

A comparative analysis of the effects of esmolol, lidocaine, nitroglycerin and placebo on hemodynamic response to extubation, and extubation quality and postoperative pain

 Gamze Kucukosman,  Bengu Gulhan Aydin

Department of Anesthesiology and Reanimation, Faculty of Medicine, Zonguldak Bulent Ecevit University, Zonguldak, Turkey

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Abstract

Aim: To comparatively analyze and determine the effects of esmolol, lidocaine, and nitroglycerin on hemodynamic response to extubation, extubation quality and postoperative pain, based on the placebo effect.

Material and Methods: Our study design covers a prospective, randomized clinical trial in 120 patients who underwent intubation. Random division was applied onto the patients to obtain 4 groups: Esmolol, Lidocaine, Nitroglycerin, and Saline. In preparation for extubation; when the train-of-four (TOF) value reached 75% (baseline), study drugs were administered. When TOF $\geq 90\%$, the patients were extubated. Heart rate (HR) and mean blood pressure (MBP) records were taken prior to induction, when TOF 75% and 90, 1st, 3rd, and 5th. minutes after drugs were administered and extubation. Extubation time, quality, and postoperative pain values were recorded.

Results: When compared to the Placebo group based on post extubation measurements, the Esmolol group had no significant difference for MBP at any time but lower HR as recorded at the fifth minute (P=0.012). For both indicators, it significantly decreased according to pre- and post extubation records, with the Nitroglycerin group (P<0.05). All the groups are indifferent at a statistical significance level for extubation quality. The Lidocaine group had lower pain scores in the postoperative period for any specified time, compared to the Placebo (P<0.05).

Conclusions: No superior agent was found in our study with regard to inhibition of the hemodynamic response to extubation, and its quality. Nonetheless, in order to limit the response esmolol and nitroglycerin were efficacious when used at the doses of 1.5 mg and 2 μg per kg, respectively. Lastly, the postoperative pain were lower in the Lidocaine group.

Keywords: Extubation quality; hemodynamic response; postoperative pain

INTRODUCTION

Extubation is performed when surgical intervention is terminated and endotracheal tube is not required for airway safety. Like in intubation, mechanical and chemical particles bring to pass respiratory and cardiovascular reflexes from the stimulated airway receptors, particularly larynx, trachea and bronchi (1). Higher plasma catecholamine concentration escalates heart rate (HR) and blood pressure and thus undesirable events can be seen such as arrhythmia, pain, cough, breath-holding spells, and laryngospasm (1-7). Cardiopulmonary events occurring during extubation are three times higher than those in intubation (5). Hemodynamic changes in extubation are well tolerated by healthy individuals and however could potentially make complications

including arrhythmias, cerebrovascular hemorrhages and myocardial ischemia in high-risk patients (1-7).

Patients first nurse postoperative pain, that's whether it can be effectively managed and under control. Tissue trauma or direct nerve injury cause inflammation, followed by acute postsurgical pain (8). A number of drugs such as opioids, lidocaine, β -blockers, nitroglycerin or propofol are used in various doses and methods to prevent cardiopulmonary responses and postoperative pain during tracheal extubation (2-7,9-35). Nonetheless, it is likely that cardiovascular stability will be shaken due to these drugs with different time requirement to act. In postoperative stage tachycardia and then hypertension can be inhibited, for example, by a very short-acting β 1-blocker called esmolol whose distribution and

