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Comparison of Esmolol to Nitroglycerine in Controlling Hypotension During Nasal Surgery

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Abstract

Objective: The aim of this study was to compare esmolol to nitroglycerine in terms of effectiveness in controlling hypotension during nasal surgery.

Materials and Methods: After approval by our institutional Ethics Committee, 40 patients were recruited and randomized into two drug groups: esmolol (Group E) and nitroglycerine (Group N). In group E, a bolus dose of 500 µg/kg esmolol was administered over 30 sec followed by continuous administration at a dose of 25-300 µg/ kg/min to maintain systolic arterial pressure at 80 mmHg. In group N, nitroglycerine was administered at a dose of 0.5-2 µg/kg/min.

Results: During the hypotensive period, systolic arterial pressure, di- astolic arterial pressure, mean arterial pressure, and heart rate were decreased 24%, 33%, 27% and 35%, respectively, in group E ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$) and were decreased 30%, 33%, 34% and 23%, respectively, in group N ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$). The decrease in heart rate was higher in group E during the hypotensive period ($p=0.048$). During the recovery period, diastolic arterial pressure and heart rate were decreased 9% and 18%, respectively, in group E ($p=0.044$, $p<0.001$). Systolic arterial pressure, diastolic arterial pressure, and mean arterial pressure were decreased 7%, 3% and 7%, respectively, in group N ($p=0.049$, $p=0.451$, $p=0.045$).

Conclusion: Esmolol provides hemodynamic stability and good sur- gical field visibility and should be considered as an alternative to nitroglycerine.

Key Words: Anesthesia, Controlled hypotension, Esmolol hydrochloride, Nitroglycerin

INTRODUCTION

Functional Endoscopic Sinus Surgery (FESS) is among the nasal surgical procedures that have increased in popularity since the late 1970s. However, serious complications such as hemorrhage, meningitis and damage to the optic nerve may occur due to the close proximity of blood vessels, nerves, and the orbital and intracranial cavities. The lack of complete distinction between the anatomic structures associated with hemorrhaging in the surgical area during the procedure con- tributes to increased complications [1, 2].

Controlled hypotension (CH) at a moderate level (mean blood pressure - MAP>60 mmHg) is often preferred during nasal surgical procedures such as FESS and septorhinoplasty in order to reduce hemorrhaging and thus reduce complica- tions via improved surgical field visibility [1, 3]

suitable patient positioning, positive pressure ventilation, medication, epidural or spinal anesthesia and high sympathetic block are among the methods used in the inten- tional reduction of blood pressure. The basic purpose is to reduce cardiac flow and/or systemic vascular resistance [4]. In addition to the commonly used sodium nitroprusside (SNP), nitroglycerine (NTG), and trimethaphan, CH can also be achieved through the administration of other agents such as prostaglandin E1, calcium canal antagonists, beta-blockers, fenoldopam, and angiotensin-converting-enzyme inhibitor (ACE) inhibitors [3].

Ease of administration, fast onset of efficiency, short half-life after discontinuation, rapid elimination of toxic metabolites, lack of a negative impact on vital organs, and expected and dose-dependent efficacy are the desired properties of the ideal hypotensive agent [3]. The use of vasodilators in CH has been reported to result in the possible development of tachyphylaxis and cyanide toxicity with SNP [3, 5]. In recent years, the rapid onset and short half-life of esmolol, as well as easy titration and close blood pressure control, has resulted in its use for CH [6-10].

There are no studies on the quality of the surgical field as they apply to nasal surgical procedures that compare the selective □-adrenergic receptor blocker esmolol and the vaso- dilator NTG. Therefore, our study compared the effects of CH as performed with esmolol and NTG in cases with planned FESS and septorhinoplasty for the purpose of evaluating surgical area quality, liver/kidney functions, and blood gas values.

