Effects of Intravenous Lidocaine on QTd and HRV Changes Due to Tracheal Intubation During Sevoflurane Induction

Bakiye UĞUR,¹ MD, Hasan YÜKSEL,² MD, Ali Riza ODABAŞI,² MD, Mustafa OĞURLU,¹ MD, Alper ONBAŞILI,³ MD, and Osman N. AYDIN,¹ MD

SUMMARY

The aim of the present study was to evaluate the effects of IV lidocaine on autonomic cardiac function changes in tracheal intubation (TI) during sevoflurane anaesthesia by using more reliable parameters, namely, the analysis of QT dispersion and heart rate variability (HRV) from Holter monitoring. In this prospective, double-blind study, 44 American Society of Anaesthesiologists class I-II patients scheduled for hysterectomy were randomly and equally divided into 2 groups; a control sevoflurane group (group S, $n = 22$) and a lidocaine sevoflurane group (group LS, $n = 22$).

Before the induction of anaesthesia, the electrocardiograms (ECG) of all patients were recorded for 3 minutes as baseline parameters. In both groups, the anaesthesia was induced with 7% sevoflurane in O₂ at 6L min⁻¹ via a facemask for 2 minutes. However, before the induction of sevoflurane anaesthesia in group LS, 1 mg kg⁻¹ of lidocaine was given intravenously (IV). For muscle relaxation during TI, vecuronium was given to all participants. Three minutes after administration of vecuronium, TI was performed and an ECG was recorded synchronously for another 3 minutes. The results from the later records were used as postintubation parameters.

Baseline and postintubation data were analysed. When compared to baseline values, postintubation LF/HF and SDNN values were increased in group S ($P = 0.005$, $P = 0.001$, respectively), whereas postintubation LF and HF values were decreased in group LS ($P = 0.014$, $P = 0.041$, respectively). Under the influence of sevoflurane anaesthesia, TI resulted in sympathetic activation. However, this activation was attenuated by the administration of IV 1 mg kg⁻¹ lidocaine 5 minutes prior to TI. (Int Heart J 2006; 47: 597-606)

Key words: Lidocaine, Tracheal intubation, Sevoflurane, Heart rate variability, QT, Holter

TRACHEAL intubation (TI) and administration of inhalation agents are common procedures during general anaesthesia. However, TI and inhalation agents may cause rapid and life-threatening changes in autonomic cardiac functions.

From the ¹ Departments of Anaesthesiology and Reanimation, ² Obstetrics and Gynaecology, and ³ Cardiology, Faculty of Medicine, Adnan Menderes University, Aydın, Turkey.

Address for correspondence: Bakiye Uğur, MD, Adnan Menderes Üniversitesi, Tıp Fakültesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı 09100 Aydın, Türkiye.

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These clinical manifestations are tachycardia, changes in blood pressure, and arrhythmia.¹⁾ It has also been demonstrated that TI²⁾ and inhalation agents^{3,4)} lead to increased QT dispersion (QTd), a parameter which may be useful in evaluating the risk of arrhythmia and the efficiency of anti-arrhythmic drugs.⁵⁾

One of the main goals of the anaesthesiologist is to prevent or minimize all of these adverse effects. Many attempts have been made to attenuate the haemodynamic response to TI, for example deep anaesthesia, use of ganglionic, calcium-channel or beta-blockers, antihypertensive agents, sodium nitroprusside, nitroglycerin, barbiturates, and opioids. Topical or intravenous (IV) lidocaine, an amide local anaesthetic, is one of the agents frequently administered before anaesthesia induction in the above-mentioned situations, even though the effects of lidocaine on these reactions during TI are still controversial.^{6,7)}

Several studies have examined the efficiency of IV lidocaine for attenuation of the cardiovascular responses to TI. However, the results of these studies have been inconsistent.^{6,8)} Moreover, most of these trials only measured simple parameters, such as heart rate (HR) and blood pressure changes, which were not able to reveal enough information. In the past 2 decades, spectral analysis of heart rate variability (HRV) has been widely used in the prediction of vulnerability to ventricular fibrillation and it has been suggested that HRV is more reliable than corrected QTd (QTcd).⁹⁾ Parameters of HRV can be defined in time and frequency domains. The standard deviation of the RR interval (SDNN), one of the indices of the time domain, represents a general measurement of autonomic nervous system balance.^{10,11)} LF and HF are the frequency domains of HRV. LF is mediated by the parasympathetic and sympathetic systems, whereas HF is mediated primarily by the parasympathetic system.¹²⁾ The LF/HF ratio can be considered to be a marker of the sympathovagal balance.¹⁰⁾

