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Comparison between lidocaine and NaCl 0.9% inhalation in heart rate and blood pressure changes during laryngoscopy and intubation

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ABSTRACT

Introduction: Laryngoscopy and intubation is an invasive procedure routinely done during general anesthesia. The cardiovascular response to these procedures can be harmful in patients who are vulnerable, especially those who have cardiac or cerebrovascular problems. One method to attenuates the cardiovascular response was the use of anesthetics, including lidocaine. This study aimed to assess the effect of inhaled lidocaine on cardiovascular responses after laryngoscopy and intubation.

Patients and Methods: This study was a randomized double-blind clinical trial on 50 subjects who underwent elective surgery, 24 subjects were given inhaled lidocaine 1.5 mg/kgBW and 25 subjects were given 0.9 % NaCl inhalation before laryngoscopy and intubation. Cardiovascular parameters being investigated were changes in systolic and diastolic blood pressure, mean arterial pressure (MAP) and heart rate in a serial manner.

Results: In the first minute after intubation, MAP and heart rate were higher in the NaCl group. The difference in MAP was 15.5 mmHg ($p < 0.001$) while heart rate was 9.5 beats/min ($p < 0.001$). In the 3rd minute after intubation, MAP and heart rate kept different in both groups: 16.6 mmHg ($p < 0.001$) and 11.2 beats/minute ($p < 0.001$), respectively. In the 5th minute after intubation, MAP and heart rate remained different between two groups: 16.7 mmHg ($p < 0.001$) and 10.0 beats/min ($p = 0.03$), respectively.

Conclusion: Lidocaine inhalation was able to attenuate cardiovascular response due to pain stimuli and sympathetic stimulation after laryngoscopy and intubation.

Keywords: blood pressure, heart rate, intubation, laryngoscopy, lidocaine

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INTRODUCTION

Laryngoscopy and endotracheal intubation are a routine part of general anesthesia.[1,2] Laryngoscopy and endotracheal intubation are routines performed in general anesthesia. Up until now, endotracheal intubation is still the best approach in protecting the airway from aspiration during general anesthesia. The endotracheal tube is also useful in giving positive pressure ventilation during general anesthesia.[1,2] However, from various invasive interventions, laryngoscopy and intubation are the strongest pain inducer, surpassing the pain caused by rib retraction, skin incision, and abdominal exploration.[3]

Manipulation and instrumentation of airway during laryngoscopy and endotracheal intubation may cause several complications, such as increased heart rate and blood pressure due to sympathetic nerve stimulation.[2-5] Shribman *et al.*[6] reported that laryngoscopy and intubation have more role in hemodynamic changes than laryngoscopy only. This cardiovascular response can be maleficence for the patients because it can increase the need for oxygen in the heart. Activation of the renin-angiotensin-aldosterone system can also increase the blood pressure during intubation. Increased intracranial pressure can occur due to increased cerebral blood flow and can cause harm to patients with decreased intracranial compliance. In patients with increased airway reactivity, intubation can trigger bronchospasm, therefore, causing a ventilation-perfusion disturbance in the lungs.[4,5]

Clinicians are struggling in performing an intervention that pharmacologically can suppress the cardiovascular response in laryngoscopy and endotracheal intubation.[7-10] Clinicians could not find a satisfying solution due to inadequate results which were not ideal to be performed or administrated routinely for their harmful side effects.[5,11]

The use of lidocaine has been the subject of several studies. Lidocaine can be given orally, through inhalation, spray, or intravenous administration.[5,12] To facilitate laryngoscopy and intubation, oral or spray administration of lidocaine provides an uncomfortable sensation for the patient. In addition, the analgesic effect is often limited to the oropharynx area, demanding the operator to combine it with block techniques or add other drugs to make sure the patient feels comfortable during the procedure.[13,14]

