Original Article

Effects of Smoking on Controlled Hypotension with Nitroglycerin during Ear-Nose-Throat Surgery

B Sinoglu, A Ersoy[1]

Anesthesiology and Intensive Care Department, Kelkit State Hospital, Gümüshane, [1]Anesthesiology and Intensive Care Department, Sultan 2, Abdülhamit Han Education and Reseach Hospital, Universty of Health Sciences, Istanbul, Turkey

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Abstract

Background and Aim: In this study, the aim was to research the effects of smoking habits on controlled hypotension administered with nitroglycerin during ear-nose-throat surgery. **Materials and Methods:** This study administered controlled hypotension with nitroglycerin and total intravenous anesthesia to a total of 80 patients undergoing septoplasty operations. The patients were divided into two groups of 40 non-smokers (Group 1) and 40 smokers (Group 2). Intravenous propofol infusion was used for anesthesia maintenance. Nitroglycerin with 0.25–1 μg/kg/min dose was titrated to provide controlled hypotension. During this process, the hemodynamic parameters of patients, total propofol and nitroglycerin amounts used, operation duration, and duration of controlled hypotension were recorded at the end of the operation. At the end of the operation, the surgeon assessed the lack of blood in the surgical field with Fromme Scale. **Results:** Fromme scale values were significantly higher in Group 2 compared to Group 1. The MAP values at 10, 20, 30 min, and end of operation were lower, while 10- and 20-min heart rate values were higher in Group 2 compared to Group 1. **Conclusion:** Nitroglycerin, chosen for controlled hypotension to reduce hemorrhage in the surgical field during nasal surgery, was shown to cause more pronounced hypotension and reflex tachycardia due to endothelial dysfunction linked to nicotine in patients who smoke. Despite lower pressure values in the smoking group, the negative effects of nicotine on platelet functions combined with similar effects of nitroglycerin to increase bleeding amounts.

Keywords: *Controlled hypotension, Fromme scale, nasal surgery, nitroglycerine, smoking*

Introduction and Aim

Though many harmful effects on human health have been proven scientifically, smoking is the type of substance addiction most commonly seen in nearly all societies. As cigarettes are legal to use and easily obtained, in addition to nicotine forming a habit in a short time and affecting not just the individual user but also those around them, it is a significant public health problem. Currently, associations between many diseases and smoking have been proven and globally large campaigns against the use of cigarettes have begun.

Cigarettes have many negative effects on many systems including the cardiovascular system. Nicotine and carbon monoxide found in cigarette smoke are the most effective components of the cardiovascular system. Nicotine affects carotid and aortic receptors increasing the release of adrenaline from the adrenal medulla and stimulating the autonomic ganglions to increase sympathetic tonus and cause a rise in blood pressure. Nicotine stimulates the sympathetic nervous system causing vasoconstriction. Many experimental and clinical studies have shown that nicotine causes endothelial injury and platelet function disorder.[1-6] Serum levels of the vasoconstrictor material

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Address for correspondence: Dr. A Ersoy, University of Health Sciences, Sultan 2, Abdülhamit Han Education and Reseach Hospital, Istanbul, Turkey.
E-mail: drersoy71@hotmail.com

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of endothelin-1 increase in a dose-linked fashion linked to smoking, while the serum levels of nitric oxide (NO) with vasodilator effects reduce as the duration of smoking increases.[7,8] Organic nitrates like nitroglycerin, affecting NO, were proven to have increased efficacy in areas with endothelial function disorder in a variety of studies.[9,10]

Controlled hypotension is applied in orthopedic, neurosurgery, and ear-nose-throat operations with the aim of reducing blood loss and ensuring a better view of the field for the surgeon. The application of controlled hypotension to improve surgical conditions by providing a bloodless field for nasal surgery is a frequently chosen method. With this aim, in addition to physiologic techniques like patient position and ventilation control, pharmacological agents like rapid and short-effect vasodilators (sodium nitroprusside, nitroglycerin), beta-blockers (propranolol, esmolol), ganglion blockers (trimethaphan) and high dose potent inhalation anesthetics (halothane, isoflurane) may be used.[11] Additionally, each method has its own unique disadvantages such as reflex tachycardia, rebound hypertension, tachyphylaxis, cyanide intoxication linked to sodium nitroprusside, the possibility of developing myocardial depression during esmolol administration, and delayed recovery from high-dose inhalation anesthetics.[12] Studies in recent years have revealed that TIVA provides a clearer surgical field.[13-15]

The primary aim of the study is to assess the efficacy and reliability of using nitroglycerine to induce controlled hypotension for ear-nose-throat surgery in terms of a bloodless surgical field among patients who smoke. The secondary aim of the study is to compare patients who do and do not smoke in terms of hemodynamic parameters and the amount of nitroglycerine used during controlled hypotension induced with nitroglycerine.