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Corresponding Author: Gamze Kucukosman, Department of Anesthesiology and Reanimation, Faculty of Medicine, Zonguldak Bulent Ecevit University, Zonguldak, Turkey **E-mail:** gamzebeu@gmail.com

elimination half-lives are 2 and 9 minutes respectively. Its effects reach up to the highest in 1-2 minutes with the administration of bolus injections of esmolol (25). There is limited evidence regarding the modulate mechanism of esmolol for pain response. Whether esmolol may be effective in anesthetics or analgesia has not been well established despite the newer papers reporting that this agent could possibly modulate the perioperative pain response (11,19,23-26). Studies have suggested that esmolol generates an analgesic effect by slowing hepatic blood flow and opioid metabolism, and that the β -agonistic effect also generates central analgesia via G-proteins that transmit nociceptive stimulation (11,19,23-26). Lidocaine is one of the most commonly used agents in suppressing hemodynamic response to intubation and extubation (the 30 min distribution and 60 to 120 min elimination half-lives). Lidocaine is a class-1B antiarrhythmic drug that could analgesically influence dorsal horn neurons of medulla spinalis when administered intravenously (iv) (27,28). Nitroglycerin is used to control intraoperative acute hypertensive responses of infusion (distribution half-life 4 min), and its bolus administration is known with its simplicity, effectiveness, practicality and safety for controlling hyperdynamic responses to intubation (13,16,17). The cell hosts a metabolism of nitroglycerin to nitric oxide (NO), where NO causes higher concentration of cyclic guanosine monophosphate inside the cell and thus pain modulation can be observed in central and peripheral nervous systems as well as anti-inflammatory and analgesic effect when it hinders the neurogenic components of hyperalgesia and inflammatory edema via topical administration (21,29-31).

This study primarily aims to comparatively analyze the effects of bolus administration of esmolol, lidocaine, and nitroglycerin as well as placebo in controlling hemodynamic response to tracheal extubation, and secondarily to evaluate the efficacy of these agents on extubation quality and postoperative pain.

MATERIAL and METHODS

The study was prospectively designed to perform from August 2012 to August 2013 as approved by the Hospital Ethics Committee (protocol no: 02/05/2012/10), and the patients' consent was received. The study included 120 patients aged between 18-65 years with an average surgical time of 45-120 min in accordance with the American Society of Anesthesiologists (ASA) risk group I-II. Other than non-participants, those who were posted for emergency surgery, those with physical status of ASA class III or more, those with any significant systemic disorder, those with uncontrolled hypertension and cerebrovascular disease, those with comorbid diseases, those having a history of sore throat, laryngeal or tracheal pathology, upper respiratory tract infection, asthma or chronic obstructive pulmonary disease, allergy to local anesthetics, and those on beta-blocker therapy were excluded from the study, as well as pregnant females.

A routine preanesthetic examination was conducted assessing the general condition of the patients on the evening before surgery and they were explained the purpose and application of the Visual Analogue Scale (VAS; 0, best-10, worse) test to be performed to evaluate postoperative pain. Demographic data (age, gender, weight) and ASA status of all patients were recorded.

For the premedicated patients iv line was established with their arrival in the operating room prior to normal saline administration. Of the patients, heart rate (HR), noninvasive blood pressure, bispectral index (BIS), peripheral oxygen saturation (SpO_2), and train-of-four (TOF) muscle relaxation could be observed on the connected multichannel monitor. For anesthesia propofol and fentanyl (2 mg and 2 μ g per kg, respectively) were administered, and the patients were intubated iv via trachea with rocuronium of 0.6 mg per kg. To keep them anesthetized an inspiratory concentration of 2% sevoflurane and nitrous oxide of 50% in oxygen were used at fresh gas flow (4 L.min⁻¹). When the preoperative TOF value was 2, supplementary rocuronium was intended to administer in a dose of 0.15 mg per kg. BIS values were maintained within the range of 40 to 60 through adjustment of the inspired concentration of sevoflurane. No additional opioid was used during the operation.

Random assignment was applied to distribute all the patients to four groups using the sealed envelope technique. Group I (n:30) is intravenously given by esmolol of 1.5 mg per kg, Group II (n:30) by lidocaine of 1.5 mg per kg, Group III (n:30) by nitroglycerin of 2 μ g per kg, and Group IV (n:30) by normal saline of 10 ml. Note that drugs were individually diluted to the volume 10 ml in total. One anesthesiologist administered the drugs whereas the observations were made by the second one who did not know what drugs were being used.

