RESEARCH ARTICLE
DOI: 10.26650/Tr-ENT.2023.1267115
The Turkish Journal of Ear Nose and Throat 2023;33(2):26-32

Effect of Controlled Hypotension by Esmolol Versus Remifentanil on Cerebral Oxygen Saturation in Patients Undergoing Endoscopic Sinus Surgery: A Randomized Clinical Trial*

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Citation: Altun D, Unsal S, Aydemir L, Kara H, Turhan O, Camci AE. Effect of controlled hypotension by esmolol versus remifentanil on cerebral oxygen saturation in patients undergoing endoscopic sinus surgery: a randomized clinical trial. Tr-ENT 2023;33(2):26-32. https://doi.org/10.26650/Tr-ENT.2023.1267115

ABSTRACT

Objective: In this prospective, single blind-randomized study, we aimed to investigate the effect of controlled hypotension by esmolol vs. remifentanil on cerebral oxygen saturation (rSO2) by near-infrared spectroscopy (NIRS) in patients undergoing functional endoscopic sinus surgery (FESS).

Material and Methods: One hundred fifty patients undergoing elective FESS under controlled hypotension were evaluated for study inclusion. Group allocation was performed in a randomized fashion. Controlled hypotension was provided using continuous remifentanil (Group R) or esmolol (Group E) infusion. rSO2 was assessed during controlled hypotension by NIRS monitoring.

Demographic data, hemodynamic values, and rSO2 were recorded preoperatively, postinduction 5th min, intraoperatively (10,20,30,45,60,90 minutes), and 5 and 10 minutes after stopping hypotensive agents. The duration of surgery and anesthesia and surgeon satisfaction score were also recorded.

Results: 126 patients were included in the study. Among the demographic data, only weight was found significantly different between the groups. The unfortunate fact is that there was no significant difference in the mean of minimum rSO2(p=0.186) and also in the median of the minimum mean arterial blood pressure (MAP) (p=0.312) between Group R and Group E. Surgeon satisfaction score was significantly higher in Group R (p<0.001).

rSO2 (p<0.001, R2=0.67) was detected as the best predicting factor by the multiple regression model. While Heart rate (HR), MAP, and pre-induction rSO2 added statistically significantly to the prediction(p<0.001), the type of hypotensive drug did not (p=0.979).

Conclusion: Esmolol and remifentanil used for controlled hypotension did not cause significant rSO2 changes. Among the factors affecting rSO2 MAP, HR, and pre-induction rSO2 were detected, while the best predictor factor was pre-induction rSO2. Remifentanil provides a better surgical field than esmolol according to the VAS scale.

Keywords: Endoscopic sinus surgery, controlled hypotension, remifentanil, esmolol, monitorization

INTRODUCTION

In order to create a bloodless surgical environment and reduce blood loss, an effective hypotensive anesthesia regimen is essential during functional endoscopic sinus surgery (FESS). The goal of controlled hypotension is to maintain arterial blood pressure low enough to reduce bleeding, to provide stable hemodynamics to maintain cerebral auto-regulation unaffected during stressful surgical events. Impairment of autoregulation during controlled hypotension might increase the rate of oxygen extraction. Therefore, cerebral oxygen

*This study was registered to ClinicalTrials.gov (Registration number NCT02967029)

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Submitted: 23.03.2023 • **Revision Requested:** 29.05.2023 • **Last Revision Received:** 31.05.2023 • **Accepted:** 09.06.2023 • **Published Online:** 16.06.2023

saturation (rSO_2) monitorization becomes mandatory to assess cerebral oxygenation, and routine clinical evaluation of cerebral oxygenation remains a challenge.

Several studies have focused on the type of anesthetic drugs and their effect on controlled hypotension (1-5). However, the impact of hypotensive anesthesia on cerebral perfusion and oxygenation and its influence on cognitive function following surgery has not been satisfactorily described yet. Furthermore, the association between rSO_2 and controlled hypotension has not been studied in patients undergoing FESS.