Materials and Methods

Our study received ethics committee permission and written informed consent was obtained from all patients. The study was completed in Ear-Nose-Throat surgery from June 12, 2017, to December 4, 2017. The study was planned as a prospective clinical study including a total of 80 cases; 40 who smoked actively and 40 who did not smoke. This study, with a prospective observational pattern, did not intervene with routine anesthesia administration in the ear-nose-throat operating room, cases were included in both groups in line with inclusion and exclusion criteria and were randomized to include the first and third cases of the day without any intervention to the surgery order. Inclusion criteria for the study were American Society of Anesthesiologists (ASA) group I and II, aged from 18 to 60 years, with planned elective septoplasty operation by the Ear Nose Throat Surgical Clinic, with no allergic history to medications mentioned in the materials and methods section and no history of coagulopathy. Patients evaluated as ASA group III or above, younger than 18 years and older than 60 years, with an allergy to medications used, and with known coagulopathy, and patients who had quit smoking were excluded from the study. The smoking group included patients with a continuous smoking history of 20/day for at least five years. Patients who smoked fewer cigarettes were excluded from the study [Figure 1].

Patients were evaluated for appropriateness with a visit 1-day preoperative, smoking habits were recorded and all patients were first informed verbally about the study and then voluntarily signed informed consent forms. Patients who did not smoke were classed in Group 1, while patients who did smoke were included in Group 2. Patients had no preoperative premedication administered.

Cases taken to the operating room had age, sex, ASA group, and body mass index (BMI) data and smoking habits recorded on the case report form. Standard ECG, heart rate (HR), noninvasive blood pressure (NIBP), and peripheral oxygen saturation (SpO_2) was applied (Dräger Infinity Delta Monitor). Intravenous access was provided by an 18 G cannula in the antecubital vein, with 0.9% isotonic sodium chloride solution infusion begun as maintenance fluid. Cases were preoxygenated with 100% oxygen for 2 min, and then intravenous 2 mg/kg propofol (Propofol 1% Fresenius, 200 mg/20 ml ampoule, Fresenius Kabi) and 1 μgr/kg fentanyl (Talinat, 0.5 mg/10 ml ampoule, VEM) for general anesthesia induction and 0.6 mg/kg rocuronium bromide (Muscuron, 50 mg/5 ml flacon, Koçak Farma) for muscle relaxation were administered. After endotracheal intubation, the placement and level of the endotracheal tube were confirmed with chest auscultation, then 6–8 ml/kg tidal volume, 10–12 respirations/min frequency, and $EtCO_2$ values of 32–35 mmHg were set as mechanical ventilation parameters and positive pressure ventilation was provided (Dräger Fabius® GS Premium). For the gas mixture, 40% oxygen and 60% air were used.

For total intravenous anesthesia, the infusion device (Plum 360™ Infusion Pump - Hospira MedNet™) had the patient's weight entered with a 5 mg/kg dose of propofol used for anesthesia maintenance. To provide controlled hypotension, 5 mg nitroglycerin (Perlinganit, 10 mg/10 ml ampoule, Adeka) was diluted in 45 ml 0.9% isotonic sodium chloride solution and the solution (0.1 mg/ml) was administered with the infusion device. Nitroglycerin infusion was titrated to 0.25–1 μg/kg/min dose interval to keep the MAP between 50 and 60 mmHg.

To provide a better field of view for the operation and reduce the amount of hemorrhage in the operation region, cases were given an almost 30° head-up position and the surgical team administered a standard dose of lidocaine-adrenalin infusion (0.5% lidocaine + 1/100000 adrenalin, 1–2 ml) to the nasal mucosa.

