Effects of Intravenous and Inhaled Nebulized Lignocaine on the Hemodynamic Response of Endotracheal Intubation Patients: A Randomized Clinical Trial

Abolfazl Jokar, Maryam Babaei, Sahar Pourmatin, Majid Taheri1, Amir Almasi-Hashiani2, Arash Yazdanbakhsh

Department of Medical Emergency, Arak University of Medical Sciences, Arak, Iran, 1Medical Ethics and Law Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran, 2Department of Epidemiology and Reproductive Health, Reproductive Epidemiology Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran

Abstract

Background: Endotracheal intubation is one of the most common measures in the Intensive Care Unit (ICU) which plays an important role in airway management of the critically ill patients. Aims: The study aimed to evaluate the effects of lignocaine spray on hemodynamic response of endotracheal intubation patients. Settings and Design: This study is a randomized clinical trial on a study population comprising patients admitted to the ICU. Subjects and Methods: The patients were divided into three groups using a permuted block randomization. In Group 1, inhaled nebulized lignocaine 4% (75.0 mg/kg) was sprayed around the patients’ epiglottis and larynx. In Group 2, intravenous (IV) lignocaine 2% (75.0/mg/kg) was injected. No lignocaine was prescribed for or administered to the control group. One and four minutes after intubation, the patients’ hemodynamic and vital signs were measured. Statistical Analysis Used: Data analysis was run using Stata 13 software through repeated measure ANOVA tests. Results: Although the mean arterial blood pressure (MAP) of Group 1 (inhaled nebulized lignocaine) was smaller than that of Group 2 (IV lignocaine), there was no significant difference between the two groups. Both groups’ MAPs were significantly different from that of the control group. As for the average number of pulses, a significant difference was observed between the inhaled and IV lignocaine groups; hence, the average number of pulses in Group 1 (inhalation) was lower than that of Group 2 (IV injection). Conclusion: As blood pressure is considered to be normal under 140/90 and may not entail any hemodynamic complications, it can be concluded that inhaled nebulized lignocaine can control the hemodynamic changes of intubation more effectively than IV lignocaine.

Keywords: Endotracheal intubation, hemodynamics, lignocaine

INTRODUCTION

One of the most common measures in the Intensive Care Unit (ICU) is endotracheal intubation which plays a key role in airway management of critically ill patients. Issues such as hemodynamic instability, hypoxemia, and acidosis in ICU patients indicate the need to maintain an adequate tracheal airway. Poor physical condition of the patient, emergency intubation, and the use of drugs to induce anesthesia during intubation may cause a variety of complications in patients. According to several studies, the rate of these complications is about 54%. One such complication is the stimulation of the sympathetic system, the adverse effects of which often include hemodynamics, hypertension, and tachycardia. This group of complications may increase the incidence of morbidity and mortality among patients with cardiovascular and underlying cerebrovascular diseases. Therefore, different drugs and methods have been proposed to relieve such stimulation-induced responses. One such drug is lignocaine.

Lignocaine is injected around the dura mater or below the spinal cord to induce spinal anesthesia. Intravenous (IV) lignocaine

Access this article online

Quick Response Code:
Website: www.aeronline.org
DOI: 10.4103/aer.AER_75_17

Address for correspondence: Dr. Arash Yazdanbakhsh, Department of Medical Emergency, Arak University of Medical Sciences, Arak, Iran. E-mail: yazdanbakhsh.arash@gmail.com

How to cite this article: Jokar A, Babaei M, Pourmatin S, Taheri M, Almasi-Hashiani A, Yazdanbakhsh A. Effects of intravenous and inhaled nebulized lignocaine on the hemodynamic response of endotracheal intubation patients: A randomized clinical trial. Anesth Essays Res 2018;12:159-64.
is used to induce cardiac arrhythmias, particularly ventricular arrhythmias. It is a Class Ib antiarrhythmic drug that is effective in the zero phase of the cardiac cells’ action potential. It reduces the electrical conduction velocity across the myocardial conduction system. Competing with calcium to sit in nerve membrane receptors, lignocaine controls the passage of sodium beyond the cell membrane and reduces the depolarization phase’s action potential. Such effects contribute to the reversible consolidation of nerve cell membranes by reducing the permeability of the membrane to sodium ions and prevent the initiation and conduction of impulses.\[7\]

Different studies evaluate the effects of lignocaine on the hemodynamic response of intubated patients. Most of these studies, however, attempt to investigate the effect of IV lignocaine in comparison to other drugs or control groups. For instance, by comparing the effects of lignocaine and fentanyl on the hemodynamic response of tracheal intubation patients, Splinter and Cervenko\[9\] observe that IV lignocaine reduces the patients’ systolic blood pressure (SBP) more effectively than fentanyl. It is also shown that lignocaine complications are less than those of fentanyl. Feng et al.,\[10\] on the other hand, do not report any effect of IV lignocaine on the hemodynamic response in patients undergoing intubation and laryngoscopy, as opposed to the reported for fentanyl.