Over the past decade, cerebral oxygen monitors using the near-infrared spectroscopy (NIRS) technique have been developed to evaluate cerebral perfusion by determining real-time changes in rSO_2 (6).

In our clinical routine, esmolol and remifentanil are the most frequently used agents for achieving controlled hypotension during oto-rhinological surgery. Therefore, the current prospective randomized, single-blind study aimed to investigate the effect of controlled hypotension provided by esmolol vs. remifentanil on rSO2 via utilizing NIRS in patients undergoing FESS.

MATERIAL and METHODS

Following approval from the local ethics committee (Date: 18.01.2013, No: 2), written informed consent was obtained from each participant prior to the process. This was a randomized comparative study conducted in 126 American Society of Anesthesiology (ASA) I and II adult patients aged between 18 and 65 years who were operated on for elective FESS under controlled hypotension. The current study was registered to ClinicalTrials.gov (registration number NCT02967029). Exclusion criteria included patients with hypertension, coronary artery diseases and cerebral inadequacy (documented clinically or radiologically), body mass index (BMI)> 30 kg m^{-2}, anticoagulant drug use, allergy to any of the study agents and operations shorter than 60 minutes. Patients were randomized to two groups to receive either remifentanil or esmolol to maintain the mean arterial blood pressure (MAP) between 60-65 mmHg.

After the premedication by intravenous midazolam 0.05 mg kg^{-1} 15 min before anesthesia induction, a balanced electrolyte solution of 5 ml kg^{-1} h^{-1} was initiated to all patients. Routine monitoring including electrocardiography (ECG), noninvasive blood pressure, and peripheral oxygen saturation (S_pO_2) was utilized. In addition, cerebral oxygen saturation (rSO_2) monitoring (INVOS system: Covidien, Levallois-Perret, France) was initiated prior to induction of anesthesia. An adult probe was cited in the median frontal zone as stated in the producer's instruction.

Following three minutes of tidal breathing preoxygenation, for anesthesia induction intravenous 2 mg kg^{-1} propofol, 2 µg kg^{-1} fentanyl was administered, and 0.6 mg kg^{-1} rocuronium was given to facilitate the endotracheal intubation. Ensuring the endotracheal intubation, ventilation was adjusted to keep the $PETCO_2$ at a level of 35-40 mmHg.

Anesthesia was maintained with sevoflurane (MAC set to 0.8 to 1) in a 50% oxygen-N_2O mixture. Later, as a part of the treatment regimen, either remifentanil or esmolol was administered to provide controlled hypotension at a targeted MAP value of 60 mmHg during the anesthesia period.

In group esmolol (Group E), following a loading dose of 0.5 mg kg^{-1} iv esmolol right after anesthesia induction a continuous esmolol infusion at a rate of 5-15 mg kg^{-1} min^{-1} was initiated. The maximum infusion rate is titrated to 300 µg kg^{-1} min^{-1} to maintain a target MAP of 60-65 mmHg. In group remifentanil (Group R) following a loading dose of 0.5 µg kg^{-1} iv remifentanil was administered at induction followed by a continuous remifentanil infusion rate of 0.1- 0.5 µg kg^{-1} min^{-1}. It was titrated between 0.1- 0.5 µg kg^{-1} min^{-1} to achieve a target MAP of 60-65 mmHg. No surgical stimulus was applied for 5 minutes after the initiation of the study drugs in both groups.

Baseline rSO_2 was noted just before anesthesia induction prior to additional O_2 administration. Cerebral desaturation

Table 1: Demographic data and duration of surgery

	Group R (n=63)	Group E (n=63)	P-value
Age (years)	27 (36-43)	29 (39-50)	0.073
Sex (n)			0.279
Male	33	40	
Female	30	23	
ASA (n)			0.061
I	59	51	
II	4	12	
Weight (kg)	61 (65-76.5)	67 (77-86)	<0.001
BMI (kg/m^2)	24 (23-26	26 (24-29	<0.001
Duration of operation (min)	85 (100-120)	75 (90-120)	0.093