All patients had mean arterial pressure, heart rate, and peripheral oxygen saturation recorded preoperative, after intubation, in the intraoperative 5th, 10th, 20th, 30th min, and after extubation, while $EtCO_2$ levels were recorded after intubation, in the 5th, 10th, 20th, 30th minutes. Additionally, the total amounts of propofol and nitroglycerin used during the operation, additional medications administered, operation duration, controlled hypotension duration, development of severe hypotension, bradycardia/tachycardia, and other complications were recorded.

Peripheral oxygen saturation values falling below 95% were evaluated as hypoxia, $EtCO_2$ values above 45 mmHg were hypercapnia, MAP below 50 mmHg or more than 35% reduction in basal values was hypotension, HR above 110 beats/min or more than 20% above basal values was tachycardia and HR below 50 beats/min was evaluated as bradycardia.

Patients were administered 10 mg metoclopramide hydrochloride (Emoject 10 mg/2ml ampoule, Tüm-Ekip İlaç) and 1 mg/kg Tramadol hydrochloride (Madol 100 mg/2 ml ampoule, Koçak Farma) 10 min before the end of the operation. All infusions were stopped after nasal buffers were sutured. Muscle relaxant effects were reversed with a 2 mg/kg dose of sugammadex (Bridion®, 200 mg/2 ml flacon, Merck Sharp Dohme) and patients were extubated.

All operations were completed by the same surgical team. At the end of the operation, the surgical team, blind to which group the patient was in, was requested to grade the bloodless status of nasal mucosa during the whole surgical procedure according to 0–5 on the Fromme Bleeding Scale.[16] Scores and all other monitoring parameters were recorded on the case report form by an anesthesia nurse, again blind to the group the patient belonged to Table 1.

After patients were taken to the recovery unit, they were assessed again for nausea-vomiting, agitation, hypotension or hypertension, bradycardia, or tachycardia. Patients with a modified Aldrete score of ≥9 were transferred from the recovery unit to the ward [Table 2].[17]

Patients were visited in the ear-nose-throat ward during the postoperative 4th and 8th hours with vital signs like hypotension, hypertension, bradycardia, and tachycardia, and side effects of medication like nausea-vomiting, allergy, and headaches were questioned.

Power Analysis

When designing the study, for calculations of sample size, the standard effect size of the study was determined as 0.83. With 80% power and 5% error, calculations determined the groups should consist of at least 24 people, so $n = 40$ was determined. Power analysis was calculated based on Fromme scale measures to assess the amount of blood in the surgical field considering the primary aim of the study.

Statistical Analysis

After sufficient case numbers were reached, descriptive statistics for the study data were used to mean, standard deviation, median, minimum, maximum, frequency, and proportion values. The distribution of variables was measured with the Kolmogorov-Smirnov test. For analysis of quantitative independent data, the independent samples t-test and Mann-Whitney U test were used, while the Wilcoxon test was used for dependent quantitative data analysis and the Chi-square test was used for qualitative independent data analysis. Analyses used the SPSS 22.0 program. Statistical significance was evaluated at $P < 0.05$ level.

Results

The demographic data and BMI of cases in Group 1 and Group 2 in the study were found to be similar [Table 3].

There was no significant difference between the ASA classification, operation duration, controlled hypotension duration, total propofol, and nitroglycerin amounts used for the duration of the operations ($P > 0.05$). The Fromme scale values for Group 2 were statistically significantly high compared to Group 1 ($P < 0.05$) [Table 4].

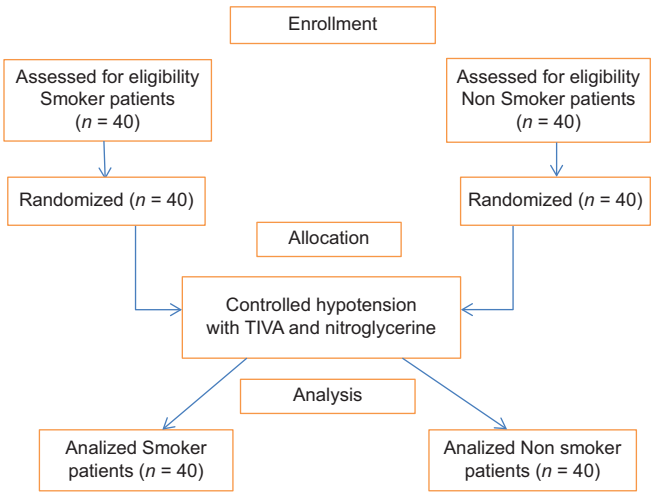

Figure 1: Effects of smoking on controlled hypotension with nitroglycerin during ear-nose-throat surgery: a prospective clinical trial, a consort flow diagram