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Intravenous administration of lidocaine will increase its plasma levels, which can increase the risk of developing side effects, especially in the central nervous system due to increased levels of toxic lidocaine metabolites. High plasma lidocaine levels can also interfere with the cardiovascular system. Barriers to sodium ion channels, especially in Purkinje fibers and ventricular cells, can cause depression of heart muscle contractility.[5,11] In a study where intravenous lidocaine was administrated on fibromyalgia patients, 17% of the subjects developed hypotension. The major side effects reported were lung edema and supraventricular tachycardia.[15] The Food and Drug Administration (FDA) issued a warning stating that even an infiltration or nerve block using lidocaine must be performed very carefully and administration of lidocaine into the blood vessels should be avoided.[16]

To suppress the cardiovascular response towards laryngoscopy, one of the alternatives is to administer lidocaine via inhalation. The administration of inhaled lidocaine will produce a topical, rather than systemic, effect on the respiratory tract. A lidocaine inhalation at a dose of 4 mg/kgBW will produce the same serum level as a 2 mg/kgBW dose of intravenous lidocaine.[5] Also, out of 25 people who received lidocaine inhalation with an average dose of 8.7 mg/kgBW, plasma levels <5 mg/L were obtained, demonstrating that lidocaine can be safely administered through inhalation without producing toxic plasma levels.[5]

The respiratory tract has a wide drug absorbance area with high permeability supported by good vascularization in airway epithelium. Drug's effectivity will be accomplished when the inhaled medication enters the systemic flow. Air-to-blood transfer starts when the drug interacts with tracheobronchial mucosa and surfactant in alveolus and can be absorbed quickly so the drug is not eliminated by the mucociliary response and macrophage in the airway. The drug absorption can occur because of the active and passive transport through the paracellular and transcellular transport pores.[17] Local anesthesia, such as lidocaine, in the airway mucosa, is effective if administrated topically and can decrease the reactivity of airway. Lidocaine is the most common airway topical anesthesia used.[18]

Aboumadi[15] and Sklar[11] reported that lidocaine inhalation can suppress the increased pulse rate and blood pressure due to laryngoscopy and intubation. With slightly deeper respiration for 15-30 minutes, lidocaine can give an anesthetic effect in oropharynx and trachea.[16] Administration of lidocaine by inhalation is relatively safer, more comfortable, easier and cheaper for the patients. This study aimed to assess the effect of inhaled lidocaine on cardiovascular responses after laryngoscopy and intubation.

PATIENTS AND METHODS

This study is a double-blind, randomized clinical trial to assess the effect of lidocaine inhalation 1.5 mg/kgBW compared to NaCl 0.9% inhalation on the changes of pulse rate and blood pressure during laryngoscopy and intubation intervention. The study was conducted in Cipto Mangunkusumo Hospital. The study protocol was approved by the local Committee of Ethical Clearance. All subjects involved provided written informed consent to be included in this study.

Inclusion criteria include patients underwent general anesthesia with laryngoscopy and endotracheal intubation, aged 18-55 years old, having a body weight of 40-65 kg, ASA I-II, with Mallampati I-II upon pre-anesthesia examination. The exclusion criteria include patients with cardiovascular diseases, pregnancy, airway difficulty, and airway reactivity. The drop-out criteria were intubations performed more than once, the time needed for laryngoscopy and intubation was more than 45 seconds, and signs of hypoxia during laryngoscopy intervention.

The subjects were assigned randomly to one of these two groups: Group L (Lidocaine) and Group P (placebo, NaCl 0.9%). Randomization was performed using a random table which was downloaded from www.randomizer.org. The choice of intervention was put in an envelope as concealment. The intervention towards subjects of both groups was prepared by the third party who was not involved in this study. The researcher, anesthetists, and the patients involved did not know the medications given. The inhalation of either lidocaine or placebo was given 15-30 minutes prior to the anesthesia by Omron nebulizer Ne-C28.