In the last skin suture, tramadol and metpamide (1 mg and 10 mg per kg respectively) were administered to all patients. When the TOF value reached 25%, neostigmine and atropine (0.04 mg and 0.02 mg per kg respectively) were reversed till closing inhalation anesthesia. At 75% of TOF, the study drugs were administered through an iv in 1 min. When TOF \geq 90%, extubation were conducted to all the patients by aspiration of oropharyngeal secretions.

The cardiovascular parameters [HR, mean blood pressure (MBP)], SpO_2 and BIS were noted as below.

- 1- Before induction (T0)
- 2- When the TOF value reached 25% (T1)
- 3- When the TOF value reached 75% (T2), these served as baseline values.
- 4- 1st, 3rd, 5th min after administration of study drug (T3, T4, T5 respectively)
- 6- TOF \geq 90% during extubation (T6)
- 7- After extubation at 1st, 3rd, and 5th min (T7, T8, T9 respectively).

Comparisons between groups and within each group and to baseline HR and MBP values.

Five-point scale for extubation quality were designed as no cough and comfortable breathing (=1 point), mild

cough (=2 points), moderate cough (=3 points), severe cough and forced breathing (=4 points), severe cough, forced breathing and laryngospasm (=5 points). The extubated patients then inhaled O₂ of 100% with face mask for 5 min. Nausea-vomiting, cough, desaturation, apnea, laryngospasm and bronchospasm were recorded during extubation. Anesthesia duration (duration from induction to discontinuation of inhalation agents), surgical duration (duration from incision to last skin suture), extubation duration (duration from discontinuation of inhalation agents to extubation), and recovery duration (duration from discontinuation of inhalation anesthesia until responses given to verbal or motor stimuli) were recorded.

Ephedrine of 5 mg was administered iv bolus when systolic pressure lowered by >25% from the baseline, or the absolute systolic value was less than <90 mmHg, which is called hypotension, and this was uncontrollable within 3 min despite increasing the fluid infusion and decreasing gas concentrations, and atropine of 0.5 mg was given iv bolus for therapy of bradycardia (HR<50).

Since the patients had motor difficulties in evaluating the first pain after extubation, doctors were allowed to help the manipulation of patients on VAS. The post extubation measurements for HR, MBP and VAS were made

immediately, in 10 min and in 1 hour by an anesthesiologist who had no knowledge of the study. In the recovery room, hemodynamic responses were evaluated. Rescue analgesics were injected intravenously in cases of VAS score ≥ 4 or upon patient request.

Statistical analysis

In this study statistical analysis was completed using a statistical package program SPSS 23.0 (SPSS Inc., Chicago, IL, USA). One-way ANOVA was appropriate to compare the quantitative data from the groups while for multiple comparison tests the applied technique was Tukey HSD. Examination of categorical data was made by chi-square test. Quantitative data were demonstrated as mean \pm standard deviation, while qualitative data were as frequency (percentage). Statistical significance level was satisfactory as $P < 0.05$.

RESULTS

There was no exclusion from 120 patients who were initially included in the study. No significant inter-group differences were observed for patient characteristics, ASA physical class, duration of surgery, anaesthesia, extubation and recovery between groups ($p > 0.05$) (Table 1).