MATERIALS AND METHODS

Our study was conducted on 40 patients classified as American Society of Anesthesiologists (ASA) groups I and II who were scheduled for nasal surgery upon approval by our faculty's Ethics Committee and following receipt of express kg/min. For group N, a titration of NTG at 0.5-2 µg/kg/min was administered. The blood pressure targets for both groups were systolic arterial pressure (SAP) 80 mmHg or mean arte- rial pressure (MAP) 60-65 mmHg, and infusion was discontinued at the end of the surgical procedure. The period was logged until the target values were achieved for all patients. The total esmolol and NTG doses administered throughout the surgical process were also recorded.

The initial SAP, diastolic arterial pressure (DAP), MAP,

HR, SpO_2 and $ETCO_2$ of all patients were logged prior to drug infusion (control) in the pre-anesthetic period, during the hypotensive period, and during post-operative compilation.

To evaluate the effects of hypotensive agents on organ systems, aspartate transaminase (AST), alanine transaminase (ALT), lactate dehydrogenase (LDH), urea and creatinine values that indicate hepatic and renal functions were recorded during both the pre-operative and post-operative periods. In addition, pH, PO_2 and lactate values in the arterial blood gas were recorded prior to the beginning of hypotensive drug infusion, during the hypotensive period, and during post- operative compilation.

A 0.5-mg atropine IV was administered in the case of bradycardia (HR <40 bpm). The administered infusion dose in the case of MAP <60 mmHg was reduced by half, and infusion of the hypotensive agent was discontinued when no response was obtained within 5 minutes. An ephedrine 10-mg IV was administered when required. Any side effects observed throughout the procedure were recorded.

The OP site was evaluated by the surgeon using the 0-5 point bleeding scale (0: no bleeding, 1: low bleeding-bleeding does not require aspiration, 2: low bleeding-bleeding requires intermittent aspiration, 3: low bleeding-bleeding requires frequent aspiration, 4: moderate bleeding-bleeding becomes serious when aspirator is withdrawn from the OP site, 5: serious bleeding-requires persistent aspiration, OP impossible) during the intra-operative period.

Side effects such as nausea/vomiting, hypotension/hypertension, bradycardia/tachycardia, gastrointestinal system dis- orders, blurry vision, allergy, headache and chest pain were considered during the post-operative period. Pre- and post- operative data were logged by an independent anesthetist not affiliated with the study.

All data were statistically analyzed using the SPSS 13.0 (SPSS Inc., Chicago IL.) statistical software package. When com- paring cases administered esmolol or NTG, a significant differ- ence between the groups concerning hypotension required 19 cases per group (power 0.84, α=0.05, □=0.16). Data normal- ity was analyzed through the Shapiro-Wilk test. A t-test was applied to compare both groups when the data were normally distributed. Data not normally distributed were compared using a Mann-Whitney U test. Comparison of the dependent groups was performed with the matching t-test for data with a normal distribution and a Wilcoxon Signed Rank test for non- normally distributed data. Categorical data were examined by Pearson chi-square and Fisher's exact chi-square tests. The level of significance difference was set at $p<0.05$.

RESULTS

The demographic and surgical data of the patients in Groups E and N as well as their target SAP achievement times, BIS values, and consumption of desflurane and remifentanil were found to be similar (Table 1).

The initial SAP, DAP, MAP, HR, SpO_2 and $ETCO_2$ values of the patients during pre-anesthetic induction were similar (Table 2).

The comparison between the values during the pre-hypotensive period and hypotensive agent infusion period, in partic- ular SAP, DAP, MAP, and HR, revealed decreases of 24%, 33%, 27% and 35%, respectively ($p<0.001$, $p<0.001$, $p<0.001$ and $p<0.001$, respectively) for Group E, and 30%, 33%, 34% and 23%, respec- tively ($p<0.001$, $p<0.001$, $p<0.001$ and $p<0.001$, respectively) for Group N. Compared to the hypotensive agent infusion period, a significant reduction of 9% and 18% ($p=0.044$ and $p<0.001$, respectively) was observed during compilation of the DAP and HR control periods, respectively, of Group E, while the reduction in SAP, DAP and MAP values of Group N were 7%, 3% and 7%, respectively ($p=0.049$, $p=0.451$ and $p=0.045$, respectively). A comparison between average SAP, DAP and MAP values and the values prior to hypotensive infusion yielded no difference between the groups. The decreases in the HR values during the hypotensive period were found to be high ($p=0.048$) in Group E. No significant difference was observed in the group and inter- group comparisons of the SpO_2 and $ETCO_2$ values (Table 3)Evaluation of surgical site hemorrhaging during the hypotensive period did not yield any significant difference between the groups.

