Hypotensive anesthesia with esmolol

Assessment of hemodynamics, consumption of anesthetic drugs, and recovery

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ABSTRACT

الأهداف: تقييم أثر عقار إسمولول المضاف إلى اتحاد عقاري بروبوفول–وريميفينتالين للتخدير منخفض الضغط على حالات حركيات الدم للأدوية المخدرة والشفاء خلال عملية التقويم الاختيارية.

الطريقة: تم تصميم دراسة عشوائية بكلية الطب بجامعة غازي – أنقرة – تركيا، خلال عام 2005م. عقب الحصول على الموافقة من لجنة الأخلاق الطبية. تم تقسيم عدد 40 مريض إلى مجموعتين متساويتين: مجموعة (RP) ومجموعة (RP-E). بعد تحريض التخدير باستعمال عقار بروبوفول بمقدار (2-2.5mg/kg)، الهدف أن يكون الضغط الشرياني الرئيسي بين 50mm Hg زئبقي و 65mm Hg للتخدير منخفض الضغط المتحكم به في كلتا المجموعتين. في مجموعة (RP) تم إجراء التسريب بعقار ريميفينتانيل بمقدار 1-0.5µg/kg/min، عقبها جرعة كبيرة بمقدار1µg/kg. تلقت مجموعة (RP-E) عقار إسمولول بالتسريب بمقدار 100-300µg/kg/min، عقبها جرعة كبيرة مقدارها 500µg/kg، لتحقيق هدف ضغط الدم. بالإضافة إلى أن عقار بروبوفول تم تسريبه وفقاً لعمق التخدير للحفاظ على التخدير في كلتا المجموعتين. تم تسجيل تخطيط أصداء القلب، معدل ضربات القلب، ضغط الدم، مخرجات القلب واستهلاك عقاقير التخدير. عقب العملية الجراحية، تمت ملاحظة أوقات الشفاء، نقاط الألم البصرية والآثار الجانبية.

النتائج: كان الانخفاض في معدل ضربات القلب أثناء العملية ملحوظاً بشكل أكثر لدى مجموعة (RP-E). كان استهلاك عقار ريميفينتانيل أقل لدى مجموعة(RP-E). كانت أوقات الشفاء متشابهة في كلتا المجموعتين.

خاتمة: إضافة عقار إسمولول إلى اتحاد عقاري بروبوفول–ريميفينتانيل يؤدي إلى انخفاض استهلاك عقار ريميفينتانيل، بدون انخفاض في نتائج مخرجات القلب خلال التخدير منخفض الضغط.

Objectives: To assess the effect of esmolol added to propofol-remifentanil combination for hypotensive anesthesia on hemodynamic conditions, consumption of anesthetic drugs, and recovery, during elective septorhinoplasty.

Methods: This prospective, randomized study was carried out at Gazi University, Faculty of Medicine, Ankara, Turkey in 2005. Following Institutional Ethical Committee approval, 40 American Society of Anesthesiologists (ASA) I patients were divided into 2 equal groups (group remifentanil infusion (RP) and group esmolol infusion (RP-E)). After anesthesia induction with propofol (2-2.5 mg/kg), the mean arterial pressure was aimed to be between 50 mm Hg and 65 mm Hg for controlled hypotensive anesthesia in both groups. In group RP, a remifentanil infusion of 0.1-0.5 µg/kg/min was titrated, following a bolus of 1 µg/kg; for group RP-E, an esmolol infusion of 100-300 mg/kg/min was titrated, following a bolus of 500 µg/kg; to achieve a target blood pressure. In addition, propofol was infused according to depth of anesthesia to maintain anesthesia in both groups. Electrocardiography, heart rate, blood pressure, cardiac output, and consumption of anesthetic drugs were recorded. Postoperatively, recovery times, visual analog pain scores, and side effects were observed.

Results: The decrease in the intraoperative heart rate was more significant in group RP-E than in group RP. The remifentanil consumption was much lower in group RP-E. The recovery times were similar in both groups.

Conclusions: Addition of esmolol to propofol-remifentanil combination leads to a decrease in remifentanil consumption, without a decrease in cardiac output during hypotensive anesthesia.