According to the existing studies, the effects of lignocaine on improving the hemodynamic response of intubation patients are yet to be fully understood,\[10,11\] and the use of lignocaine spray – rather than IV lignocaine – is more convenient and brings about fewer complications.\[11,12\] Hence, it seems quite feasible to carry out a clinical study to evaluate the effects of lignocaine spray on the hemodynamic response of intubation patients. In addition, due to the complications associated with the hemodynamic response of intubation patients, improving such responses is of great significance. The aim of the present study is to evaluate the effects of lignocaine spray on the hemodynamic response of endotracheal intubation patients admitted to Vali-Asr Hospital.

**Subjects and Methods**

**Trial design**

The study is a single-blind randomized clinical trial designed in a parallel.

**Participants**

The participants of the trial were selected among patients admitted to the ICU showing indications of orotracheal intubation. Based on the patients’ history, they were categorized under Classes I and II of the American Society of Anesthesiologists (ASA). Sampling was carried out through availability sampling, using some inclusion and exclusion criteria.

Patients admitted to the ICU comprised the target population of this study. Patients in the age group of 25–40 years admitted to the ICU of the Vali-Asr Hospital constituted the study population. The sampling technique used in the study is availability sampling.

Inclusion criteria include being 25–40-years old; being admitted to the ICU; showing indications of endotracheal intubation; not having such underlying diseases as diabetes, hypertension, cardiovascular disease, kidney and liver diseases, respiratory diseases, and recent respiratory infection; belonging to ASA Grade I and II; and filling out the informed consent form. Patients with a history of treatment with and/or allergy to lignocaine, patients with past life-threatening medical complications, and pregnant and nursing patients were excluded from the study.

**Interventions**

The main drugs for intubation of the three groups of patients include fentanyl 2 mg/kg, midazolam 2 mg, atracurium 5.0 mg/kg, and nesdonal 5 mg/kg. After being prepared and made ready for injection, they were intravenously injected into the patients in 1 min. We waited for another minute for the maximum effect of drugs and the induction of anesthesia. Then, the orotracheal intubation was carried out. After confirmation of the orotracheal intubation and the accuracy of endotracheal tube placement, the endotracheal tube was fixed in its place.

For patients placed in Group 1, the following procedure was followed. First, their mouth was opened and 75.0 mg/kg of inhaled nebulized lignocaine 4% was sprayed around their epiglottis and larynx. Having sprayed the lignocaine, the main drugs including fentanyl 2 mg/kg, midazolam 2 mg, atracurium 5.0 mg/kg, and nesdonal 5 mg/kg were administered to the patients within 1 min. The patients’ hemodynamic and vital signs were measured. About 2 min after the start of administration of anesthetic drugs, intubation was carried out. Immediately after intubation, another 75.0 mg/kg of inhaled nebulized lignocaine 4% was sprayed around the patients’ epiglottis and larynx.

For patients placed in Group 2, the following procedure was followed. First, 75.0 mg/kg of IV lignocaine 2% was intravenously injected into the patients. Having injected the lignocaine, the same main drugs used for Group 1 were administered to them within 1 min. Their hemodynamic and vital signs were then measured. About 2 min after the start of anesthetic drugs prescription, intubation was carried out. Immediately after intubation, another 75.0 kg⁻¹ of lignocaine 2% was intravenously injected into the patients. For patients in the control group, no lignocaine was administered to patients; only the essential drugs were injected. In all three groups, both 2 and 5 min after anesthesia induction (i.e., 1 and 4 min after intubation), the patients’ hemodynamic and vital signs were measured.

**Outcome**

Hemodynamic and vital signs include SBP, diastolic blood pressure (DBP), heart rate (HR), and mean arterial blood pressure (MAP). Using a prepared checklist, these parameters were all measured for all patients and values were recorded.
both “before” and (2 and 5 min) “after” anesthesia induction. SBP and DBP values were measured using noninvasive blood pressure amplifier pressure gauges, HR was measured through cardiac monitors, and arterial blood pressure was calculated using the following formula:

\[
\text{MAP} = \frac{\text{SBP} + 2\text{DBP}}{3}
\]

**Sample size**

For each of the three groups of 64 participants each and the total number of 192 patients, the sample size was set based on the alpha coefficient of 0.05, effect size of 10, and 80% power.