The comparison between the hepatic and kidney function parameters of the patients did not yield any statistically significant differences in the ALT, AST and urea values during the pre- and post-operative periods. The increase in the post-operative creatinine and LDH values compared to the pre-operative control values was found to be similar in both groups ($p=0.003$, $p=0.024$ for Group E and $p=0.003$, $p=0.005$ for Group N) (Table 4).

No significant difference in arterial blood samples received during the hypotensive period and compilation period in terms of pH, PO_2 and lactate values was found between the groups prior to hypotensive drug infusion. While the group assessments yielded a statistically significant decrease in the PO_2 during the pre-hypotensive drug infusion period, ($p=0.039$ for Group E and $p<0.001$, $p=0.032$, $p<0.001$ for Group N), the increase in the lactate values during the hypotensive and compilation period was also found to be statistically significant for both groups compared to the pre-drug infusion period ($p=0.032$, $p=0.043$ for Group E and $p=0.027$, $p=0.017$ for Group N) (Table 5).

A category ASA I patient in Group E developed bradycardia following esmolol bolus dose administration, and 0.5 mg atro- pine was administered intravenously. Esmolol infusion was initi- ated after stabilization of the hemodynamic parameters, and no further pre-operative complications were observed.

Except for nausea/vomiting, no post-operative side effects were observed. Nausea/vomiting was observed in 6 patients in Group E (30%) and 3 in Group N (15%).

Table 1. Demographic data of patients, intraoperative BIS values, and drug consumption

	Group E (n=20)	Group N (n=20)	p
Gender (F/M)	12/8	13/7	0.807
Age (year)	29.80±7.80	32.30±10.70	0.738
Weight (kg)	69.10±12.30	72.20±12.60	0.436
Height (cm)	169.40±8.40	172.00±9.10	0.353
ASA (I/II)	19/1	17/3	0.605
Operation time (min)	92.70±21.20	106.00±25.50	0.705
Anesthesia time (min)	109.70±19.50	120.20±24.30	0.080
Target MAP time (sec)	68.00±8.30	75.00±11.70	0.143
BIS value	48.20±4.90	45.90±4.70	0.350
Desflurane consumption (MAC)	0.70±0.30	0.70±0.40	1.000
Remifentanil (µg/kg/min)	0.14±0.01	0.13±0.02	0.052

Data are given as n or mean±SD
MAP: Mean arterial pressure, MAC: Minimum alveolar concentra- tion, BIS: Bispectral index score

Table 2. Baseline values before anesthesia induction

	Group E (n=20)	Group N (n=20)	p
SAP (mm Hg)	111.5±20.5	115.6±20.8	0.538
DAP (mm Hg)	71.9±12.6	72.9±12.1	0.799
MAB (mm Hg)	83.6±14.9	86.6±14.3	0.519
HR (bpm)	84.2±13	83.1±14.3	0.800
SpO_2 (%)	99.1±0.8	99.3±0.9	0.462
$ETCO_2$ (mm Hg)	34.2±2.6	35.2±3.7	0.328

Data are given as n or mean±SD
SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, HR: Heart rate, SpO_2: Peripheral oxy- gen saturation, $ETCO_2$: End-tidal carbon dioxide