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Controlled hypotension is defined as a reduction of the systolic blood pressure to 80-90 mm Hg, a reduction of mean arterial pressure to 50-65 mm Hg, or a 30% reduction of the baseline.[1] The main purpose of controlled hypotension is to reduce bleeding, facilitate surgery, and decrease the need for blood transfusions.[2] It has been indicated in oromaxillofacial surgery, endoscopic sinus, or middle ear microsurgery, spinal surgery and other neurosurgery, major orthopedic surgery, prostatectomy, cardiovascular surgery, and liver transplant surgery. A critical factor in the management of septorhinoplasty operations is to provide a relatively bloodless field to optimize visibility with controlled hypotensive anesthesia for the surgeon.[3] Remifentanil, an ultra short-acting opioid, has been used to achieve controlled hypotension in previous studies.[4-6] To provide controlled hypotension by remifentanil, a high dose of remifentanil is required, and then postinfusion hyperalgesia occurs. Rescue analgesic necessity leads to sedation, respiratory depression, prolonged recovery, and delayed discharge after operation. Esmolol, a short-acting cardioselective β1 adrenergic receptor antagonist, has been proposed as an alternative to intraoperative use of opioids for controlled hypotensive anesthesia.[4,7,8] Esmolol is reported to enhance the analgesic effects of opioids, but no analgesic effect has been reported when the drug is given alone.[9-11] There is evidence to suggest that ß-blockers have significant effects on the central nervous system[12,13] ß-blockers attenuate excitatory neuronal responses in the cingulated cortex or epileptiform responses in the limbic system in the rat.[14] Despite some contradictions,[11-15] it certainly seems that ß-blockers potentate the hypnotic and analgesic parts of anesthesia. The aim of this study was to assess the effect of esmolol added to propofol-remifentanil for induced hypotensive anesthesia on hemodynamic conditions, consumption of anesthetic drugs, and recovery characteristics during the early period.

Methods. *Patients.* After approval of Gazi University Hospital's Ethics Committee and informed consent of all the patients was obtained, 40 premedicated ASA physical status I patients, aged 18-48 years and undergoing elective septorhinoplasty procedure were studied. This study was carried out at Gazi University Hospital Plastic and Reconstructive Surgery Operating Theatres in 2005, Ankara, Turkey. The exclusion criteria were as follows: history of carotid artery stenosis, previous ischemic stroke, recent subarachnoid hemorrhage, raised intracranial or spinal pressure, hypertension, aortic stenosis, cardiomyopathy, hypovolemia, pregnancy, glaucoma, consumption of drugs that affect hemostasis, preoperative use of beta-blockers, hematologic disorders, anemia (hemoglobin [Hb]<10 g/dl), heart rate <60 beat/min, atrioventricular blocks, known β–blocker intolerance, neurologic, cardiovascular, respiratory, renal, hepatic, or metabolic diseases, and refusal by the patient.

Study design. The patients were equally assigned via computer-generated random numbers to the remifentanil-propofol induced hypotensive anesthesia (group RP) or remifentanil-propofol-esmolol induced hypotensive anesthesia (group RP-E). Hypotensive anesthesia was administered to keep the systolic arterial pressure (SAP) above 80 mm Hg and the mean arterial pressure (MAP) above 50 mm Hg.

Monitoring procedures. All the patients received midazolam 0.03 mg/kg intravenous (iv) for premedication. Electrocardiography (ECG), heart rate (HR), systolic arterial blood pressure (SAP), mean arterial pressure (MAP), end tidal CO2 (ETCO2) and peripheral oxygen saturation (SPO2) were monitored (Odam Physiogard SM 786, Wissenbourg, France) noninvasively. Cardiac output (CO) was measured with a noninvasive device (NICO, Novametrix Medical Systems Inc., Wallingford, Connecticut, USA). Depth of anesthesia was measured by depth of anesthesia (SNAP index score) (Nicolet Biomedical, VIASYS Healthcare, Madison, Wisconsin, USA).