Table 1. Patient characteristics, ASA, duration of surgery, anaesthesia, extubation and recovery

	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)	p
Gender (F/M),(n)	24/6	29/1	26/4	27/3	0.240
Age (year)	45.5 \pm 11.2	46 \pm 10.2	45.3 \pm 11.2	46.4 \pm 10.1	0.982
Weight (kg)	70.6 \pm 14.1	75.9 \pm 18.1	75.3 \pm 12.7	75 \pm 14.8	0.503
ASA (I/II),(n)	11/19	4/26	5/25	8/22	0.133
Surgery time (min)	118.6 \pm 36.1	103 \pm 39.2	96.7 \pm 33.7	106.4 \pm 29.5	0.104
Anaesthesia time (min)	124.9 \pm 36.7	109 \pm 40.1	102.2 \pm 33.4	113.5 \pm 29.5	0.090
Extubation time (min)	6.3 \pm 3.8	5.9 \pm 3.1	5.4 \pm 1.7	7.1 \pm 2.7	0.178
Recovery time (min)	10.1 \pm 4.1	10.1 \pm 4.1	9.3 \pm 2.2	11.9 \pm 4.2	0.058

Group I: Esmolol, Group II: Lidocaine, Group III: Nitroglycerin, Group IV: Placebo; F: Female, M: Male; ASA: American Society of Anesthesiologists, min: minute; Mean \pm SD; $p < 0.05$

These groups were statistically significantly not separate from one another for MBP values measured before the study drug was administered ($p > 0.05$) (Table 2). The MBP measurements carried out 3 minutes after the study drug was administered (T4) were significantly higher in Group II compared to Group I ($p = 0.015$), but inter-group difference was statistically insignificant in terms of MBP values measured at all other times ($p > 0.05$) (Table 2). When the intragroup MBP values were compared according to the T2 measurement time, which was measured just before the study drug was administered and accepted as the baseline value; the values measured in T8 and T9 times were found to be lower than those measured in other times for Group I ($p = 0.036$, $p = 0.048$ respectively), the values measured at T5 were higher for Group II ($p = 0.038$), and the values measured in T9 were lower for Group III ($p = 0.039$). These were statistically significant changes despite no there was no statistically significant difference

between the MBP values of Group IV measured at all times compared to T2 ($p > 0.05$) (Table 2).

Inter-group differences were no statistically significant in terms of HR values measured before the study drug was administered ($p > 0.05$) (Table 3). Group IV had significantly higher HR measurements performed 5 minutes after extubation (T9) than Group I ($p = 0.012$), however the groups were statistically significant indifferent from each other in terms of HR values measured at all other times ($p > 0.05$) (Table 3). When the intragroup HR values were compared according to the T2 measurement time, which was accepted as baseline value; the values measured at T7, T8 and T9 were lower than those in other measurement times for Group I ($p = 0.002$, $p < 0.001$, $p < 0.001$ respectively), those measured at T8 and T9 for Group II ($p = 0.006$, $p = 0.001$ respectively), and those measured at T7, T8 and T9 for Group III ($p = 0.029$, $p = 0.006$, $p = 0.001$ respectively). In spite of these statistically significant changes, Group

Table 2. Changes in mean blood pressure (mmHg)

HR	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)	p
T0	106.1 ± 19.8	103.1 ± 18.6	102.9 ± 13.6	97.0 ± 12.2	0.193
T1	98.4 ± 18.1	94.5 ± 13.2	102.2 ± 16.5	99.9 ± 18.9	0.355
T2	106.2 ± 21.2	103.3 ± 14.0	105.7 ± 15.3	106.0 ± 16.3	0.900
T3	104.1 ± 20.3	109.2 ± 17.3	104.7 ± 14.9	109.1 ± 20.4	0.573
T4	97.2 ± 15.0*	110.8 ± 14.7*	102.9 ± 12.2	103.9 ± 16.6	0.015
T5	98.1 ± 14.3	113.7 ± 16.4 ^o	103.3 ± 12.5	107.4 ± 19.6	0.063
T6	104.5 ± 20.9	109.9 ± 17.9	106.1 ± 14.2	107.9 ± 17.8	0.672
T7	102.7 ± 17.9	109.8 ± 16.2	104.6 ± 11.3	107.5 ± 17.4	0.326
T8	96.0 ± 22.5 [#]	101.4 ± 16.3	101.5 ± 11.2	103.3 ± 15.6	0.376
T9	96.6 ± 15.4 [#]	98.8 ± 16.2	98.9 ± 12.1 ^{&}	104.0 ± 16.8	0.288