Table 3. Before infusion (control), hypotensive period and recovery period data

	Group E (n=20)	GroupN (n=20)	p
SAP (mmHg)			
Before infusion	116.7±17.8	129.6±25.5	0.713
Hypotensive period	86.5±7.9**	86.7±4.3**	0.921
Recovery period	117.1±11.0	117.2±18.2*	0.983
DAP (mmHg)			
Before infusion	74.2±12.4	80.3±12.7	0.132
Hypotensive period	50.5±9.0**	51.0±5.3*	0.733
Recovery period	72.2±6.4*	71.9±14.0*	0.931
MAP (mmHg)			
Before infusion	88.8±14.2	96.4±16.3	0.124
Hypotensive period	61.4±8.4*	61.7±5.2**	0.892
Recovery period	85.7±8.8	87.1±14.7*	0.716
HR (atım dk^{-1})			
Before infusion	93.6±14.4	86.1±10.6	0.068
Hypotensive period	59.7±7.2**	64.7±8.3**	0.048
Recovery period	74.6±11.1*	79.2±13.3	0.242
SpO_2 (%)			
Before infusion	99.3±0.7	99.4±0.6	0.630
Hypotensive period	99.2±0.6	99.3±0.5	0.570
Recovery period	99.3±0.5	99.3±0.6	1.000
$ETCO_2$ (mm Hg)			
Before infusion	31.6±3.3	32.2±2.9	0.545
Hypotensive period	31.1±3.3	31.4±2.9	0.761
Recovery period	34.7±6.2	36.4±7.1	0.424

Data are given as n or mean±SD
SAP: Systolic arterial pressure, DAP: Diastolic arterial pressure, MAP: Mean arterial pressure, HR: Heart rate, SpO_2: Peripheral oxy- gen saturation, $ETCO_2$: End-tidal carbon dioxide
*p<0.05 and **p<0.001, intra-group comparison, compared to before infusion

Table 4. Preoperative and postoperative hepatic and renal functions

	Group E (n=20)	GroupN (n=20)	p
ALT (mg/dL)			
Preoperative	20.0±12.0	24.1±32.2	0.596
Postoperative (Day 1)	17.7±6.8	22±21.7	0.403
AST (mg/dL)			
Preoperative	21.1±9.0	21.8±12.5	0.840
Postoperative (Day 1)	21.8±9.5	23.0±12.3	0.731
Urea (mg/dL)			
Preoperative	24.6±9.4	25.0±7.5	0.882
Postoperative (Day 1)	27.0±8.7	24.4±5.5	0.265
Creatinine (mg/dL)			
Preoperative	0.7±0.2	0.7±0.1	1.000
Postoperative (Day 1)	0.9±0.2*	0.9±0.2*	1.000
LDH (mg/dL)			
Preoperative	122.4±16.7	124.5±14.5	0.673
Postoperative (Day 1)	136.3±20.6*	138.5±15.7*	0.706

Data are given as n or mean±SD
AST: Aspartate transaminase, ALT: Alanine transaminase, LDH: Lactate dehydrogenase
*p<0.05, intra-group comparison, compared to preoperative values

Table 5. Arterial pH, PaO_2 and lactate values

	Group E (n=20)	Group N (n=20)	p
pH			
Before infusion	7.40±0.05	7.40±0.30	1.000
Hypotensive period	7.40±0.04	7.30±0.40	0.272
Recovery period	7.30±0.04	7.30±0.50	1.000
PaO_2 (mmHg)			
Before infusion	273.70±65.07	278.20±68.20	0.832
Hypotensive period	247.40±57.60*	238.90±80.20*	0.702
Recovery period	152.30±67.50*	147.40±36.10*	0.776
Lactate (mmol/L)			
Before infusion	9.00±3.60	10.10±5.70	0.470
Hypotensive period	16.00±7.65*	16.00±7.60*	1.000
Recovery period	14.70±6.01*	20.10±10.40*	0.051

Data are given as the mean±SD
*p<0.05, intra-group comparison, compared to before infusion values

DISCUSSION

Our study compared the effects of the short-acting β-adrenergic receptor blocker esmolol and the vasodilator NTG for HR control under general anesthesia (desflurane and remifentanil) in patients with a planned nasal surgical proce- dure. Anesthetic depth in both groups was maintained at a stable rate with BIS monitoring.