Anesthetic management. In both groups, anesthesia was induced with propofol after administering lidocaine hydrochloride 0.5 mg/kg iv. It was started at a bolus dose of 2-2.5 mg/kg iv and was titrated until unresponsiveness to verbal commands was achieved, and SNAP index score was maintained between 40-60%. In all the patients, tracheal intubation was facilitated after neuromuscular blockage was provided with 0.6 mg/kg rocuronium iv. The O_2 (50%) was administered with air at a flow rate of 4 L/min. Ventilation was adjusted to keep $ETCO_2$ within normal range (40±5 mm Hg) and the tidal volume at 6-8 ml/kg, respiratory rate at 10-12 breath/min by intermittent positive pressure ventilation (IPPV). In group RP, after 1 mg/kg bolus dose of remifentanil over 30 seconds, continuous infusion of remifentanil was started at an infusion rate of 0.1-0.5 μg/kg/min iv. In group RP-E, 500 μg/kg bolus dose of esmolol was given over 30 seconds and continuous esmolol infusion of 100-300 μg/kg/min and also remifentanil infusion of 0.1-0.5 μg/kg/min was started. For maintenance of anesthesia in group RP, propofol (4-10 mg/kg/h) and remifentanil (0.1-0.5 μg/kg/min) infusions were given to keep MAP between 50-65 mm Hg and SNAP index score at 50±10%. For group RP-E, propofol (4-10 mg/kg/h) and remifentanil (0.1-0.5 mg/kg/min) infusions were maintained to keep the SNAP index score at 50±10% and then 100-300 μg/kg/min of esmolol infusion was applied to keep MAP at 50-65 mm Hg. The operation was initiated 10 minutes after

lidocaine hydrochloride 2% (Jetokaine Ampul®-Adeka ilac ve kimyasal urunler A,S, Istanbul, Turkey) with adrenaline was given for infiltration anesthesia.

Parameters and recording times. The HR, SAP, MAP, SPO_2 and SNAP index scores were recorded at the following time points: on arrival at the operating room as control (T0), 3 minutes after the induction (T_1), 3 minutes after the intubation (T_2), 3 (T_3), 6 (T_4) and 10 (T_5) minutes after the local anesthetic infiltration, 3 (T_6), 6 (T_7), 10 (T_8), 15 (T_9), 30 (T_{10}), and 45 (T_{11}) minutes after the surgical incision, and 3 (T_{12}) minutes after the extubation. The CO and $ETCO_2$ values were recorded at all the time points, except when the patients were not intubated (T_0, T_1, and T_{12}). All the operations were performed by the same surgeon to ensure consistency in the evaluation of the surgical field. He was blinded to the hypotensive agent used and the monitor recording the hemodynamic variables. The surgeon evaluated the quality of the operative field using a predefined average category scale (ACS).[7] This evaluation was made when the MAP reached the target level and was maintained for at least 10 minutes. The target was to maintain the ACS between 0 and 3. Propofol was discontinued in both groups and esmolol infusion was ceased in group RP-E at the last surgical suture. Remifentanil infusion was maintained at an infusion rate of 0.05-0.1 μg/kg/min until the nose was covered with plaster in both groups. Extubation was performed after neuromuscular block was reversed at the end of the surgery with neostigmine (0.05 mg/kg) and atropine (0.015 mg/kg) iv. Durations of the anesthesia, operation, controlled hypotension, and for reaching controlled hypotension were recorded. Recovery characteristics such as awakening and orientation were determined at one-minute intervals from discontinuation of the anesthetics. Drug consumptions (propofol, remifentanil, esmolol, rocuronium) were recorded. After the extubation, the patients were transferred to the postanesthesia care unit (PACU), where further recordings were carried out by an independent observer blinded to the anesthetic regimen. During one hour of postoperative period, hemodynamic parameters, shivering, postoperative nausea, and vomiting (PONV) were recorded. Every 10 minutes until discharge from PACU, the patients were asked to indicate their level of pain on a visual analog scale (VAS) of 10 mm (0=no pain, 10=unbearable pain). Pain (VAS>4) was treated with 1 mg/kg of pethidine intramuscularly. Recovery characteristics were assessed with the Aldrete recovery score (ARS). The moment when ARS reached 9 was noted, and considered as an index to discharge from the PACU. Surgeon and patient satisfaction were rated on a scale of 0 to 10.