MBP: Mean blood pressure, Group I: Esmolol, Group II: Lidocaine, Group III: Nitroglycerin, Group IV: Placebo; T0: Pre-induction, T1: TOF 25%, T2: TOF 75%, T3: 1 min after drug administration, T4: 3 min after drug administration, T5: 5 min after drug administration, T6: Pre-extubation, TOF_≥ 90%, T7: 1 min after extubation, T8: 3 min after extubation, T9: 5 min after extubation.

*p<0.05: Comparison of Group I with Group II

[#]p<0.05: Group I, intra-group comparison by base value (T2)

^op<0.05: Group II, intra-group comparison by base value (T2)

[&]p<0.05: Group III, intra-group comparison by base value (T2)

IV was statistically indifferent from T2 based on their HR values measured at all times (p>0.05) (Table 3)

Any inter-group difference was statistically insignificant for SpO₂, BIS values and extubation quality scores (p>0.05). The number of the patients whose extubation quality score was 1 in Group I, II, III and IV was 27, 26, 22, 19, respectively; the number of those with 2 was 2, 4, 6, 10, and the number of those with 3 was 1, 0, 1, 1 (p=0.173). No patients had an extubation quality score of 4 or 5.

The mean VAS measurements performed at different times were significantly lower in the Lidocaine group compared to

the Placebo (p=0.013). Despite no statistically significant inter-group difference for postoperative pain onset times, that of the placebo was shortest while the longest was of the lidocaine group (p>0.05) (Table 4)

In our study, there were no complications such as postoperative nausea/vomiting, cough, desaturation, hypotension, bradycardia, laryngospasm, bronchospasm, or breath holding. No requirement for escape medications could not be prescribed to any patient during our experiment.

Table 3. Changes in heart rates (beats/min)

HR	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)	p
T0	85.2 ± 14.6	80.7 ± 15.6	82.2 ± 13.7	79.3 ± 11.1	0.394
T1	84.3 ± 15.6	81.7 ± 19.7	82.6 ± 13.4	78.6 ± 12.6	0.543
T2	92.3 ± 16.7	94.1 ± 15.9	96.8 ± 21.3	92.2 ± 14.0	0.708
T3	90.5 ± 16.1	95.4 ± 16.1	98.6 ± 21.1	93.5 ± 16.9	0.364
T4	84.9 ± 14.1	93.5 ± 17.4	91.3 ± 18.2	89.9 ± 15.2	0.324
T5	84.3 ± 13.1	87.5 ± 22.5	88.5 ± 19.5	86.4 ± 13.8	0.914
T6	84.7 ± 14.3	91.2 ± 19.1	90.5 ± 19.4	91.5 ± 18.0	0.406
T7	80.5 ± 14.8 [#]	85.1 ± 21.9	86.5 ± 16.5 ^{&}	88.4 ± 15.4	0.346
T8	76.4 ± 15.6 [#]	81.3 ± 18.9 ^o	83.9 ± 15.4 ^{&}	87.7 ± 16.5	0.071
T9	75.0 ± 15.4 [#]	78.5 ± 16.7 ^o	80.6 ± 16.3 ^{&}	88.4 ± 14.8 [*]	0.012

HR: Heart rate, Group I: Esmolol, Group II: Lidocaine, Group III: Nitroglycerin, Group IV: Placebo; T0: Pre-induction, T1: TOF 25%, T2: TOF 75%, T3: 1 min after drug administration, T4: 3 min after drug administration, T5: 5 min after drug administration, T6: Pre-extubation, TOF_≥ 90%, T7: 1 min after extubation, T8: 3 min after extubation, T9: 5 min after extubation

*p<0.05: Comparison of Group I with Group IV

[#]p<0.05: Group I, intra-group comparison by base value (T2)