P values show the results of Friedman test. ASA: American Society of Anesthesiologists, BMI: Body Mass Index, R: Remifentanil, E: Esmolol

was described as a decrease of rSO_2 to more than 20% of the baseline value over a period of 15 seconds and/or longer (7). If cerebral desaturation appeared, it is compensated by halving the remifentanil and esmolol infusion doses, and 250 ml bolus intravascular fluid was administrated to increase the MAP. A bolus dose of ephedrine 5 mg iv and atropine 0.1 mg kg^{-1} iv were administered to treat hypotension below the target MAP and bradycardia (heart rate (HR) ≤ 45 beats min^{-1} lasting longer than one minute, respectively. To provide coherence in the prediction of the surgical field, each operation was performed by the same specialist surgeon.

Although the anesthesiologist was not blind to the treatment allocation, the surgeon and patients were blind. The surgeon's surgical site satisfaction was measured via an 11-point scale (0= no bleeding, virtually bloodless field; 10= uncontrolled bleeding). The surgeon scored the surgical site in terms of blood loss and dryness 10 minutes after achieving the target MAP of 60-65 mmHg.

Hemodynamic data (Diastolic blood pressure (DBP), MAP, systolic blood pressure (SBP), HR), S_pO_2 and rSO_2 were noted as a baseline value before the induction of anesthesia, following the induction of hypotensive and anesthetic agent's 5th min, per operative (10th, 20th, 30th, 45th, 60th), and 5 and 10 minutes after the interruption of the hypotensive drugs. In addition, the duration of surgery, duration of anesthesia time, and surgeon satisfaction score were recorded.

Statistical analysis

Power analysis for two independent group comparisons was performed in G*Power (University of Düsseldorf-Düsseldorf) to determine an adequate sample size with an alpha of 0.05, a power of 0.8, and a medium effect size (d = 0.5). Based on the assumptions above, the required sample size was calculated as 118 (59 for each group). We decided to invite 150 patients to compensate for the possible dropouts.

We compared hemodynamic measurements (HR, MAP, and rSO_2) based on the time of measurement between the remifentanil and esmolol groups. Additionally, each parameter was compared between the time intervals in the groups separately. We also investigated the differences in demographic data (mentioned above), duration of surgery, minimum MAP, minimum rSO_2, and surgeon satisfaction scores between the groups.

Shapiro-Wilk test was performed for normality; data were analyzed as mean (standard deviation) for each parameter with a normally distributed and as median (first to third quartile) for each parameter without a normally distributed data. Mann-Whitney U test and independent t-test were used for intragroup comparisons. Friedman test was performed for intergroup analysis. A chi-square test of homogeneity was performed for categorical variables. A pairwise comparison was performed with a Bonferroni correction for multiple comparisons. In addition, we investigated the relative contribution of some parameters (the type of the hypotensive drug, HR, MAP, and pre-induction rSO_2) to the variation in rSO_2 during operation. A multiple regression was run. The statistically significant difference of the test was $P < 0.05$.

RESULTS

In the study, 150 patients aged between 18-65 years undergoing FESS were invited to study and assessed for study eligibility. Among them, four patients refused study participation. Fourteen patients were excluded because their operation times were shorter than 60 minutes. Six patients were not eligible due to persistent hypertension: four of them were in Group R [4/63 (6%)], and two of them were in Group E [2/63(3%)]. The data of these patients were not further