Statistical analysis. Statistical analysis was performed using SPSS for Windows 11.5. Demographic data and differences between the groups were tested using unpaired student's t-test and Chi square test. Hemodynamic changes within each group were compared using paired t-test. Comparison of the VAS value changes was made using Wilcoxon test within each group and Mann-Whitney U test between the 2 study groups. Fisher's Exact test was used to compare the other parameters, including side effects, and complications. All the data were presented as mean (±SD) or percentage (%). A p-value <0.05 was considered statistically significant.

Results. There were no significant differences between the groups with respect to demographic data and the durations of operation, anesthesia, reaching controlled hypotension, and controlled hypotension time (**Table 1**).

Heart rate (HR). The control HR value was lower in group RP-E than in group RP. The HR values were significantly different between 2 groups at the third (p=0.05), sixth (p=0.003), and tenth minutes after the local anesthetic infiltration (p=0.001), at the third (p=0.009), sixth (p=0.013), tenth (p=0.003), fifteenth (p=0.002), thirtieth (p=0.003), and forty-fifth minutes after the surgical incision (p=0.006), and one minute after the extubation (p=0.001). They were lower in group RP-E than in group RP (**Figure 1**).

Systolic arterial pressure (SAP). The SAP values were significantly different within group RP at all the recording times compared to the control value (p=0.0001). They were significantly different between 2

Table 1 - Demographic characteristics and perioperative data (mean± SD [min-max]).

Parameters	Group RP (n=20)	Group RP-E (n=20)
Age (year)	28.90 ± 7.31 (18-43)	29.50 ± 8.25 (19-48)
Weight (kg)	59.85 ± 7.31 (49-72)	62.50 ± 6.58 (55-70)
Height (cm)	164.00 ± 7.61 (150-178)	164.05 ± 8.03 (150-173)
Gender (F/M)	3/17	3/17
Duration of anesthesia (min)	86.70 ± 7.42 (75-100)	84.05 ± 8.44 (65-95)
Duration of operation (min)	59.45 ± 9.98 (45-83)	60.50 ± 8.64 (54-105)
Duration of reaching controlled hypotension (min)	7.35 ± 3.51 (3-13)	6.25 ± 4.15 (3-16)
Duration of controlled hypotension (min)	68.85 ± 12.18 (43- 87)	66.5 ± 12.76 (45-106)

Non-significant, comparison between the groups. Group RP - a remifentanil infusion of 0.1-0.5 μg/kg/min was titrated, following a bolus of 1 μg/kg, group RP-E - an esmolol infusion of 100-300 mg/kg/min was titrated, following a bolus of 500 μg/kg

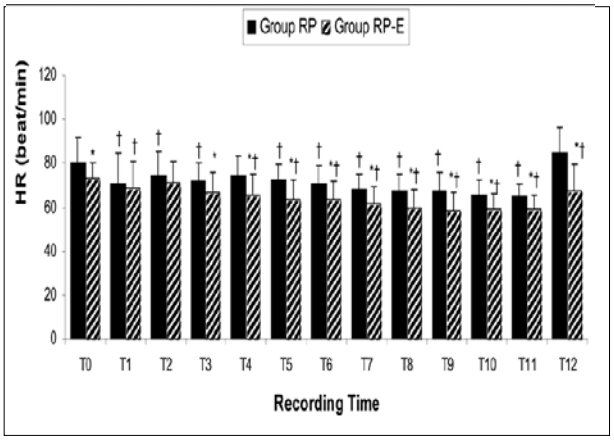

Figure 1 - Distribution of heart rate (HR) values (beat/min) (Mean± SD). *non-significant, compared between the groups, †non-significant, compared to control values. Group RP - a remifentanil infusion of 0.1-0.5 µg/kg/min was titrated, following a bolus of 1 µg/kg, group RP-E - an esmolol infusion of 100-300 mg/kg/min was titrated, following a bolus of 500 µg/kg.