**Randomization and sequence generation**

Patients were randomly allocated to three groups using a balanced block randomization technique. For this, they were divided into six blocks. The subjects were allocated to the three groups with the help of an online application called “Sealed Envelope.”\(^\text{13}\) In this study, allocation concealment was ensured through the use of balanced block randomization and allocation of unique codes to each individual. Owing to random allocation, the distribution of potential confounding variables can be considered to be identical between the two groups; hence, their confounding role was controlled.

**Ethical considerations**

Before inclusion in the study, all patients were provided with proper explanation about the study and signed the informed consent form. The participants were free to refuse to participate and to withdraw from the study. All the research group members were required to comply with all the provisions of the Declaration of Helsinki.

**Implementation**

Random allocation sequence was performed by our colleague, who is a methodologist, through the Sealed Envelope website. Eligibility assessment of the patients and their allocation were conducted by the emergency resident under the supervision of the main researcher responsible for the project.

**Blinding**

In this study, the researcher in charge of measuring the desired outcomes in different groups and the statistical analyst were both blind to the allocation of patients to different groups.

**Statistical procedure**

Data analysis was run using Stata 13 (Stata Corp, College Station, TX, USA) software through ANOVA and repeated measure ANOVA statistical tests. \(P < 0.05\) was set as the significance level.

**RESULTS**

In this study, 192 patients were randomly allocated to three treatment groups (64 patients/group) and analyzed. The study analysis approach was that of intention to treat. Patients’ flowchart is shown in Chart 1.

The baseline data for each of the three groups are shown in Table 1. Gender distribution among the three groups is similar \((P = 0.618)\). In all, 58 people in Group 1 (inhaled nebulized lignocaine) (90.63%), 55 people in Group 2 (IV lignocaine) (85.94%), and 58 people in the control group (90.63%) were male. As shown in Table 1, at the baseline, the confounding variables were evenly distributed among the three groups, and no significant difference was observed between them. This indicates that the randomization process had created three comparative groups. Table 1 also shows the extent to which the results of this study are generalizable.

Table 2 displays the mean MAP and the number of pulses at different times for different treatment groups. Repeated measure ANOVA test showed a significant difference between the mean MAP of different treatment groups \((P = 0.001)\). Changes in MAP mean over time were also statistically significant \((P = 0.001)\). The interaction between time and groups, on the other hand, was statistically significant \((P = 0.001)\). This means that changes in MAP mean over time were different among the treatment groups. The average reduction of MAP in Group 1 was faster than those in other groups. As seen in Figure 1, although the MAP of Group 1 (inhalation) was clinically smaller than that of Group 2 (IV lignocaine), there was no significant difference between the two groups \((P = 0.116)\). There was, however, a significant difference between these two groups, as compared to the control group.

Repeated measure ANOVA test showed a significant difference between the average number of pulses in different treatment groups \((P = 0.001)\). The average number of pulse changes over time was also statistically significant \((P = 0.001)\). The relationship between time and groups, on the other hand,

| Table 1: Comparison between the basic characteristics of independent variables for each group |
|-----------------------------------------------|
| Variables | Inhaled group | Group IV | Control group | P |
| Age | 31.46 (5.29) | 31.95 (4.32) | 33.12 (4.01) | 0.111 |
| Weight | 75.48 (16.15) | 73.42 (15.40) | 77.07 (16.49) | 0.434 |
| SBP | 138.7 (13.69) | 138.95 (13.50) | 138.73 (13.69) | 0.994 |
| DBP | 76.23 (8.40) | 76.84 (8.07) | 76.23 (8.40) | 0.891 |
| MAP | 97.06 (8.24) | 97.54 (7.80) | 97.06 (8.24) | 0.928 |
| SBP=Systolic blood pressure, DBP=Diastolic blood pressure, MAP=Mean arterial blood pressure |

| Table 2: Average mean arterial blood pressure and number of pulses at different times for different treatment groups |
|-----------------------------------------------|
| Variables | Inhaled group | Group IV | Control group |
| Pulse | 89.14 (6.44) | 88.11 (7.77) | 88.73 (6.84) |
| Pulse 2 | 77.37 (6.58) | 90.12 (6.83) | 90.50 (11.56) |
| Pulse 3 | 71.87 (8.02) | 74.32 (9.81) | 76.23 (8.40) |
| MAP | 97.06 (8.24) | 97.54 (7.80) | 97.06 (8.24) |
| MAP 0 | 83.58 (7.16) | 86.60 (9.10) | 94.63 (10.06) |