Sevoflurane is a widely used inhalation agent for its favourable property of low blood-gas solubility that permits a more rapid induction of anaesthesia. However, the effects of sevoflurane anaesthesia on HRV parameters have not been well established. To our knowledge, the effects of IV lidocaine on autonomic cardiac changes due to TI under the influence of sevoflurane anaesthesia have not been studied.

The changes related to TI occur within a short period of time. Holter monitors are advantageous with respect to providing easy implementation and fast computation in recording changes within this short period of time. Therefore, the aim of the present study was to evaluate the effects of IV lidocaine on autonomic cardiac function changes due to TI during sevoflurane anaesthesia by using more reliable parameters, namely, the analysis of QTd and HRV from Holter monitoring.

METHODS

Subjects: After approval from The Institutional Committee of Ethics and obtaining informed consent in accordance with the principles defined in the Declaration of Helsinki, 44 American Society of Anaesthesiologists (ASA) class I or II premenopausal patients scheduled for elective total abdominal hysterectomy who were between 35-47 years of age were studied in this prospective, randomized, double-blind trial.

Patients with abnormal serum electrolytes, cardiovascular disease, chronic obstructive pulmonary disease, diabetes mellitus, or cancer, or who were either receiving medication or refused induction via a facemask were excluded from the study. No premedication was given to any of the patients before surgery.

Using a computer-generated binary number sequence, the patients were randomly and equally divided into 2 groups; a control group administered sevoflurane (group S, $n = 22$) and a lidocaine-sevoflurane group preadministered lidocaine (group LS, $n = 22$).

Intervention method: Electrocardiograms (ECGs) were recorded in all patients using a 12-lead digital Holter monitor (Rozinn Electronics RZ152PM12) for a 3-minute period prior to anaesthesia induction. The data from these first recordings were considered baseline data. An 18-gauge catheter was inserted into a forearm vein and used for fluid and drug administration.

In group S, the anaesthesia was induced with an inspiratory concentration of sevoflurane (7%) in O₂ at 6 L min⁻¹ fresh gas flow via a facemask for 2 minutes. The same procedure was used for group LS. However, in order to test the effects of lidocaine on group LS patients, we administered 1 mg kg⁻¹ of IV lidocaine immediately before sevoflurane induction. After all subjects in both groups had inhaled 7% sevoflurane in O₂ at 6 L min⁻¹ fresh gas flow for 2 minutes, the concentration of sevoflurane was reduced to 2%. The patients breathed the gas mixture of sevoflurane and oxygen spontaneously and the nondepolarizing-muscle relaxant vecuronium at a dose of 0.1 mg kg⁻¹ IV was given to all participants to facilitate TI. Three minutes after administration of vecuronium, TI was performed and an ECG was recorded synchronously for another 3 minutes. In the LS group, there was a 5-minute interval between the administration of lidocaine and TI. The data obtained from this second recording was considered postintubation data. The study was terminated at this point, and surgery was allowed to proceed. Normoventilation was maintained with intermittent positive pressure ventilation (IPPV). The electrocardiograms, noninvasive blood pressure, pulse oximetry, end-tidal CO₂, and inspired and expired sevoflurane concentrations were routinely monitored (AS/3®; Datex-Ohmeda, Helsinki, Finland) throughout the entire operation in all patients.

Data analysis: The QTcd and HRV values were analyzed by a cardiologist who was blinded to the type of anaesthesia. Electrocardiographic data were transferred to a personal computer and digitized via an analog-to-digital conversion board. All records were visually examined and manually over-read to verify beat classification. Abnormal beats and areas of artefact were automatically and manually identified and excluded. HRV analysis was performed using North East's Holter LX Analysis Software, Version 5.2. Both time and frequency domain analyses were performed. For the time domain, the mean R-R interval (SDNN) was measured in milliseconds (ms). For the frequency domain analysis, power spectral analysis based on the Fast Fourier transformation algorithm was used. Two components of the power spectrum were computed at the following band widths: HF (0.15-0.4 Hz) and LF (0.04-0.15 Hz). The LF/HF ratio was also assessed.