^op<0.05: Group II, intra-group comparison by base value (T2)

[&]p<0.05: Group III, intra-group comparison by base value (T2)

Table 4. Changes in postoperative VAS scores and pain onset times

	Group I (n=30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)	p
Immediately after extubation VAS	1.8 ± 2.1	1.1 ± 1.5*	2.0 ± 1.9	2.6 ± 1.8*	0.013
10 min after extubation VAS	1.8 ± 1.9	1.4 ± 1.5*	2.3 ± 1.4	3.1 ± 1.5*	<0.001
1h after extubation VAS	1.1 ± 1.5	0.7 ± 1.1*	1.2 ± 1.1	2.0 ± 1.8*	0.005
Pain onset time (min)	14.7 ± 23.6	17.5 ± 20.4	8.5 ± 12.9	7.0 ± 12.8	0.081

Group I: Esmolol, Group II: Lidocaine, Group III: Nitroglycerin, Group IV: Placebo; VAS: Visual Analog Scale; min: minute

* p<0.05: Comparison of Group II with Group IV

DISCUSSION

In this study, no statistically significant inter-group difference was observed for post-extubation MBP values measurements; and the HR value measured 5th min after extubation was lower in the esmolol group compared to the placebo. In the groups of esmolol and nitroglycerin, the HR and MBP factors significantly decreased throughout the post-extubation period, unlike pre-extubation time. No inter-group difference was found to be statistically significant for extubation quality. The mean postoperative VAS score from the measurements at all the times was lower in the lidocaine group compared to the placebo, and despite no significant intergroup difference, the pain onset time was longer in the lidocaine group.

During recovery from general anesthesia, smooth emergence and hemodynamic stability are important. In particular, airway reflex caused by endotracheal extubation may elicit various complications such as bucking, breath holding, coughing, and laryngospasm, the stimulated sympathetic nervous system may lead to severe hypertension and tachycardia (1-7). Although the exact mechanism of the cardiovascular hyperdynamic condition occurring during tracheal extubation is unknown, studies have reported that it is associated with the release of catecholamines, which starts 1 minute after extubation and continues up to 5-15 min to escalate HR and systemic vascular resistance. (1-3) In tracheal extubation, 70% of patients experience increases in both HR and arterial pressure by 20% or more (14). Studies have also reported that pain of the wound during extubation, changes in body temperature, drugs used for the antagonist of neuromuscular block, transition from controlled ventilation to spontaneous breathing, and tracheal irritation may also affect cardiovascular responses (32).

Although there are many studies investigating the dose, type and timing of administration (bolus, infusion), combination, and postoperative analgesic effects of drugs used to decline airway reflexes and hemodynamic responses that have increased from extubation, they have not demonstrated a completely successful treatment yet (2-7, 9-35). Dyson et al. have compared the effects of different doses of esmolol (1, 1.5, 2 mg per kg iv) to saline on hemodynamic response to extubation in noncardiac patients and found that the agent of 1 mg per kg administered before extubation was ineffective