A close relationship between reduced MAP value and surgical site quality in surgical procedures has been shown [11]. A 38% reduction in hemorrhaging in 6298 patients who underwent FESS with HR control has been reported [12]. Cincikas and Ivaskevicius [13] have shown reduced bleeding and improved surgical view quality with 50 to 60 mmHg MAP maintenance an endoscopic nasal surgery with NTG (0.79±0.34 µg/kg/min).

In their study comparing the effects of esmolol (500 µg/ kg load, 100-300 µg/kg/min) and SNP (0.25-4.0 µg/kg/min) on

HR control (target MAP 55-65 mmHg) during orthognathic surgery, Blau et al. [14] reported the average MAP as 58.7±0.7 mmHg with esmolol and 61.8±0.4 mmHg with SNP. Furthermore, they suggested that 40% of the values observed in the esmolol and 53% in the SNP group remained outside of the target MAP range and that the reduction of blood loss with esmolol was more effective and controlled. Boezaart et al. [15] reported that while the surgical conditions during FESS with moderate hypotension (MAP>65 mmHg) and SNP (0.25 µg/kg/min) were not good, optimum surgical area was achieved with esmolol (500 µg/kg load, 100-300 µg/kg/min). The authors suggested that increased hemorrhage in the mucous membrane associated with the vasodilator effect of SNP and increased cardiac flow accounted for this result. The esmolol-related improvements in surgical conditions, howev er, were associated with the effective vasoconstriction of pre- capillary sphincters and arterioles in the mucous membranes. Pilli et al. [16] reported that the use of esmolol at an average infusion rate of 330±10 µg/kg/min in tympanic surgery provided a bloodless surgical site with a 28.7% decrease in SAP, 26.5% in MAP and 33.4% in DAP. In addition to the reductions of a similar nature in blood pressure induced by esmolol and NTG in our study, a similar improvement was also observed in surgical site quality. We believe that the lower dose of the medication administered compared to other studies resulted from a minimized stress response to surgical stimulants, along with the reverse Trendelenburg positioning achieved through BIS monitoring.

Yoshikawa et al. [17] reported that the target MAP 60-70 mmHg during an NTG-accompanied mandibular osteotomy was achieved at 1-5 µg/kg/min by an infusion rate of 13.3±1.5 min. Degoute et al. [8] reported that the target SAP (80 mmHg) in tympanoplasty procedures was achieved in 53.3±4.4 seconds with esmolol (210±33 µg/kg/min). Using esmolol at 50-300 µg/kg/min, Turan et al. [9] demonstrated that MAP (>60 mmHg) was achieved in 13.35±8.4 min. Although in our study, the period in which the target SAP (80 mmHg) achieved was statistically similar, it was achieved in a shorter period of time in the esmolol group (Group E: 68.0±8.3 sec, Group N: 75.0±11.7 sec).

SNP and NTG are frequently preferred for HR control during procedures. Yet, SNP can cause vasodilatation, reflex tachycardia and increased cardiac flow. When compared to SNP, the negative effects of NTG on reflex tachycardia, “rebound” hypertension, and organ perfusion - along with risk of overdose are reported to be lower [18].

In contrast, esmolol causes a dose-dependent, controlled and slow decrease in blood pressure, with no observable tachycardia, unlike the deep fluctuations in blood pressure observed with SNP administration. In a study comparing esmolol and SNP in the achievement of target HR in patients scheduled for lumbar fusion and cerebrovascular surgery, Ornstein et al. [19] reported a 15.9% CAD increase in the SNP and 12.1% decrease in esmolol groups. They also suggested that discontinuation of the hypotensive agents resulted in a significant increase in MAP in the SNP group. Increases in CAD at 30 and 60 min were reported upon NTG application in a different study [17]. When comparing CAD control values, the decrease in the hypotensive and compilation period was 35% and 18% in the esmolol and 23% in the NTG groups. Our study did not find a significant decrease in the compilation period. In addition, bradycardia responsive to treatment after bolus administration in the esmolol group was observed in only one subject. Although a decrease in blood pressure after discontinuation of the drug infusions was lower in the NTG group, no difference was found between the groups.