Cardiovascular variables such as systolic and diastolic blood pressure, mean arterial pressure (MAP), and pulse rate, was measured in series. Data T0 was the measurement of pulse rate and blood pressure right before inhalation was given. Data T1 was the measurement after the inhalation was given. Premedication used was 0.05 mg/kgBW midazolam and 2 µg/kgBW fentanyl. Two minutes after the premedication, T2 was recorded. Induction was performed using propofol 2 mg/kgBW followed by muscle relaxant of 0.5 mg/kgBW atracurium and manual ventilation support. Just before the laryngoscopy and intubation procedure, T3 was recorded. Endotracheal intubation was performed by an advanced anesthesiology resident. This procedure must be done in less than 45 seconds and in one attempt. One minute after

intubation, T4a was measured, followed by T4b and T4c on minute-3 and minute-5, respectively.

The data were processed using the SPSS 16.0 software. The result was described in mean and standard deviation. The difference test of both numeric variables was the comparison of the mean of both groups using unpaired t-test if the data distribution was normal and the data variance was indifferent. If the data distribution was not normal or the data variance was different, Mann-Whitney test would be performed. A p-value of <0.05 was considered significant.

RESULTS

This study was conducted in 50 subjects. One subject dropped out due to the time duration needed to perform laryngoscopy and intubation was more than 45 seconds. Therefore, the total number of patients analyzed was 49. The majority of the subjects (63.3%) was female with a median age of 33 (18-55) years old. Description of subjects' characteristics is shown in Table 1.

In both groups, the baseline value (T0) does not have any significant difference in the mean of the four cardiovascular variables (systolic blood pressure, diastolic blood pressure, MAP, and pulse rate) as shown in Table 2. The mean of post-inhalation cardiovascular response until 5 minutes after intubation (T1-T4C) can be seen in Table 3. From T1-T3 data, we found that both groups did not have any significant differences.

T2 and T3 values showed no significant difference in the tendency of cardiovascular responses to decrease. Measurements of T3-T4C in both groups showed more pronounced changes, with the lidocaine group showing smaller values than the NaCl group.

The researchers then compared the differences in cardiovascular variables between the two groups after laryngoscopy and intubation to determine the significance level of these differences with unpaired t-test or Mann-Whitney test (Table 4). There were significant differences in all cardiovascular parameters in the 1st, 3rd and 5th-minute post-intubation (p <0.05).

Mean difference of changes in the cardiovascular responses are schematically presented in figure 1, 2, 3 and 4. It appears that in all four cardiovascular variables, the group with lidocaine inhalation was more stable post-intubation. The unpaired t-test or Mann-Whitney between the two groups showed a significant difference in the four cardiovascular variables in T4A to T4C (p <0.05).

Three minutes after intubation (T4B), the difference in systolic blood pressure between the two groups became 13.8 (95% CI 5.4-22.2) mmHg (p <0.001), diastolic blood pressure 11.8 (95% CI 6, 5-17.2) mmHg (p <0.001), difference in MAP 12.9 (95% CI 6.4-19.3) mmHg (p <0.001) and difference in heart rate 12.0 (95% IK 6, 3-17.8) beats/minute (p <0.001).

This difference continued up to five minutes post-intubation (T4C). The difference in systolic blood pressure became 15.2 (95% CI 10.4-20.1) mmHg (p <0.001), diastolic blood pressure 11.7 (95% CI 7.0-16.3) mmHg (p < 0.001), MAP

Table 1 Characteristics of Subjects

Characteristic	Lidocaine (L) group N = 24	NaCl 0.9% (P) group N = 25
Sex, n(%)		
Male	10 (41.7)	8 (32.0)
Female	14 (58.3)	17 (68.0)
Age (years), median(min-max)	30 (18-55)	42 (19-55)
ASA physical status, n(%)		
1	7 (29.2)	8 (32.0)
2	17 (70.8)	17 (68.0)

ASA: American Society of Anesthesiologists

Table 2 Characteristics of cardiovascular response in both group in T0 (mean±SD)