Table 1: Fromme Hemorrhage Scale

	Fromme Hemorrhage Scale
0	No bleeding
1	Slight bleeding so blood evacuation not necesarry
2	Slight bleeding so sometimes blood has to be evacuated
3	Low bleeding so blood has to be often evacuated and operative field is visible for some seconds after evacuation
4	Average bleeding so blood has to be often evacuated, and operative field is visible only right after the evacuation
5	High bleeding so constant blood evacuation is needed, sometimes bleeding exceeds evacuation, and surgery is hardly possible.

Table 2: Modified Aldrete Scoring System

Activity level	4 Extremities	2
	2 Extremities	1
	No	0
Breathing	Able to breathe deeply and cough freely	2
	Dyspnea, shallow or limited breathing	1
	Apnea	0
Circulation (BP)	±20% of pre-anesthesia level	2
	±20% to 49% of pre-anesthesia level	1
	±50% of pre-anesthesia level	0
Conciousness	Fully awake	2
	Arousable on calling	1
	Unresponsive	0
SpO2	Maintains SpO2 >92% in ambient air	2
	Maintains SpO2 >90% with O2	1
	Maintains SpO2 <90% with O2	0

There were no significant differences in mean arterial pressure preoperative, after intubation, 5th min, and 5th min after extubation between Group 1 and Group 2 ($P > 0.05$). The mean arterial pressure in Group 2 in the 10th, 20th, and 30th min, and after the operation was significantly lower compared to Group 1 ($P < 0.05$) [Table 5].

In Group 1, the mean arterial pressure after intubation, in the 5th, 10th, 20th, and 30th min after the operation, and in the 5th min after extubation displayed significant falls compared to the preoperative period ($P < 0.05$) [Table 5].

In Group 2, the mean arterial pressure after intubation, in the 5th, 10th, 20th, and 30th min after

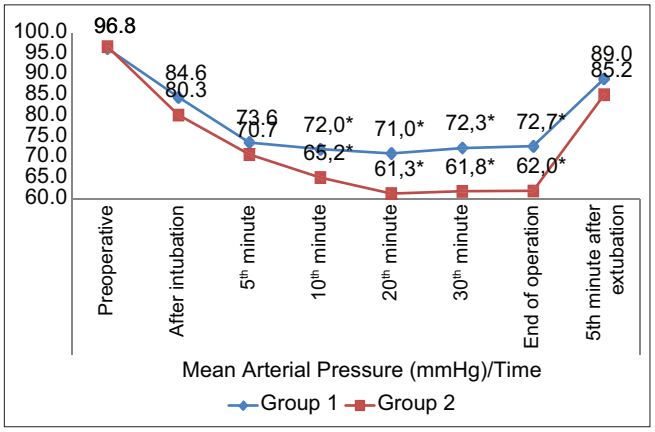

Figure 2: When the mean arterial pressure mean values of the groups were compared; There was a significant difference in the values of the 10th, 20th, and 30th min, and the end of the operation. (* $P < 0.05$)

Table 3. Demographic data and patient characteristics

		Group 1			Group 2			*P*	
		Mean±SD/*n*-%		Median	Mean±SD/*n*-%		Median		
Age		30,6±8,0		30,5	32,2±6,8		31,5	0,330	*t*
Sex	Woman	20	50,0%		14	35,0%		0,175	X^2
	Man	20	50,0%		26	65,0%			
BMI		24,1±3,3		23,2	22,0±2,4		22,2	0,528	m
ASA classification	I	35	87,5%		37	92,5%		0,456	X^2
	II	5	12,5%		3	7,5%			

t: *t* test/m: Mann-whitney *U* test/X^2: Chi-square test

Table 4: Fromme scale values, operation duration, controlled hypotension duration, total propofol and nitroglycerine amounts use