MAP=Mean arterial blood pressure
was statistically significant ($P = 0.001$). This means that the average number of pulse changes over time was different among the treatment groups. The average reduction of pulses in Group 1 (inhalation) was faster than those in other groups. As it can be seen in Figure 2, there was a significant difference between the two treatment groups ($P = 0.001$). However, there was no significant difference between Group 2 (IV lignocaine) and the control group ($P = 0.404$).

**Discussion**

According to the findings of this study, there is a significant difference between the MAP means of the three treatment groups. Although the Group 1 (inhalation) MAP was smaller than that of Group 2 (IV lignocaine), there was no significant difference between the two groups. There was, however, a significant difference between these two groups and the control group. In addition, MAP mean changes over time were also significant. The interaction between time and groups was also statistically significant, which means MAP mean changes over time were different among the treatment groups. Moreover, the average reduction of MAP in Group 1 (inhalation) was faster than those in other groups.

Splinter and Cervenko\(^8\) show that fentanyl increases SBP, diastolic pressure, average arterial blood pressure, and HR. However, as illustrated in this study, lignocaine leads to a significant reduction in arterial blood pressure. The results of the study also show that the incidence of drug complications in the group receiving lignocaine is significantly lower than that of the group treated with fentanyl. Nevertheless, the results of our study indicate that administration of lignocaine through inhalation leads to a decrease in MAP and HR of the patients even more rapidly than IV injection.
Venus et al.\cite{12} report that mean blood pressure and HR after intubation in the inhaled nebulized lignocaine group was significantly less than that of their control group of patients who received normal saline spray. In addition, the number of premature ventricular contraction in their case group was significantly less than that in their control group. The findings of our study are in line with those of Venus et al.; the MAP and HR after intubation were significantly lower in the inhaled nebulized lignocaine group than the control group.

Ugur et al.\cite{14} divided patients into four groups, all of them were under the administration of routine induction of anesthesia. Group 1, the control group, received 5 ml of dextrose 5%; Group 2 received 5.1 mg/kg Esmolol; Group 3 received 1 mg/kg fentanyl; and Group 4 received 1.5 mg/kg lignocaine. In this study, HR and MAP were measured before intubation, upon intubation, and 1, 3, 5, 7, and 10 min after intubation. The results indicate that – in comparison to the control group – HR in the esmolol 5.1 mg/kg group decreased significantly immediately after intubation and 1 min afterward. In Group 3 (administered 1 mg/kg fentanyl), arterial blood pressure increased immediately after intubation. The amount of increase, however, was lower than those of other groups. Overall, the results show that administering esmolol 2 min before intubation can effectively prevent tachycardia.

Lee and Park studied the effect of lignocaine spray on the hemodynamic changes of intubation in 60 patients. They report that MAP (2.5 and 5 min after intubation) and HR (2.5 min after intubation) were significantly higher in the control group than in the case group.\cite{11} However, in our study, the interaction between time and groups was significant. The process of change was also significantly different among the groups; MAP in the two groups (inhaled vs. IV lignocaine) was lower than that in the control group at different times. As for the HR, however, no significant differences were observed between the control group and the IV lignocaine group. Moreover, the mean HR at time 2 as compared to time 1 was not significantly different between the IV lignocaine group and the control group.

Feng et al. did an elective surgery to evaluate the effect of esmolol, IV lignocaine, and fentanyl on patients’ hemodynamic response during laryngoscopy and endotracheal intubation. Their results indicate that, among all drugs, only esmolol may have a protective effect against the increase of HR and SBP, and lignocaine has no effect on hemodynamic response.\cite{9} However, their study findings contradict the findings of our study. In the study done by Feng et al., 80 patients were treated in four groups; while in our study, sample size was larger (192 patients in three groups); the present study is more powerful in determining the meaningful and significant differences. However, it is recommended that further studies with larger sample sizes be carried out in this regard.

A study by Hanci et al. on 80 patients in the age group of 18–60 years, divided into four groups, indicated that using esmolol 0.5 mg/kg before intubation can be a protective factor against tachycardia and arterial blood hypertension during endotracheal intubation and laryngoscopy.\cite{7}

Since this study was conducted on emergency department patients, one of its limitations is that the department was almost always busy. The other limitation of our study is its eligibility assessment of the patients and their allocation as well as problems in taking informed consent due to the special conditions of emergency departments. The main strengths of the present study include the appropriate sample size of patients as compared to similar studies and no loss in follow-up with the patients. Since some of the results of this study contradict the findings of our study, it is recommended that further studies with larger sample sizes should be conducted in different population groups.