Cardiovascular variables	Lidocaine N= 24	NaCl N=25
Systolic blood pressure (mmHg)	125,6 ± 9,7	125,6 ± 13,9
Diastolic blood pressure (mmHg)	80 (64-90)	77,0 ± 7,0
MAP (mmHg)	92,3 ± 6,3	93,3 ± 10,8
Pulse rate (x/minute)	80 (65-116)	84,2 ± 13,4

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Table 3 Post-inhalation cardiovascular responses in the two groups during intervention

Hemodynamic variable	T1	T2	T3	T4A	T4B	T4C
NaCl 0.9%						
Systolic (mmHg)	126.0 ± 12.0	113.5± 11.4	96.3 ± 14.6	127 (80-135)	123.2 ± 18.5	119.9 ± 9.2
Diastolic (mmHg)	78.5 ± 8.4	71.0 ± 8.2	61.4 ± 10.8	79 (50-91)	77.8 ± 9.3	75.0 ± 8.2
MAP (mmHg)	93.9 ± 9.8	85.0 ± 8.6	72.9 ± 11.1	96 (60-101)	92.4 ± 13.3	90.0 ± 7.9
Heart rate (beats/minute)	88 (53-105)	76.0 ± 9.6	72.2 ± 9.8	82.2 ± 13.2	82.6 ± 12.0	80.7 ± 13.6
Lidocaine						
Systolic (mmHg)	125.0 ± 10.3	111.6 ± 10.5	104.2 ± 7.2	109.6 ± 9.3	112 (90-120)	104.6 ± 7.7
Diastolic (mmHg)	77.9 ± 8.1	69.3 ± 7.2	63.3 ± 8.1	66.4 ± 10.1	66.0 ± 9.3	65 (40-83)
MAP (mmHg)	92.2 ± 8.1	82.3 ± 6.7	76.7 ± 6.7	80.2 ± 9.4	81 (55-91)	76 (55-96)
Heart rate (beats/minute)	80 (64-106)	75(60-106)	69 (58-100)	71.9 ± 7.6	71 (54-80)	72 (51-81)

Numerical data with normal distribution are shown in mean ± SD.
Numerical data with abnormal distribution are displayed in the median with minimum and maximum values.
T1: post-inhalation; T2: post-coinduction; T3: post-induction; T4 A-C: 1, 3, and 5 minutes after laryngoscopy and intubation; MAP: mean arterial pressure

Table 4 Comparison of the cardiovascular response changes after laryngoscopy and intubation between the two groups

Cardiovascular variable	Lidocaine N= 24	NaCl N=25	p	95% CI
Systolic blood pressure				
1 minute post-intubation	5.4 ± 8.4	27.8 ± 14.9	<0.001[a]	22.5 (15.5-29.4)
3 minutes post-intubation	5.3 ± 11.1	32.0 (-22.0-51.0)	<0.001[b]	21.7 (12.8-30.6)
5 minutes post-intubation	0.4 ± 9.7	23.6 ± 12.8	<0.001[a]	23.2 (16.6-29.7)
Diastolic blood pressure				
1 minute post-intubation	3.1 ± 10.4	13.8 ± 14.1	0.004 [a]	10.7 (3.6-17.8)
3 minutes post-intubation	2.7 ± 10.1	16.4 ± 12.8	<0.001[a]	13.7 (7.1-20.4)
5 minutes post-intubation	0.1 ± 9.9	13.6 ± 10.7	<0.001[a]	13.6 (7.6-19.5)
MAP				
1 minute post-intubation	3.5 ± 9.2	19.0 ± 12.2	<0.001[a]	15.5 (9.2-21.7)
3 minutes post-intubation	2.9 ± 9.7	19.5 ± 14.1	<0.001[a]	16.6 (9.6-23.6)
5 minutes post-intubation	0.4 ± 8.9	17.1 ± 9.9	<0.001[a]	16.7 (11.3-22.2)
Heart rate				
1 minute post-intubation	1.5 (-27.0-10.0)	10.0 ± 8.6	<0.001[b]	9.5 (4.8-14.2)
3 minutes post-intubation	1.0 (-34.0-14.0)	10.4 ± 10.7	<0.001[b]	11.2 (5.2-17.2)
5 minutes post-intubation	0.0 (-42.0-10.0)	8.5 ± 11.6	0.003 [b]	10.0 (3.5-16.5)