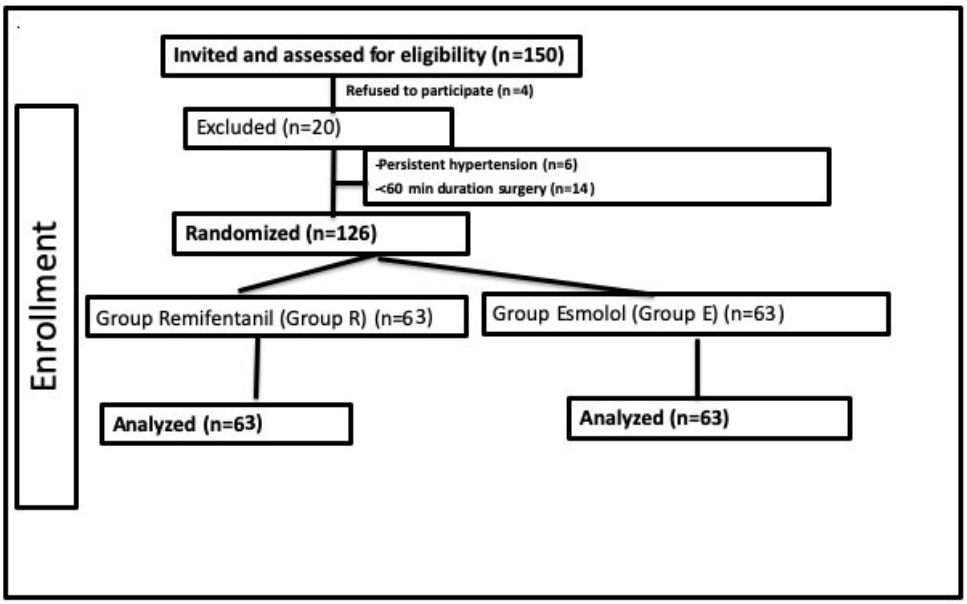

Figure 1: Study of flow diagram

Table 2: Comparison of hemodynamics based on the time of measurement between and within Remifentanil and Esmolol groups [a]

		Pre-ind. (basal level)	5 min. after ind.	Start of Op.	10th min.	20th min.	30th min.	45th min.	60th min.	End of Op.	P-values[+]
HR	R	87 (78-91)	77 (71-85)	73 (65-78)*	68 (63-74)*	64 (60-71)*	63 (58.5-70)*	64 (61-73)*	66 (61-72.5)*	67 (62.5-74)*	<0.001
	E	85 (80-87.5)	78 (73-80)	72 (66-77)*	67 (61-70)*	66 (61.5-69)*	64 (60-68)*	63 (59-66)*	63 (59-67)*	61 (58.5-66.5)*	<0.001
MAP	R	87 (83-91)	74 (70-77.5)	68 (65-71)*	65 (61-69)*	63 (60-66)*	63 (60.5-65)*	61 (58-63)*	64 (61-66)*	63 (61-66)*	<0.001
	E	86 (83.5-89)	77 (72-80)	71 (68-75)*	67 (63.5-71)*	67 (62-70)*	66 (63-68)*	63 (60-66)*	62 (60-65)*	63 (61-65)*	<0.001
rSO^2	R	71 (66-76)	74 (67-81)	70 (63-78.5)	68 (62.5-74)	67 (61-73.5)*	67 (65-74)*	67 (64-73)*	67 (64-74)*	67 (63-74)*	<0.001
	E	77 (71.5-84.5)	82 (79-86)*	78 (70-83.5)	73 (71-81)	73 (68-79)	72 (68-78.5)	71 (65-77)*	70 (64-77)*	69 (64-75)*	<0.001
Delta $rSO^{2\#}$	R		2 (-1 - 7)	-1 (-3 - 3)	-2 (-5 - 0)	-5 (-7 - -1)	-3 (-6 - -1)	-4 (-8 - -0.5)	-4 (-7.5 - -1.5)	-4 (-6 - -1)	
	E		3 (1 - 8)	-1 (-3 - 2)	-1 (-5 - 2.5)	-4 (-7 - 2)	-5 (-7 - 1)	-6 (-10 - -1.5)	-7 (-10 - -1)	-7 (-10 - -1)	

[a] Mann-Whitney U test was used to analyze between-subject variables. Friedman test was used to analyze within-subject variables. Data are presented as median (first to third quartile). Colored lines show where the statistically significant differences were seen between the groups. ($p<0.05$), [+]P values show the results of Friedman test, *Pairwise comparison (with Bonferroni correction) shows where the real difference is seen compared to basal level within each group, [#]Delta rSO_2 is calculated by extracting the measured level on each time from basal level. Within-subject comparing was not performed for Delta RSO_2 variable Abbreviations: ind: induction, min.: minute, Op.: Operation, HR: Hear rate, MAP: Mean arterial pressure, rSO_2: Cerebral oxygen saturation, R: Remifentanil, E: Esmolol.