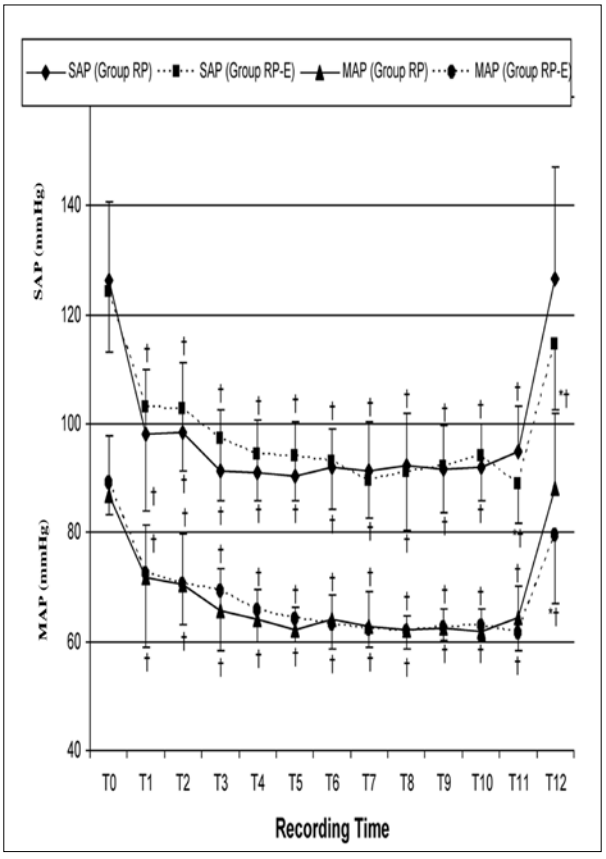

Figure 2 - Distributions of SAP and MAP values (mmHg) (Mean± SD). *non-significant, compared between the groups, †non-significant compared to control values. Group RP - a remifentanil infusion of 0.1-0.5 µg/kg/min was titrated, following a bolus of 1 µg/kg, group RP-E - an esmolol infusion of 100-300 mg/kg/min was titrated, following a bolus of 500 µg/kg, SAP - systolic arterial pressure, MAP - mean arterial pressure

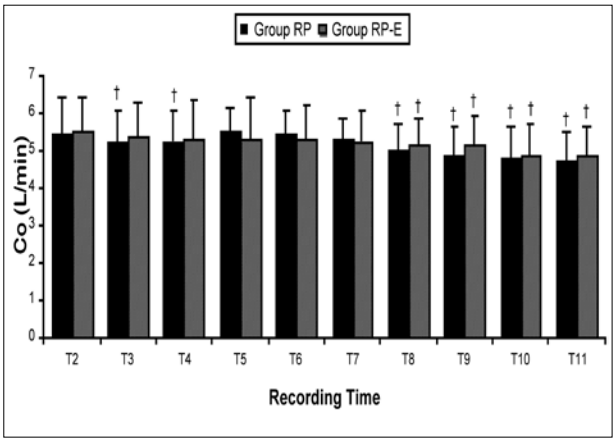

Figure 3 - Distributions of CO values (Mean± SD). Non-significant compared between the groups, †non-significant compared to control values. CO - cardiac output, group RP - a remifentanil infusion of 0.1-0.5 µg/kg/min was titrated, following a bolus of 1 µg/kg, group RP-E - an esmolol infusion of 100-300 mg/kg/min was titrated, following a bolus of 500 µg/kg.

Table 2 - Consumption of anesthetic drugs (mean±SD [min-max]) (N=20).

Drugs	Group RP	Group RP-E
Total propofol (mg)	666.60 ± 131.50 (450-990)	634.5 ± 126.5 (440-840)
Total rocuronium (mg)	46.5 ± 7.62 (40-60)	47.00 ± 7.327 (30-60)
Total remifentanil (µg)	2120.5 ± 130.51 (1200-2900)	890.0 ± 269.3* (500-1300)

*p=0.0001 compared between the groups

Table 3 - Recovery characteristics during early period (mean±SD [min-max]) (N=20).

