaction in terms of surgical field of view.

Remifentanil is a clinical anesthetic drug that can activate the N-methyl-D-aspartate receptor. The fact that remifentanil has a single ester structure makes it susceptible to rapid ester hydrolysis by blood and tissue esterases in a similar manner to esmolol. The

### Table 3: Preoperative and postoperative TOL, TAL, SOD, MDA, and OSI levels. (Values expressed as median (minimum–maximum))

| Variable | Preoperative | Postoperative | p-value † |
|----------|--------------|---------------|-----------|
| TOL      |              |               |           |
| Remifentanil | 0.29 (0.09–2.51) | 0.23 (0.05–1.05) | 0.022     |
| Esmolol  | 0.42 (0.10–2.37) | 0.23 (0.10–1.28) | 0.563     |
| Control  | 0.21 (0.09–1.57) | 0.16 (0.05–0.27) | 0.003†    |
| TAL      |              |               |           |
| Remifentanil | 0.90 (0.57–1.24) | 0.95 (0.60–1.25) | 0.003†    |
| Esmolol  | 0.98 (0.48–1.52) | 1.00 (0.77–1.54) | 0.495     |
| Control  | 1.18 (0.63–1.58) | 1.06 (0.57–1.52) | 0.055     |
| SOD      |              |               |           |
| Remifentanil | 54.84 (41.94–96.39) | 58.07 (38.71–83.76) | 0.403     |
| Esmolol  | 69.36 (50.00–138.72) | 64.52 (53.23–140.33) | 0.098     |
| Control  | 75.81 (33.87–158.07) | 64.52 (40.33–191.95) | 0.166     |
| MDA      |              |               |           |
| Remifentanil | 0.30 (0.11–3.04) | 0.21 (0.04–1.52) | 0.003†    |
| Esmolol  | 0.39 (0.11–2.57) | 0.21 (0.06–1.50) | 0.577     |
| Control  | 0.18 (0.07–1.57) | 0.14 (0.06–0.29) | 0.007†    |

† According to the Bonferroni correction, the results were considered statistically significant for p < 0.017. TOL: total oxidant level, TAL: total antioxidant level, SOD: superoxide dismutase, MDA: malondialdehyde, OSI: TOL/TAL, Oxidative stress index.
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**Figure 1**: Preoperative and postoperative total antioxidant levels; A. TOL—total oxidant level, B. TAL—total antioxidant level, C. SOD—superoxide dismutase, D. MDA—malondialdehyde, E. OSI—oxidative stress index (TOL/TAL) levels of the groups.
Biotransformation is so rapid and complete that the duration of remifentanil infusion has little effect on waking time. The half-life is approximately 3 min, regardless of the duration of infusion. Remifentanil achieves the highest effect in 1.5 min with a single dose and shows rapid onset of action. It also has a high performance owing to its ability to form a balanced blood–brain barrier rate within a short time. Owing to its rapid rate of clearance, it is an opioid receptor agonist that does not cause any delay in recovery, even when applied at high intraoperative infusion doses.

Hepatic ischemia-reperfusion injury (IRI) caused by free oxygen radicals and inflammatory mediators is one of the most frequently occurring complications in liver transplantation. In animal studies, one of the most frequently occurring complications of hepatic ischemia-reperfusion injury (IRI) caused by free oxygen radicals and inflammatory mediators is the release of S-100β protein. This protein increased during CABG, exceeding the normal range.

Studies have shown that the concentration of S-100β protein increased during CABG, exceeding the normal range. The primary adverse effect of remifentanil is usually intravenous administration for 1 min with an initial loading dose of 500 µg/kg/min, followed by a continuous infusion of 25–300 µg/kg/min. The half-life of remifentanil is 9 min. Its primary side effect, hypotension, can be minimized by careful dosage titration and patient follow-up. Numerous recent studies have shown that in a perioperative setting involving tracheal intubation and extubation, esmolol can be safe and effective, through careful titration, in reducing the incidence of myocardial ischemia. The primary adverse effect of esmolol is usually concomitant hypotension (0%–50%). The incidence of hypotension increases with doses exceeding 150 µg/kg/min and in patients with low basal blood pressure. In case of hypotension, any intervention other than reducing the dose or stopping the infusion is usually not necessary. Symptoms often disappear within 20–30 min after discontinuation of the drug.
bradycardia. Therefore, more titration was required in the infusion dose of the drug. When the three groups were evaluated in terms of hemodynamics, it was found that the targeted MAP was reached within a shorter time in the RG, and that this group achieved more stable hemodynamics during the operation (Figure 1). In a study conducted by Guan et al. in 2011, stress response and cardiovascular stability were investigated by remifentanil or esmolol infusion in the patients during electro shock therapy procedure performed under anesthesia. Remifentanil was found to be superior to esmolol in sustaining cardiovascular stability and inhibiting a stress response.20

Studies have shown that free oxygen radicals contribute to reperfusion injury in myocardial infarction (MI). A prospective study performed by Daqa et al. in 2003 investigated the clinical and antioxidant effects of esmolol in patients with acute MI. All patients who were admitted with acute MI were treated with streptokinase and thrombolysis, after which an esmolol infusion was performed in 15 patients randomly selected among 30 patients, while the remaining 15 patients were recorded as CG. MDA, SOD, and Glutathione peroxidase (GPX) levels were measured and compared in blood samples obtained from the patients at the 0th, 2nd and, 24th h. The antioxidant effect of esmolol was clearly observed with a significant increase in MDA level and GPX's protective effect.21 SOD, an enzyme that plays a major role against free oxygen radicals, eliminates free radicals by catalyzing superoxide anions, and plays a protective role in tissues and cells by enhancing the regulatory function of hydrogen peroxide. MDA is the final metabolite resulting from the lipid peroxidation of polyunsaturated fatty acids by free radicals, and hence reflects the activity of free radicals and the degree of cell damage.16 In our study, it was found that the level of SOD significantly increased only in the CG. In the RG, the TAL was found to increase significantly. In this study, MDA level did not show any significant change in any of the groups.

CONCLUSION

The results of our study conclude that during a hypotensive anesthesia induced by remifentanil or esmolol, remifentanil ensured more stable operating conditions in terms of hemodynamics compared to esmolol, and that remifentanil was also superior to esmolol in reducing oxidative stress.

Conflict of interest: Nil

Authors' contribution:

HK, RiD: Contributed to introduction, method and discussion parts
MG, SK: Contributed to results and discussion parts
HE, MN: Analyzed biochemicals
UY: Patient monitoring; collection of blood samples from patients
AY: Performed surgical operations

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