		Group 1			Group 2			*P*	
		Mean±SD/*n*-%		Median	Mean±SD/*n*-%		Median		
FROMME Score	I	19	47,5%		8	20,0%		0,018	X^2
	II	17	42,5%		24	60,0%			
	III	3	7,5%		8	20,0%			
	IV	1	2,5%		0	0,0%			
Operation duration		37,0±8,0		35,0	40,3±8,4		40,0	0,055	m
Controlled hypotension duration		24,9±6,5		25,0	25,4±6,5		25,0	0,684	m
Total Propofol amount used (mg)		174,3±63,4		160,0	175,7±50,1		172,5	0,560	m
Total Nitroglycerine amount used(µg)		1782±1013		1525	1829±1012		1570	0,912	m

m: Mann-whitney *U* test/X^2 :Chi-square test

Table 5: Preoperative, intraoperative and postoperative mean arterial pressure values for cases

	Group 1		Group 2		*P*	
	Mean±SD	Median	Mean±SD	Median		
Mean Arterial Pressure						
Preoperative	96,3±13,7	97,0	96,8±13,8	96,0	0,996	m
After intubation	84,6±14,6	82,0	80,3±14,3	80,5	0,234	m
5th minute	73,6±9,8	72,0	70,7±10,4	69,5	0,280	m
10th minute	72,0±6,3	72,0	65,2±7,9	63,5	0,000	m
20th minute	71,0±5,5	70,0	61,3±6,3	61,0	0,000	m
30th minute	72,3±6,9	70,0	61,8±6,3	59,0	0,000	m
End of operation	72,7±7,2	70,0	62,0±6,3	59,5	0,000	m
5th minute after extubation	89,0±11,9	89,5	85,2±10,5	87,0	0,128	m
Changes compared to the preopertive period						
After intubation	-11,8±10,0	-11,5	-16,5±10,7	-15,5	0,107	m
intra-group differences *P*	0,000	w	0,000	w		
5th minute	-22,7±11,5	-20,5	-26,0±10,9	-24,0	0,146	m
intra-group differences *P*	0,000	w	0,000	w		
10th minute	-24,3±10,8	-24,0	-31,6±12,2	-30,0	0,012	m
intra-group differences *P*	0,000	w	0,000	w		
20th minute	-25,4±11,6	-25,5	-35,5±11,5	-35,0	0,000	m
intra-group differences *P*	0,000	w	0,000	w		
30th minute	-25,1±12,1	-24,0	-35,3±13,0	-34,0	0,001	m
intra-group differences *P*	0,000	w	0,000	w		
End of operation	-23,6±11,9	-23,5	-34,8±12,8	-34,0	0,000	m
intra-group differences *P*	0,000	w	0,000	w		
5th minute after extubation	-7,3±10,1	-6,0	-11,6±11,0	-9,5	0,070	m
intra-group differences *P*	0,000	w	0,000	w		

m Mann-whitney *U* test/w Wilcoxon test

the operation, and in the 5th min after extubation displayed significant falls compared to the preoperative period ($P < 0.05$) [Table 5].

There were no significant differences between the two groups for the mean arterial pressure reductions after intubation, in the 5th min, and the 5th min after extubation compared to the preoperative period ($P > 0.05$). In Group 2, the mean arterial pressure reduction in the 10th, 20th, and 30th min and after the operation compared to the preoperative period was significantly greater than in Group 1 ($P < 0.05$) [Figure 2].

The preoperative, after intubation, 5th and 30th min after the operation, and 5th min after extubation HR values did not show significant differences ($P > 0.05$) between the groups. In Group 1, the 10th and 20th min HR values were significantly lower compared to Group 2 ($P < 0.05$) [Table 6].

In Group 1, the HR value after intubation, in the 5th, 10th, 20th, and 30th min after the operation, and the 5th min after extubation displayed significant increases compared to the preoperative period ($P < 0.05$) [Table 6].

In Group 2, the HR values after intubation, in the 5th, 10th, 20th, and 30th min after the operation, and the 5th min after extubation displayed significant increases compared to the preoperative period ($P < 0.05$) [Table 6].

The HR increase after intubation, in the 5th and 30th min after the operation, and the 5th min after extubation compared to the preoperative period did not show significant differences between the two groups ($P > 0.05$). In Group 2, the 10th and 20th min HR increases compared to the preoperative period were significantly higher compared to Group 1 ($P < 0.05$) [Figure 3].