on hemodynamic response, that the dose of 2 mg per kg caused hypotension and severe bradycardia, and that the dose of 1.5 mg per kg had the optimum effectiveness in controlling hemodynamic response to extubation (14). Similarly, Wang et al. have also analyzed the effects of esmolol with a variety of doses (0.5, 1, 1.5, 2 mg per kg iv) and saline on hemodynamic response to extubation in five patient groups, in which they compared the drug doses administered 2 minutes before extubation with pre-medication values, and found that esmolol of 1.5 and 2 mg per kg significantly decreased systolic blood pressure without any adverse effects in patients as well as HR value, and that the best response was received at these doses (22). Alkaya et al. made comparison of the outcomes of esmolol 2 mg per kg and saline administered to prevent hemodynamic response to extubation after elective craniotomy, and determined that esmolol provided a hemodynamic stability, increasing the quality of extubation (20). In this present study, inter-group post-extubation MBP measurements were not significantly different from each other, and the esmolol group have lower HR value measured 5 min after extubation than the placebo group. For intra-group comparisons, the esmolol of 1.5 mg per kg iv bolus significantly decreased the post-extubation MBP measurements made 3 min and 5 min later and the post-extubation HR measurements 1 min, 3 min and 5 min later, compared to those measured just before the medication (T2 = TOF 75%). The insufficient effect of the esmolol dose administered before extubation to control blood pressure in one minute may be because its hypotensive effect appears in a later period. Therefore, we think that besides the dose and type of administration, there is a need for further studies to examine whether the administration time and duration may contribute to the efficiency of the esmolol agent in limiting the hemodynamic reactions to extubation. We found the effects of esmolol of 1.5 mg per kg administered iv bolus on preventing hemodynamic responses to extubation similar to those in the literature.

Lidocaine, a sodium channel blocker, inhibits sodium channels in the neuronal cell membrane for weaker hemodynamic response to tracheal extubation. It is a direct cardiac depressant and practically has minimal hypotensive effect. It also suppresses airway reflexes and has analgesic properties. Lidocaine minimizes the incidence and severity of cough, breath holding, bronchospasm following extubation (2-6,9,10,12,16-18,24,

27,28,33-35). Savitha et al. have compared the effects of lidocaine of 0.5 and 1 mg per kg and placebo and observed that lidocaine 1 mg per kg was superior to 0.5 mg per kg in vitiating the hemodynamic reactions to tracheal extubation and cough afterwards (33). Nagrale et al. have examined how such agents as propofol, lidocaine and esmolol relieve hemodynamic response, laryngospasm and cough by administering iv for two minutes before extubation and reported that hemodynamic response, laryngospasm and cough decreased in lidocaine group, where lidocaine suppressed these reflexes by deepening anesthesia (12). Several studies have recommended lidocaine of 1.5-2 mg per kg bolus in order to control hemodynamics in airway applications (intubation, extubation, laryngoscopy), where it should be administered 2-4 minutes before the procedure (10,12,16-18, 3-35). In this present study, lidocaine 1.5 mg per kg iv bolus did not affect the MBP values measured after extubation, however, significantly reduced the post-extubation HR measurements 3 min and 5 min later from the baseline value, and these have no significant difference from other values measured. Although we use it at the dose recommended and reported to be effective, we think that lidocaine of 1.5 mg per kg administered iv bolus is insufficient to prevent hemodynamic response to endotracheal extubation.

In their studies performed administering iv saline and nitroglycerin 1.5 and 2.5 µg per kg just before intubation, Mikawa et al. have reported that the features of simplicity, practicality, effectiveness and safety can be provided with a single, rapid iv dose of nitroglycerin in attenuating the hypertensive response to laryngoscopy and tracheal intubation. They have also reported that MBP started to decline in a half minute following the iv administration of nitroglycerin and reached at maximum level three quarter minutes later and then reduced again to the baseline in 2 minutes (13). Singh et al. have compared the efficacy of saline of 5 ml, lidocaine of 1.5 mg per kg, esmolol 1.4 mg per kg, and nitroglycerin 2 µg per kg, which were administered iv 30 seconds before laryngoscopy, to alter the hemodynamic response to laryngoscopy and intubation and found that lidocaine of 1.5 mg per kg iv and nitroglycerin 2 µg per kg iv did not work out to limit the acute hemodynamic response from laryngoscopy and intubation, and however esmolol 1.4 mg per kg iv was significantly more effective than either lidocaine or nitroglycerin to limit the HR and MBP as a response to laryngoscopy and intubation (17). In this study, nitroglycerin 2 µg per kg iv bolus significantly decreased the MBP values measured at 5th minute after extubation and the HR values measured at 1st, 3rd, and 5th minute after extubation compared to baseline value, therefore we think that it may be sufficient to prevent hemodynamic response to endotracheal extubation