Characteristic	Group RP	Group RP-E
Extubation time (min)	3.70 ± 1.92 (2-10)	4.65 ± 1.84 (2-8)
Respond to verbal command time (min)	4.30 ± 2.81 (2-14)	5.00 ± 2.10 (2-8)
Spontaneous eye opening time (min)	4.45 ± 2.62 (2-13)	5.05 ± 2.03 (2-8)
Time of correctly telling name (min)	4.80 ± 3.00 (2-15)	6.00 ± 2.07 (2-9)
Time of correctly telling place (min)	4.90 ± 3.070 (2-15)	6.19 ± 2.13 (2-9)
Time of correctly telling date (min)	4.95 ± 3.03 (2-9)	6.15 ± 2.13 (2-15)
Aldrete ≥9 time (min)	7.35 ± 3.4 (2-13)	8.45 ± 2.98 (2-13)

*non-significant compared between the groups. Group RP - a remifentanil infusion of 0.1-0.5 µg/kg/min was titrated, following a bolus of 1 µg/kg, group RP-E - an esmolol infusion of 100-300 mg/kg/min was titrated, following a bolus of 500 µg/kg

Table 4 - Side effects at anesthesia induction, maintenance and recovery (%) (N=20).

Side effects	Group RP	Group RP-E
At induction		
Bradycardia	15	10
Allergic reaction	10	10
Muscle rigidity	10	5
At maintenance		
Bradycardia	0	15
Hypotension	5	5
At recovery		
Hypotension	5	25
Bradycardia	5	15
Dyspnea	20	0
Allergic reaction	15	0
Agitation	10	0
Nausea/vomiting	15	20
Shivering	35	5*
Gastric irritation	10	10
Awareness	1	0

*p<0.022 compared between the groups. Group RP - a remifentanil infusion of 0.1-0.5 μg/kg/min was titrated, following a bolus of 1 μg/kg, group RP-E - an esmolol infusion of 100-300 mg/kg/min was titrated, following a bolus of 500 μg/kg

groups at the forty-fifth minute of the operation (group RP: 94.95±8.41, group RP-E: 88.70±6.90) (p=0.014) and during the extubation time (group RP: 126.75± 20.30, group RP-E; 114.50±11.78) (p=0.025) (**Figure 2**).

Mean arterial pressure (MAP). The MAP values were significantly lower in both groups at all the recording times compared to the control value (p=0.0001), except after the extubation in group RP. There were no statistically significant differences between the MAP values of the groups at the control times and all the other anesthesia periods except after the extubation (group RP; 88.00±13.81, group RP-E; 79.45±12.58 mmHg, p=0.048). They were significantly higher after the extubation in group RP (**Figure 2**).

Cardiac output (CO). The CO values were within clinically normal range (4-8 L/min) during the study. Although there were no differences between the groups during all the periods of the anesthesia, there were significant decreases within the groups (**Figure 3**).

Consumption of anesthetic drugs. The amount of propofol used at the induction of anesthesia to maintain SNAP index values at 50±10% was similar in group RP and group RP-E (129±14 and 128±15 mg). Rocuronium consumption was similar in both groups, but the total amount of remifentanil used was significantly lower in group RP-E than in group RP; (p=0.0001) (**Table 2**).

Average category scale (ACS, 0-5). The amount of blood loss did not differ between the groups, but the ACS decreased in group RP-E (2.80±0.95 versus 3.60± 0.94) (p=0.011).

Recovery characteristics. After the extubation, the VAS was ≥4 at 17.35±20.3 min in Group RP, and at 47.5±34.8 min in group RP-E (p=0.0011). There were no differences between the groups in terms of the extubation time, spontaneous eye opening, response to verbal command time, name, place and day orientations, and ARS>9 time (**Table 3**). Significantly more shivering was observed in group RP than in group RP-E (p=0.022). The rates of the other effects were not significantly different (**Table 4**). Although the patients satisfaction was the same in both groups (8±1), the satisfaction of the surgeons was higher in group RP-E (8±1) than in the other group (7±1) (p=0.003).