Note: Numerical data with normal distribution are shown in mean ± SD. Numerical data with abnormal distribution are displayed in the median with minimum and maximum values. The data shows differences in cardiovascular variables between post=intubation (T4A-C) and post-induction (T3). [a]Unpaired t-test; [b]Mann-Whitney test

113.0 (95% CI 8.4-17.5) 2.9 (95% CI 6.4-19.3) mmHg (p <0.001) and heart rate 10.8 (95 % CI 4.4-17.2) beats/minute (p <0.001).

In the first minute after intubation (T4A), the comparison of cardiovascular variables between the NaCl and lidocaine groups was as follows. The difference in systolic blood pressure between the NaCl and lidocaine groups was 14.5 (95% CI 8.3-20.7) mmHg (p <0.001). The diastolic blood pressure of the NaCl group was 8.8 (95% CI 3.0-14.7) mmHg (p = 0.001). MAP difference was 11.7 (95% CI 6.4-17.0) mmHg (p <0.001) while the difference in pulse rate was 10.3 (95% CI 4.0-16.5) beats/minute (p <0.001).

In this study, researchers also collected data on the subjects' convenience when given lidocaine inhalation. As many as 17 of the 24 subjects with lidocaine inhalation (70.8%) reported a bitter sensation in the mouth during inhalation. No other complaints were found during monitoring.

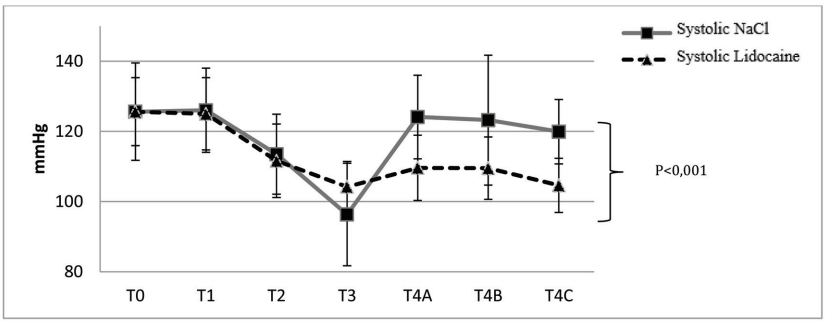

Figure 1 Mean difference of changes in systolic blood pressure between subjects with NaCl and lidocaine inhalation

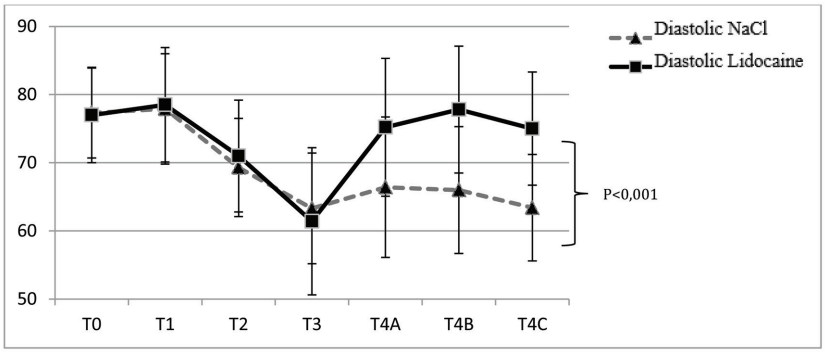

Figure 2 Mean difference of changes in diastolic blood pressure between subjects with NaCl and lidocaine inhalation