Cough is the most common airway reflex response to endotracheal intubation (34). Activation of cough reflex has a protective effect in preventing airway obstruction during breathing. However, coughing can cause serious complications such as cardiovascular instability, surgical

bleeding, laryngospasm, and increased intracranial and thoracic pressure. Therefore, various drugs (lidocaine, propofol, dexmedetomidine and remifentanyl) are used to prevent coughing during extubation (3,10-24,28,34,35). Sibai et al. have reported that the administration of nitroglycerin of 4 µg per kg iv was an effective therapy for post-extubation partial laryngospasm in two patients with ASA 1 risk group (36). In the present study, no significant intergroup difference was found in terms of the contributing factors to extubation quality such as cough, breathing difficulty, and laryngospasm. The study drugs were administered at a fixed time of TOF 75% in all patients, therefore this may be the reason for the absence of inter-group difference for extubation timing and quality. We think that TOF monitoring is important in determining the quality of extubation.

A number of studies have reported that esmolol reduces anesthesia requirements by its direct antinociceptive properties, relieves intraoperative MBP and HR, accelerates recovery time, and significantly reduces postoperative analgesic requirements without causing any side effects (11,19,23-26). Studies have also demonstrated that postoperative pain can be prevented by lidocaine (24,28,35). One randomized controlled study have examined the efficacy of lidocaine infusion iv for treatment of postoperative analgesia, and reported that it was safe to use, decreased the patients' pain scores, and reduced the need for postoperative analgesics (28). In studies suggesting that intravenous lidocaine has an analgesic effect varying between postoperative 2-48 hours, this difference is reported to be due to the difference in surgery regions (15,35). Patients with acute pain had perfect results except for minimal side effects when treated with transdermal nitroglycerin (21,31). The present study found that the mean VAS score computed from the measurements at all the times was lower in the lidocaine group compared to the placebo. As with the literature, we also determined that lidocaine of 1.5 mg per kg administered iv decreased the postoperative early analgesic requirement, and prolonged the time to first analgesic requirement in postoperative period, despite no statistically significant difference.

Our study has some limitations. First; the patient population in this study was not uniform, having different types of surgery. Second; the patients under the ASA I-II risk groups in the study may have affected our results. Because the patients in ASA risk group III and above (especially those with hypertension, diabetes or ischemic heart condition) are particularly prone to greater alteration in HR and MBP in the middle of anesthetic induction and extubation. Third; the evaluation of airway reflexes was limited to extubation time. Although adverse respiratory events typically occur shortly after tracheal extubation, allocating a longer time interval for the observation should be considered during the recovery period. The patients could not be followed up initially, and therefore the duration of symptoms and subsequent recovery could not be observed for a long time in the postoperative period.

Forth; other critical dimensions for pain threshold including ethnic or cultural background, educational level, fear or sleep deprivation were also left out of the evaluation. Fifth; endotracheal intubation may cause pain even partly in association with the difficulty of tracheal intubation or the physician's limited experience. It was a defect for the study that such indicators stayed out of record. Finally, the inner diameter and cuff pressure (high or low) of the tube used in endotracheal intubation, whether there is a need for re-intubation, and there was no record on the purulence of tracheal secretions before endotracheal tube and ventilation in the prone position were taken out.

CONCLUSION

In conclusion, all three agents administered at specific doses and times had no superiority to each other in preventing the hemodynamic response to extubation and higher quality of extubation, however, the inter-group comparisons revealed that esmolol and nitroglycerin (1.5 mg and 2 µg per kg) administered iv bolus were more effective in limiting the hemodynamic response to extubation. In addition, the iv administration of lidocaine of 1.5 mg per kg reduced the postoperative early VAS scores in patients as well as analgesic requirements and extended the necessary time for the first analgesic intervention in the postoperative period.

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