**Conclusion**

Although the MAP of Group 1 (inhalation) was smaller than that of Group 2 (IV lignocaine), there was no significant difference between the two groups. There was, however, a significant difference between these two groups and the control group. As for the average number of pulses, a significant difference was observed between the two treatment
groups (inhaled vs. IV lignocaine); the average number of pulses in the Group 1 (inhalation) was lower than that of the Group 2 (IV lignocaine). As long as blood pressure is considered to be normal under 140/90 and is deemed unlikely to bring about any hemodynamic or cardiovascular complications, it can be concluded that inhaled nebulized lignocaine can control the hemodynamic changes of intubation better than IV lignocaine.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Al-Khafaji A, Cho SM. Airway management in critically ill patients. Chest 2007;132:1714.
2. Jablonka D, Rosenblatt W. Airway management in the Intensive Care Unit. In: O’Donnell J, Nácul F, editors. Surgical Intensive Care Medicine. US: Springer; 2010. p. 13-24.
3. Kord Valeshabad A, Nabavian O, Nourijelyani K, Kord H, Vafainejad H, Kord Valeshabad R, et al. Attenuation of hemodynamic responses to laryngoscopy and tracheal intubation: Propacetamol versus lidocaine - A randomized clinical trial. Anesthesiol Res Pract 2014;2014:170247.
4. Ege EM, Bilgin BA, Alanoglu Z, Akbaba M, Denker C. Comparison of bolus and continuous infusion of esmolol on hemodynamic response to laryngoscopy, endotracheal intubation and sternotomy in coronary artery bypass graft. Braz J Anesthesiol 2014;64:247-52.
5. Reid C, Chan L, Tweeddale M. The who, where, and what of rapid sequence intubation: Prospective observational study of emergency RSI outside the operating theatre. Emerg Med J 2004;21:296-301.
6. Talikoti AT, Dinesh K, Deepak VD, Nanda A, Somasekharam P. Comparison of injection lignocaine (preservative free) 1.5 mg/kg i.v with oral pregabalin 150 mg for attenuation haemodynamic response to laryngoscopy and tracheal intubation. J Indian Med Assoc 2013;111:692-6.
7. Hanci V, Yur tłu S, Karabağ T, Okyay D, Hakimoğlu S, Kayhan G, et al. Effects of esmolol, lidocaine and fentanyl on P wave dispersion, QT, QTc intervals and hemodynamic responses to endotracheal intubation during propofol induction: A comparative study. Braz J Anesthesiol 2013;63:235-44.
8. Splinter WM, Cervenko F. Haemodynamic responses to laryngoscopy and tracheal intubation in geriatric patients: Effects of fentanyl, lidocaine and thiopentone. Can J Anaesth 1989;36:370-6.
9. Feng CK, Chan KH, Liu KN, Or CH, Lee TY. A comparison of lidocaine, fentanyl, and esmolol for attenuation of cardiovascular response to laryngoscopy and tracheal intubation. Acta Anaesthesiol Sin 1996;34:61-7.
10. Lee SY, Min JJ, Kim HJ, Hong DM, Kim HJ, Park HP, et al. Hemodynamic effects of topical lidocaine on the laryngoscope blade and trachea during endotracheal intubation: A prospective, double-blind, randomized study. J Anesth 2014;28:668-75.
11. Lee DH, Park SJ. Effects of 10% lidocaine spray on arterial pressure increase due to suspension laryngoscopy and cough during extubation. Korean J Anaesthesiol 2011;60:422-7.
12. Venus B, Polassani V, Pham CG. Effects of aerosolized lidocaine on circulatory responses to laryngoscopy and tracheal intubation. Crit Care Med 1984;12:391-4.
13. Sealed Envelope Ltd. 2017. Create a blocked randomisation list. [Online]. Available from: https://www.sealedenvelope.com/simple-randomiser/v1/lists. [Last accessed on 2017 Aug 13].
14. Ugar B, Ogurlu M, Gezer E, Nuri Aydin O, Gürsoy F. Effects of esmolol, lidocaine and fentanyl on haemodynamic responses to endotracheal intubation: A comparative study. Clin Drug Investig 2007;27:269-77.