Discussion. The results of this study have indicated that applying esmolol along with propofol-remifentanil leads to a decrease in remifentanil consumption, without a decrease in cardiac output during hypotensive anesthesia or a change in recovery characteristics during the postoperative period. Various methods and different pharmacological drugs are used to optimize these factors.[1,2,7,16] Among these drugs, esmolol has been used to achieve induced hypotension, especially during middle ear, endoscopic sinus, spinal, tympanoplasty and rhinoplasty surgeries.[7,8,17,18] It is known that total intravenous anesthesia with propofol and remifentanil allows controlled hypotension and achieves a bloodless surgical site.[4,6] Remifentanil has been found to be as effective as esmolol in reaching the target systolic blood pressure of 80 mm Hg.[4] We also observed that the time for reaching the same target mean arterial blood pressure was similar with both remifentanil and esmolol.

In our study, although lidocaine with adrenaline was infiltrated to the surgical field before the operation, an increase in blood pressure or HR was not observed in either group. This might have been because of the fact that the anesthetics blocked the hemodynamic response to adrenaline, or adrenaline caused vasoconstriction and decreased self absorption. Normally, invasive blood pressure should be monitored during controlled hypotension. Because in this study, informed consent could not be obtained from our patients for invasive hemodynamic monitoring, the blood pressure and CO were observed non invasively. This is an important limitation of the study. Esmolol is reported to enhance the analgesic effects of opioids, but no analgesic effect has been reported when the drug is given alone.[9,11] Orme et al[19] showed that when propofol is infused without an opioid, there is no evidence to suggest that

esmolol affects anesthetic requirement during propofol anesthesia. Esmolol reduced the amount of propofol required to prevent response to skin incision when given with opioids.[20] In our study, in which esmolol or remifentanil was titrated in each group according to the target blood pressure, the total amount of remifentanil used was significantly lower in the esmolol group. Esmolol is a hypotensive agent that induces hypotension without reflex tachycardia. It should be noted that tachycardia increases myocardial oxygen consumption and shortens the diastolic period. This dual effect causes more stress than an increase in blood pressure. Another study found that esmolol decreased heart-rate from 76 to 63 beat/min and 78 to 66 beat/min.[7] In the present study, esmolol was associated with a significant decrease in heart rate (from 73 to 68 beat/min) without reflex tachycardia during hypotensive period. Esmolol possesses negative inotropic and chronotropic effects, thereby decreasing CO in healthy patients. This decrease in CO is dose dependent and was observed with both 100 and 200 mg continuous infusion of esmolol.[21] Since septorhinoplasty is an operation that is carried out under controlled hypotension, and invasive procedures are not routinely used, noninvasive CO monitoring is a good choice for this type of operations. In our study, a statistically significant decrease was observed in in the HR of group RP-E compared to the control value, but the control value of CO could not be technically measured. Therefore, a comparison of the esmolol-associated reduction of CO values was not possible. Furthermore, the CO changes during the 3-minute cycle could not be measured due to this property of the non-invasive CO monitor. These technical disadvantages are the other important limitation of our study. However, all the values of CO were within normal clinical range.

ß-blockers can mask the signs of light anesthesia and thus, increase the risk of intraoperative awareness. For monitoring of anesthesia depth, both SNAP and BIS devices are safer than MAP and HR monitoring.[22,23] In our study, depth of anesthesia was observed with SNAP monitor to sustain the target hypnotic level, and remifentanil was titrated according to depth of anesthesia especially in the esmolol group. Thus, while esmolol was used as a hypotensive drug instead of remifentanil, the consumption of this opiod was lower. When esmolol is compared to remifentanil, recovery times are not different.[24] In our study, which compared esmolol and remifentanil, the recovery times of both groups were also similar. Our results were parallel to the findings of Coloma et al.[24]

In conclusion, both esmolol and remifentanil successfully reached and maintained target blood pressure for controlled hypotension by providing hemodynamic stability during the operation. Applying esmolol along with propofol-remifentanil leads to a decrease in remifentanil consumption, and it does not decrease CO during controlled hypotensive anesthesia or change the recovery characteristics during the postoperative period.

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