Table 3: Summary of Multiple Regression Analysis

Variable	B	SE_B	Beta
Intercept	-25.406	3.021	
Type of the hypotensive drug	-0.012	0.465	-0.001
HR during operation	0.189	0.026	0.151*
MAP during operation	0.287	0.038	0.162*
Pre-induction RSO_2	0.888	0.023	0.788*

* $p<0.001$, B: Unstandardized regression coefficient, SE_B: Standard error of the coefficient, Beta: Standardized coefficient, [+]P values show the results of Friedman test, HR: Heart Rate
MAP: Mean Arterial Pressure, RSO_2: Cerebral Oxygen Saturation

used for statistical analysis. Finally, 126 patients completed the study and were analyzed (Figure 1).

There was a significant difference between the groups in weight among the demographic data (Table 1).

The significant fact in our findings is that the mean value of the lowest rSO_2 between Group R [65.70 (12.37)] and Group E [68.40 (10.29)] ($p=0.186$) was not statistically different (Figure 3). The median value of the minimum MAP was similar between Group R [60 (57-61)] and Group E [60 (57-64)] ($p= 0.312$) (Table II) (Figure 2). The surgeon was more satisfied with the surgical area in Group R [10 (9-10)] patients compared to Group E [8 (7-8)] patients ($p< 0.001$).

The multiple regression model enabled the detection of factors that had affected rSO2 during surgery and among four variables (type of the hypotensive drug, HR, MAP, and pre-induction rSO_2) pre-induction rSO_2 ($p < 0.001$, adjusted $R^2= 0.67$) was found as the best predicting factor. While HR, MAP, and pre-induction rSO_2 added statistically significantly to the prediction ($p< 0.001$), the type of hypotensive drug did not ($p=0.979$). The value of the slope coefficient for pre-induction rSO_2 was 0.89, which means that an increase in pre-induction rSO_2 of 1% is associated with an increase in rSO_2 of 0.89% during operation (Table III).

DISCUSSION

The interesting fact in the primary findings of the current study was that both esmolol and remifentanil did not cause significant rSO_2 changes during FESS surgery. Of all the factors affecting rSO_2, the best predictor was found to be pre-induction rSO_2. The others were heart rate and mean arterial blood pressure.

Finally, remifentanil has provided a better operative condition compared to esmolol according to the VAS scale assessed by the surgeon.

In the current study, the demographic profile of the patients between the groups was similar except for the patients' weight. However, this statistical significance has no clinical sense in our opinion because all drugs applied for premedication, induction, and maintenance of anesthesia were administered according to the patient's body weight.

This current study was designed to compare the most commonly used two agents for controlled hypotension and evaluate their effect on cerebral oxygenation monitored by