Between the groups, the preoperative, after intubation, 5th min, 10th min, 20th min, and 30th min after the operation, and 5th min after extubation SpO_2 values did not show significant differences ($P > 0.05$)

In Group 1, SpO_2 values after intubation, 5th min, 10th min, 20th min, and 30th min after the operation, and 5th min after extubation had significant increases compared to the preoperative period ($P < 0.05$)

In Group 2, SpO_2 values after intubation, 5th min, 10th min, 20th min, 30th min after the operation, and 5th min after extubation had significant increases compared to the preoperative period ($P < 0.05$)

Compared to the preoperative period, the SpO_2 increase after intubation, in the 5th, 10th, 20th, and 30th min after the operation, and the 5th min after extubation did not show significant differences between the two groups.

Table 6: Preoperative, intraoperative and postoperative heart rate values of cases

	Group 1		Group 2		*P*	
	Mean±SD	Median	Mean±SD	Median		
Heart Rate						
Preoperative	78,3±14,4	76,0	78,3±13,0	78,5	0,965	m
After intubation	96,7±13,3	96,5	93,3±12,4	92,0	0,326	m
5th minute	95,8±11,8	95,0	98,5±11,4	95,5	0,161	m
10th minute	91,8±7,0	93,0	97,2±9,2	95,5	0,004	m
20th minute	89,7±8,4	90,0	95,7±8,0	96,5	0,000	m
30th minute	87,9±8,9	88,0	91,1±9,1	92,5	0,091	m
End of operation	87,7±8,8	87,5	91,0±9,1	92,5	0,061	m
5th minute after extubation	83,2±11,2	82,0	84,0±12,2	84,5	0,843	m
Changes compared to the preop. period						
After intubation	18,4±13,2	17,5	15,0±11,4	15,0	0,134	m
intra-group differences *P*	0,000	w	0,000	w		
5th minute	17,5±13,2	18,5	20,2±10,7	20,0	0,281	m
intra-group differences *P*	0,000	w	0,000	w		
10th minute	13,5±11,2	16,0	18,9±11,6	20,0	0,036	m
intra-group differences *P*	0,000	w	0,000	w		
20th minute	11,4±12,6	13,5	17,4±12,6	17,5	0,046	m
intra-group differences *P*	0,000	w	0,000	w		
30th minute	9,5±12,8	10,0	12,8±14,3	14,5	0,183	m
intra-group differences *P*	0,000	w	0,000	w		
End of operation	9,4±13,0	10,0	12,7±14,3	14,0	0,132	m
intra-group differences *P*	0,000	w	0,000	w		
5th minute after extubation	4,9±11,1	4,0	5,7±9,1	5,0	0,765	m
intra-group differences *P*	0,000	w	0,000	w		

m Mann-whitney *U* test/w Wilcoxon test

The $EtCO_2$ values did not display significant differences after intubation, in the 5th, 10th, 20th, and 30th min, and after the operation between the two groups ($P > 0.05$)

In Group 1, the $EtCO_2$ values in the 5th, 10th, 20th, and 30th min and after the operation displayed a significant fall compared to the period after intubation ($P < 0.05$)

In Group 2, the $EtCO_2$ values in the 5th, 10th, 20th, and 30th min and after the operation displayed a significant fall compared to the period after intubation ($P < 0.05$)

Compared to the period after intubation, the $EtCO_2$ fall in the 5th, 10th, 20th, and 30th min and after the operation did not display significant differences between the two groups ($P > 0.05$) Postoperative visits to patients in both groups in the 4th and 8th hours did not encounter side effects like hypotension, hypertension, bradycardia, tachycardia, nausea-vomiting, headache or allergic reactions.

Discussion

Total intravenous anesthesia is a method chosen for most anesthesia administrations because the effect begins rapidly, the dose-response relationship is predictable and it provides cardiovascular stability. Formation of arrhythmia and myocardial depression is rare. All of these make TIVA an advantageous anesthesia method.[18] Many studies about ear-nose-throat surgery especially have emphasized that TIVA is more reliable.[19,20] Our study of septoplasty operations used TIVA as an anesthesia method.

To provide a bloodless surgical field for ear-nose-throat surgery, controlled hypotension is a chosen method. Reducing bleeding in the surgical field reduces the duration of operations and reduces the possibility of complications developing.[11,21,22]

Many studies about controlled hypotension administration recommend keeping mean arterial pressure between 55 and 70 mmHg to ensure tissue perfusion.[23,24] In our study, the 55–65 mmHg interval was determined for controlled hypotension.