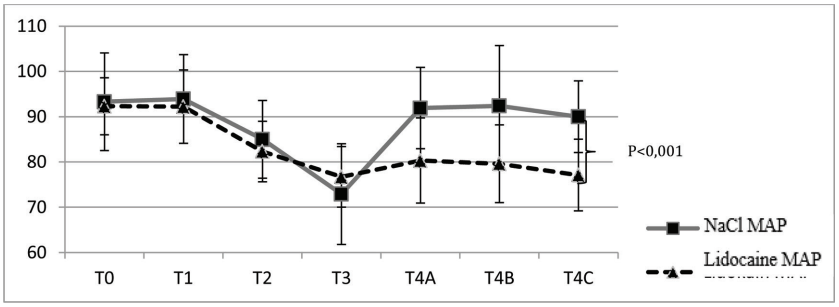

Figure 3 Mean difference of changes in MAP between subjects with NaCl and lidocaine inhalation

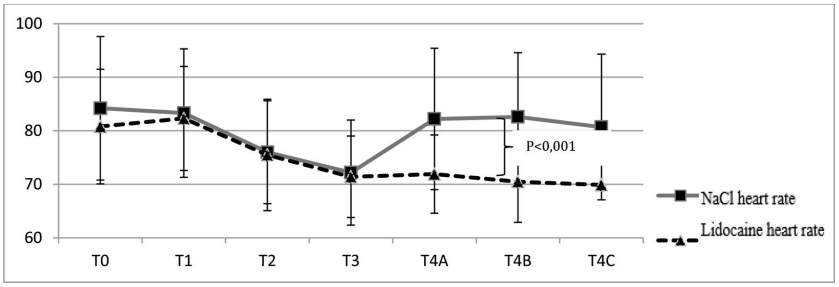

Figure 4 Mean difference of changes in heart rate between subjects with NaCl and lidocaine inhalation

DISCUSSION

In this study, we found that lidocaine inhalation before laryngoscopy and intubation provided benefits in maintaining the cardiovascular conditions of post-intubation patients. The study by Shribman et al.[19] demonstrated that laryngoscopy stimulates pain, observed from the surge of sympathoadrenal response, which then increases both the patient's blood pressure and heart rate. This response comes from the stimulation of the supraglottic region. In addition, intubation further increases this response due to tube placement through the vocal cords and the presence of expanding cuffs in the infraglottic region.

Laryngoscopy only provides a moderate stimulus while intubation increases the degree of the stimulus. Changes in cardiovascular responses occur due to these stimulations and can be objectively measured by an increase in the patient's catecholamine levels. Efferent sympathetic stimuli toward the heart originate from the T1-T4 spinal cord, and those toward the adrenal medulla originate from T3-L3. Supraspinal modulation also plays a role in this arrangement.[17] The sympathoadrenal response can cause a surge in blood pressure up to 40-50% in the first to fifth minutes post-intubation.[18]

A similar phenomenon is observed from changes in cardiovascular variables in the control group of this study. A surge of cardiovascular response changes occur from the first minute after intubation with an increase in blood pressure and MAP up to around 20-30% (table 3). Such responses remained pronounced even when the patient was under general anesthesia. Therefore, efforts to reduce these responses are needed to improve patient safety and comfort.

Kovac[5] stated that efforts to minimize cardiovascular responses are important especially if the patient has cerebrovascular or cardiovascular abnormalities because intubation can increase intracranial and intraocular pressure. Nearly half of patients with coronary heart disease experience episodes of post-intubation ischemia.[20-22]

The findings of this study are in line with findings by Venus et al.[23] and Sklar et al.,[11] who found that lidocaine inhalation was able to suppress heart rate changes in post-intubation subjects. Compared to changes in cardiovascular variables at the time after induction, systolic and diastolic blood pressure, MAP, and heart rate at 1 minute, 3 minutes, and 5 minutes after intubation in both groups had significant mean differences. After induction of anesthesia, the lidocaine group had more stable cardiovascular variables and the smaller changes compared to the control group.