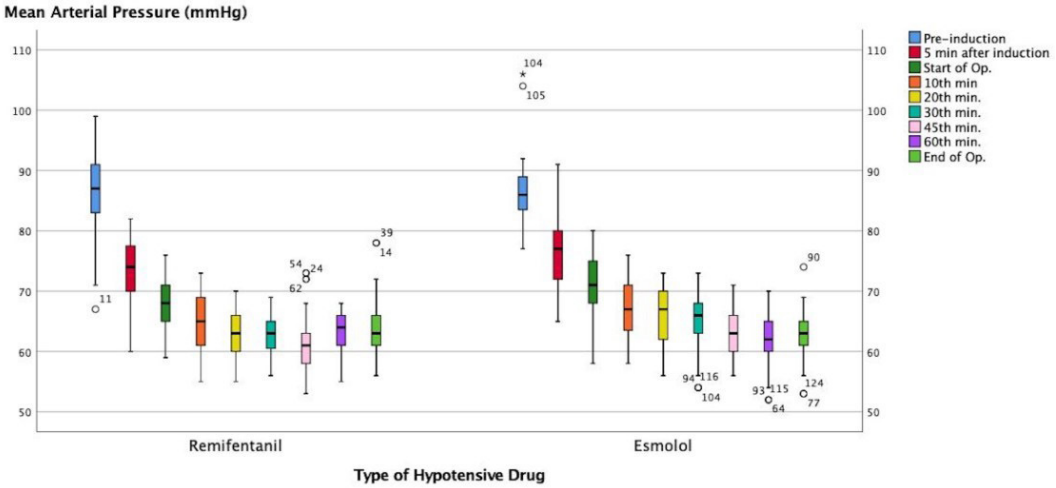

Figure 2: The analysis of mean arterial pressure based on the time of measurement between and Remifentanil and Esmolol groups.

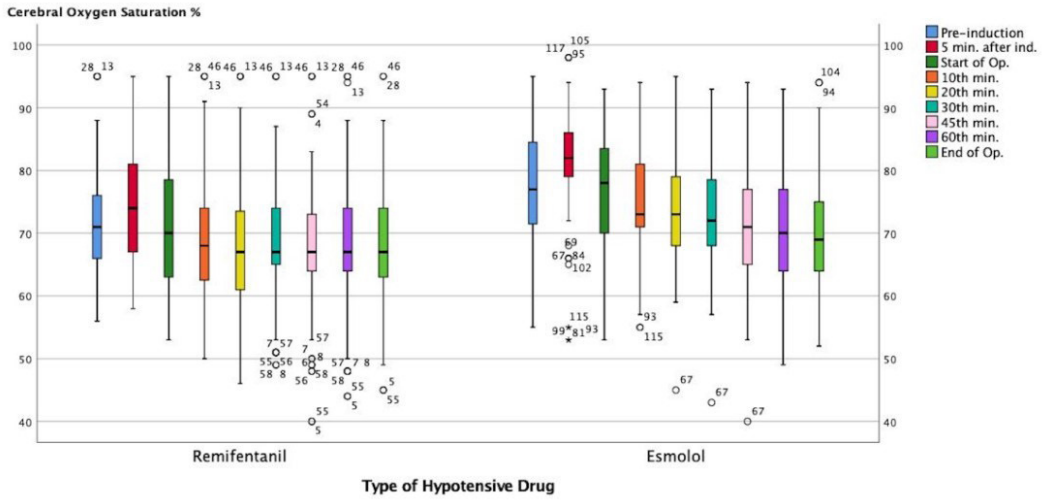

Figure 3: The analysis of cerebral oxygen saturation based on the time of measurement between and Remifentanil and Esmolol groups.

rSO_2. There are studies in the literature stating that immediate reduction in cerebral blood flow was observed when MAP was below 80 mmHg (8,9). Cerebral blood flow impairment which results in a fall on the rSO_2 may occur because MAP fall exceeds cerebral autoregulation lower boundary. In our study targeted MAP range (60-65 mmHg) was achieved with both drugs without any statistical difference. The baseline and the mean values of rSO_2 recorded throughout the study were also similar between groups. Our study shows that controlled hypotension in the FESS is reliable in terms of cerebral oxygenation, and this is similar to results of Farzanegan et al. (10). On the other hand, the agents' we used for controlled hypotension had a similar effect on mean rSO_2 without any statistically significant differences. However, the intragroup comparison has revealed that baseline rSO_2 levels in both groups were significantly different from the follow-up values, which is coherent with the literature (11-16). All mean rSO_2 levels, except the 5th minute after induction, were lower than basal levels without statistical significance. This increase at the 5th minute as was observed in a study by Farzanegan et al. may be associated with the commencement of relatively high FiO_2 exposure by preoxygenation followed by the start of mechanical ventilation (10). In addition, the study evaluated rSO_2 at each time interval. Although a statistically significant rSO_2 decrease compared to the basal level occurred at the 20th minute in group R and the 45th minute in group E this fall in rSO_2 is not clinically relevant, because the clinically meaningful cerebral desaturation was stated as reduction of 20% from baseline in different studies (17, 18).