To provide controlled hypotension, many agents like nitroglycerin, high-dose inhalation anesthetics, sodium nitroprusside, and beta blockers are used alone or in combination. The ideal hypotensive agent should have a short effect duration, be rapidly eliminated, not have toxic metabolites, be easy to administer, have effect ending rapidly after cessation, and have dose-linked predictable effects.[11,25,26] In our study, nitroglycerin was used to induce controlled hypotension.

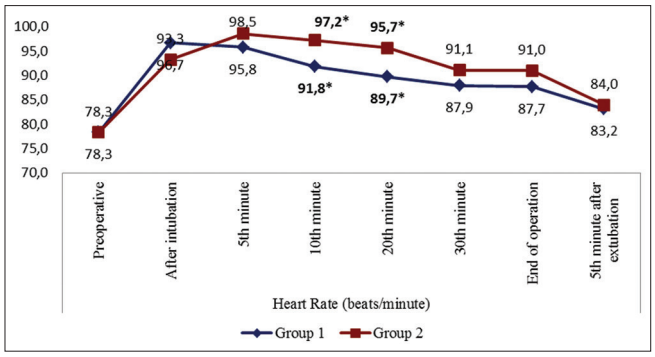

Figure 3: When the heart rate mean values of the groups were compared; There was a significant difference in the values of 10th and 20th min (* $P < 0.05$)

Nitroglycerin causes hypotension with direct vasodilatory effects on veins especially. Along with the effect of inducing hypotension, adverse reflex tachycardia may occur.[25]

Nitroglycerin has been known to induce vasodilatation by intracellular NO release from both the coronary and peripheral vascular bed for many years. NO activates guanylate cyclase which results in cGMP accumulation. Nitroglycerin is frequently used for angina pectoris treatment due to its effect on reducing myocardial oxygen requirements. Additionally, this result contributes to lowering preload with effects reducing arterial wall stress and increasing coronary perfusion.[27] Additionally, under *in vitro* conditions, nitroglycerin shows inhibiting effect on platelet aggregation linked to concentration. The nitroglycerin dose required to induce arterial blood pressure reduced by 10% level causes a clear reduction in platelet aggregation and was shown to reduce arterial injury linked to vasoconstriction. Nitroglycerin under *in vivo* conditions has been shown to reduce venous injury caused by platelet-arterial wall relationships and vasoconstriction and platelet-linked vasoconstriction by directly affecting arterial smooth muscle.[28]

Many studies have used the Fromme scale to evaluate the amount of hemorrhage in the surgical field. A surgeon with no knowledge of the groups is requested to numerically assess the surgical field with values from 0 to 5 according to this scale.[22,29] All cases in our study had bloodless surgical fields assessed with the Fromme scale by the same surgical team operating and blind to the group the patient was in.

Each day new effects of smoking on the systems and organs of the body are recognized. Studies about the effects of smoking on the respiratory tract generally focus on the lower respiratory tract. However, smoking affects organs found in the regions of ear-nose-throat and head-neck surgical specialisms at severe levels. Individuals who smoke have disrupted nasal mucociliary functions and increased frequency of upper respiratory tract infections. Patients undergoing ear-nose-throat surgery frequently have a smoking history.[30]

The most important destructive health problem caused by smoking is vascular injury created in vital organs like the brain, lungs, circulation system, and heart. Many studies have shown the injury to peripheral vascular tissues caused by smoking. This injury includes endothelial cell swelling, external endothelial edema, subendothelial vesicles, and increased macrophages in the arterial wall. It was especially shown that smoking inhibits the dilatation of peripheral arterioles caused by nitric oxide synthase.[31] The nicotine present in cigarettes is held responsible for this effect.[32] Many animal studies have shown that nicotine inhibits endothelial-sourced arteriolar dilatation, especially. Nicotine in endothelial dysfunction creates injury to endothelial cells under *in vitro* conditions, while *in vivo* it increases superoxide anion production and causes adhesion of monocytes to the endothelium.[33] New studies in recent years have blamed disrupted enzyme activity like GTP cyclohydrolase for nicotine-linked endothelial dysfunction.[34] Nicotine reduces gap-junction proteins between cells and was shown to negatively affect the relationships between cells.[4]