The mechanisms that keep microcirculation under control should be taken into consideration while implementing tech- niques to reduce blood flow and provide a dry operation site. Auto-regulation through minimal tissue metabolism assumes the role of a local protective mechanism against excess reduc- tion in blood flow. HR control should target sustainable protective auto-regulatory mechanisms, while deep hypotension should be avoided. Deep hypotension reducing organ perfusion may be associated with morbidity and mortality (0.02-0.06%) [3]. Therefore, our study refrained from deep HR control (MAP = 50 mmHg), and the target MAP was maintained in the 60-65 mmHg range. In a study where they researched the impact of NTG on the liver during HR control (MAP approx. 60 mmHg), Fukusaki et al. [20] found increased AST and LDH activity even though the patients were maintained in the nor- mal range. Kol et al. [10] found that esmolol did not affect liver and kidney functions during HR control where the target MAP was 65-75 mmHg. Piper et al. [7] reported that the alpha-glutathione-D-transferase (Alpha GST) level in the blood samples collected from patients with and without the administration of esmolol and SNP, and deep hypertension (MAP 50-55 mmHg) in the endonasal sinus surgery, was higher in the hypotensive group and that such difference would return to normal by the second hour of the procedure. However, standard liver enzymes (alanine aminotransferase, aspartate aminotransfer- ase, gamma-glutamyl transferase) were unchanged. Therefore, they suggested that deep hypotension could result in hepato- cellular damage at a minimal level.

In their study researching the effects of isoflurane, esmolol and NTG on splanchnic perfusion during a hypotensive procedure (30% of control SAP, MAP>50 mmHg) of elective maxillofacial surgery, Andel et al. [21] suggested that gastric intra-mucous pH remained unchanged, no increase in the blood lactate levels was observed, and thus, organ perfusion was sustained. In an approx. 2-hour HR control procedure where SAP was performed at 70 to 79 mmHg, Nagata et al. [22] reported that the urinary NAG (n-acetyl-glucosaminidase) activity indicative of tubular renal function and gamma-GTP activity were higher at 3 post-

operative days, and reduced post-op creatinine clearance, free water clearance and urinary volume returned to normal within 3 days. It was suggested that mildly reversible renal tubular cell damage could be observed. However, serum SGOT and SGPT levels were shown to remain unchanged throughout the 21-day post-operative period. Our moderate HR control procedure demonstrated that while liver functions were not affected by standard tests, the increase in post-operative creatinine and lactate values in both groups was similar but within normal ranges. However, we believe that the possible minimal effects on organ functions require more elaborate testing in cases of risk.

Degoute et al. [8] reported that the changes in PaO_2, PCO_2 and lactate in the arterial blood gas samples in the administration of remifentanil, SNP and esmolol for HR control (SAP 80 mmHg) in patients with planned tympanoplasty were similar. Pilli et al. [16] reported that there was no significant difference in the arterial blood gas samples in hypotensive anesthesia achieved with esmolol (28.7% reduction in SAP). In their study comparing NTG and SNP with normo-tensive anesthetic procedures in mandibular osteotomies, Yoshikawa et al. [17] demonstrated a similar reduction in the PaO_2 values

in the blood gas samples taken from of all three groups 60 minutes post-surgery. They suggested that the reductions in the PaO_2 value were not affected by the administration of both drugs and that this could be explained by the ventilation/perfusion mismatch associated with artificial ventilation during anesthetic administration. Moreover, they considered the lack of difference in increased lactate associated with

tissue hypoxia and the fact that pH, BE and HCO_3 values remained within the normal range to be proof of tissue oxygenation continuing throughout hypotension. In addition to similar hemodynamic changes, our study yielded no significant difference in arterial blood gas and lactate values between the groups.

Consequently, we believe that esmolol can be safely used as an alternative to NTG. Its HR control-related surgical site quality in nasal surgical procedures is superior, and its effects on hepatic/renal functions and arterial blood gas parameters are similar to NTG. In addition, esmolol produces easy control of blood pressure with no“rebound”tachycardia and hypertension.

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