Hemodynamic stability during hypotensive anesthesia is another important subject regarding another end-organ perfusion status beside cerebral circulation. There are numerous studies about controlled hypotensive agents in the

literature investigating this. Degoute et al concluded that the heart rate is lower, and the onset of hypotension is delayed with remifentanil in comparison with esmolol (19). Alkan et al compared esmolol, remifentanil, and nitroglycerin during controlled hypotension for FESS. They observed that the targeted MAP was reached faster, and the HR was lower with remifentanil (1). In our study, we achieved targeted MAP at the beginning of surgery and did not detect any differences between the groups in terms of mean HR and MAP.

Controlled hypotension is of paramount importance for better visualization of the surgical site, which may lead to a shorter surgery time and prevent complications in FESS. There are many reported trials assessing the influence of controlled hypotension on operative area visualization or bleeding. Although many studies showed that controlled hypotension was helpful for better surgical field or less bleeding (20-22) other results did not support the beneficial effects of controlled hypotension (23). A study investigating the effects of esmolol, remifentanil, and nitroprusside on middle ear blood flow deduced that esmolol reduced blood flow more than the others whereas remifentanil provided a better surgical field (24). This property of remifentanil as a controlled hypotensive agent has been reported (1). We found a significantly better surgical field in group R using the VAS scale which was evaluated by A senior surgeon in a single-blind manner (Group R [10 (9-10)] than Group E [8 (7-8)] ($p<0.001$)). Even though the difference was found statistically significant it may not affect the decision process regarding which agent should be preferred.

Heller et al. demonstrated a cross-correlation between $EtCO_2$ and rSO_2 but not MAP and rSO_2 (25). On the other hand, Farzanegan et al. found a cross-correlation between MAP and $EtCO_2$ with rSO_2 (10). In our study, we found a cross-correlation between MAP, HR, and pre-induction rSO_2 with rSO_2.

The study had some limitations first, there was no normotensive control group in the study, even though controlled hypotension is routinely used in almost all endoscopic sinus surgery in the absence of any contraindication. Secondly, the inhalation anesthesia technique we used may have created an effect on rSO_2. As the third, two hemispheres were not separately monitored, only one side monitoring was performed because of financial reasons. However, based on the literature, bilateral monitoring is not necessary for all procedures except for special cardiopulmonary bypass techniques such as aortic arch reconstruction or bilateral superior vena cavae operations (26).

Finally, results cannot be extrapolated to patients other than young and healthy.

CONCLUSION

Our study findings indicated that controlled hypotension provided with both esmolol and remifentanil is feasible in terms of cerebral oxygenation during endoscopic sinus surgery. We found that while the factors affecting rSO_2 were MAP, HR, and pre-induction rSO_2, it was determined that drugs did not affect rSO2, and the most important factor on rSO_2 during the operation was pre-induction rSO_2.

Although the results between the groups were similar, remifentanil provided a better surgical field than esmolol according to our evaluation with the VAS scale.

Ethics Committee Approval: This study was approved by Istanbul Faculty of Medicine Clinical Research Ethics Committee (Date: 18.01.2013, No: 2).

Informed Consent: Written informed consent was obtained.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- D.A., E.Ç., S.Ü.; Data Acquisition- S.Ü., L.A., Ö.T.; Data Analysis/Interpretation- L.A., H.K., Ö.T.; Drafting Manuscript- D.A., E.Ç.; Critical Revision of Manuscript- D.A., E.Ç.; Final Approval and Accountability- D.A., E.Ç.; Material or Technical Support- S.Ü., D.A., Ö.T.; Supervision- E.Ç., D.A.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: This study was funded by Istanbul University Research Center (IUBAPSIS)

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