Nicotine stimulates the sympathetic nervous system causing vasoconstriction. Serum levels of the vasoconstrictor agent endothelin-1 increase linked to a dose of smoking, while the effect of nitric oxide, with vasodilatory effects, reduces with smoking. A variety of studies have shown that the efficacy of nitrates increases in areas with disrupted endothelial function.[35] In our study, in accordance with the literature, the smoking group was found to have higher rates of hypotension induced by nitroglycerin compared to the control group. Similarly, the adverse effect of reflex tachycardia was seen at higher rates in the smoking group. Nitroglycerin was observed to have higher efficacy in the smoking group, though there was no statistical difference between the amounts of nitroglycerin used in the groups. In summary, smoking increased the strength of the nitroglycerine effect; as a result, it can be said that the same dose increases the probability of observing side effects among people who smoke.

There are many studies showing that the endothelial dysfunction occurring is reversed when smoking stops.[4,36] Inclusion criteria for the smoking group were based on smoking 20/day for at least 5 years; thus, an attempt was made to standardize the smoking history and injury induced among patients. Patients who had smoked but quit were not included in our study.

Nitroglycerin reducing mean arterial pressure by 10% is associated with notable values of platelet inhibition.[37]

In this situation, platelet function inhibition should be expected in patients with controlled hypotension induced with nitroglycerine. This inhibition caused by nitroglycerine is not a problem alone during surgeries where attempts are made to create a bloodless surgical field; however, it may cause notable negativity when combined with platelet membrane damage caused by smoking. Because new studies have shown that smoking causes changes in platelet membrane habits and Na-K-ATP activity.[38]

Smoking is known to cause changes in the normal coagulation cascade and vascular hemostasis. Many studies have shown that smoking causes changes in platelet membranes and disruption of function. Patients with a smoking history were observed to have higher rates of blood loss during operation and transfusion requirements compared to those who did not smoke.[39,40] Du Plooy *et al*.[41] found smoking reduced the elastic module of platelets and as a result caused softer thrombocytes to occur. In our study, in accordance with the literature, the smoking group had higher Fromme scale values showing hemorrhage in the surgical field.

The inhibitory effect of nitroglycerin on thrombocyte functions was first shown by Hampton *et al*.[42] Later many studies stated that nitroglycerin infusion reduced the cGMP concentration in platelets and inhibited calcium ion mobilization and platelet aggregation.[43] The smoking group was found to have higher levels of surgical field hemorrhage evaluated with the Fromme scale. Nitroglycerin had increased efficacy linked to endothelial dysfunction in the smoking group which is considered to have increased the amount of bleeding.

When the negative effects of smoking on the coagulation cascade, negative effects of nitroglycerine on platelet functions and additionally increased nitroglycerine efficacy due to smoking are combined, it makes it difficult to create a bloodless field and the controlled hypotension does not achieve its aims. When the reliability of nitroglycerine used for controlled hypotension in patients who smoke is interrogated, it is concluded that it may be more appropriate to choose another agent.

Our study is the first about this topic. There are a range of limitations. Only routine monitoring is applied to cases lasting less than 30 min for ear-nose-throat surgery in our clinic. Our study was designed to be observational and BIS monitoring could not be applied as there was no intervention to the routine surgical procedure. BIS monitoring of cases would have provided more objective data by standardizing the depth of anesthesia.

Additionally, prospective randomized studies comparing controlled hypotension administration using nitroglycerine with other agents for smoking patients will provide great contributions. However, our study is valuable in terms of investigating the topic and guiding future studies.

In our study, designed to be prospective and observational, there was no intervention in the routine treatment of cases, and no financial support was received from any organization or institution.

Conclusion

Our study shows that the efficacy of nitroglycerine, administered for controlled hypotension purposes, increases linked to the endothelial dysfunction developing due to nicotine in patients who smoke and that more hypotension and accompanying reflex tachycardia is induced. Additionally, the negative effect induced by nitroglycerine on platelet activity combines with the similar effects of smoking to increase the amount of bleeding in the surgical field. The use of nitroglycerine to create a bloodless surgical field was shown not to be reliable for patients who smoke. Our study is the first about this topic in the literature and requires support from new prospective randomized studies.

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Nil.

Conflicts of Interest

There are no conflicts of interest.

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