Both the lidocaine and NaCl 0.9% in this study were given through inhalation. The types of drugs given to the subjects also do not affect blood pressure and heart rate, so from the beginning, the two groups were in a balanced hemodynamic condition. A clinical trial that specifically compared

lidocaine inhalation and control (NaCl) came from the study by Venus et al.[23] who found that inhaled (aerosolized) lidocaine did not cause changes in cardiovascular responses, compared to the significant increase in cardiovascular responses that the control group experienced.

At toxic doses or at plasma levels that are high enough, a level of lidocaine exceeding 5 mg/L can induce several adverse effects, one of which is cardiovascular impairment, which can cause hemodynamic disorders. At the usual dosage of lidocaine, these adverse effects can be avoided and impose no effects on hemodynamics.[22] This is in line with our current study, which compared the effect of lidocaine inhalation with a control group. Statistically and clinically, there were no significant differences in post-inhalation cardiovascular responses in the two treatment groups.

The right dose of lidocaine to suppress cardiovascular responses during laryngoscopy and intubation cannot yet be determined. This is because subjects also received fentanyl at 2 μg/kgBW, deeming it possible for the drugs to create a synergistic effect in suppressing cardiovascular responses during laryngoscopy and intubation.

This study also found that patients given lidocaine inhalation felt quite comfortable. General complaints such as a bitter taste in the mouth do not have a significant impact on patients, therefore still acceptable for routine use. This study did not find any significant adverse effects of lidocaine inhalation. Available evidence reveals the safe dosage of lidocaine inhalation to be 100-200 mg with a maximum tolerable dose of 600 mg. Inhaled lidocaine can prevent bronchial hyperreactivity, making it possible for off-label use in asthmatic patients. Inhaled lidocaine provides local and spasmolytic anti-inflammatory effects.[23] Regarding the safety of lidocaine inhalation, Lim et al. conducted a long-term study in patients using lidocaine inhalation for symptoms of chronic cough and discovered no significant adverse effects.[24]

LIMITATIONS OF THE STUDY

This study has several limitations. First, the equipment used for inhalation was an inhalation mask. This mask has a maximum limit for accommodating the fluid that will eventually evaporate from the administration of oxygen at 8-10 L/minute, demanding the researchers to limit the weight of patients who could participate in this study.

Another limitation was that the researchers did not monitor swallowing difficulties and hemodynamic changes after anesthesia, because the incidence of complications and adverse effects due to lidocaine inhalation still has the potential to occur at more than 5 minutes after the induction of anesthesia. Undetected problems related to side effects and complications from lidocaine inhalation may exist beyond the time of post-induction observation. The occurrence of sore throat related to post-intubation complications was also not assessed, considering its frequent occurrence after intubation. The same applies for swallowing difficulties during inhalation. The administration of lidocaine through inhalation can cause difficulty in swallowing, which may be dangerous for the patient or significantly reduce comfort. In the treatment group, the majority of patients only reported a bitter taste in the mouth, so it can be assumed that the dose of 1.5 mg/kgBW of lidocaine did not cause difficulty in swallowing.

This study did not measure systemic levels of catecholamine and lidocaine. Blood catecholamine level is a systemic marker of increased sympathetic tone associated with cardiovascular responses. Measurement of the plasma level of lidocaine in this study can help inform the safety and tolerance of lidocaine inhalation.

The disadvantage of the inhalation technique in this study is a prolonged time for anesthesia preparation. The inhalation procedure needs 30 minutes to perform before anesthesia.

CONCLUSION

Lidocaine inhalation was able to attenuate cardiovascular response due to pain stimuli and sympathetic stimulation after laryngoscopy and intubation better compared to NaCl 0.9% inhalation.

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The authors report no conflict of interests.

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