For QT analysis, the start of the Q wave and the end of the T wave were located separately for each of the 12 leads. The T wave end was defined as the point when the T wave returned to the isoelectric line. If this point was not clearly defined, then the reading would be omitted. If the T wave was followed by a U wave, then the interval between the T wave and the U wave (ie, the lowest point of the curve) would be taken as the point where the T wave ended. These readings were entered into the digitising program, which calculated the mean QT and the QTc interval for each lead for up to 3 readings. To determine the QTc interval, R-R intervals (RR) were calculated in a similar way. Thus, 3 (QT, RR) pairs of coordinates were entered for each lead. The QTc interval was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$). QTd was defined as the difference, in ms, between the maximum and minimum QT intervals.

Statistical analysis: All parameters are expressed as the mean $\pm$ SD. The Wilcoxon test was used to compare baseline and postintubation data within the same group. Statistical significance was defined as $P < 0.05$. Data from the 2 groups were compared using the Mann-Whitney test. Data were analysed using SPSS for Windows, Version 10.0.

RESULTS

The demographic data of the 2 groups were similar. Mean age was 42.8 ± 3.0 and 41.4 ± 2.7 years and body weight was 70.5 ± 9.2 and 74.0 ± 11.2 kg, respectively, in the S and LS groups.

Baseline data of the groups were also similar. The QT and HRV values at baseline and in the postintubation period are presented in the Table. There were no significant changes between the baseline and postintubation LF and HF values of HRV in group S. However, the SDNN values of HRV in the postintubation period were significantly higher than the baseline values ($P = 0.001$). In group

Table. QT and Heart Rate Variability Values at Baseline and in Postintubation Period

Variable	Sevoflurane (<i>n</i> = 22)			Lidocaine-Sevoflurane (<i>n</i> = 22)			
	Baseline	Postintubation	<i>P</i> *	Baseline	Postintubation	<i>P</i> *	<i>P</i> †
QTcd (ms)	44.8 (12.7)	48.3 (16.1)	0.560	45.3 (15.5)	47.4 (12.1)	0.999	0.074
LF ((beat min ⁻¹) ²)	1.08 (0.07)	1.10 (0.11)	0.609	1.09 (0.08)	1.04 (0.03)	0.041	0.096
HF ((beat min ⁻¹) ²)	1.07 (0.06)	1.04 (0.06)	0.221	1.05 (0.05)	1.02 (0.01)	0.014	0.898
LF/HF	1.01 (0.06)	1.06 (0.06)	0.005	1.03 (0.03)	1.02 (0.02)	0.346	0.149
SDNN (ms)	76.7 (26.4)	112.8 (25.6)	0.001	86.5 (30.1)	97.7 (31.8)	0.234	0.142

QTcd indicates corrected QT dispersion; LF, low frequency; HF, high frequency; and SDNN, standard deviation of R-R interval; *intragroup comparisons for baseline and postintubation; †between group comparisons for postintubation. Values are mean (SD).

LS, the postintubation values of LF and HF were significantly decreased compared to the baseline values ($P = 0.041$, and $P = 0.014$, respectively), while the SDNN values showed no significant changes.

The LF/HF ratio in group S increased significantly during the postintubation period compared to the baseline values ($P = 0.005$), whereas it decreased insignificantly in group LS. There were no significant differences in any postintubation variables between the groups.

DISCUSSION

Haemodynamics changes in mechanical stimulation due to TI (increased blood pressure and heart rate, and cardiac arrhythmia) are claimed to be caused by sympathoadrenal activity and catecholamine discharge. Pharyngeal and laryngeal nerves are still stimulated by TI despite enough deep anaesthesia. These stimulations trigger a wide range of sympathetic activations in the nervous system via the vagus and glossopharyngeus nerves.^{13,14)}

Tracheal intubation is considered a stressful situation for a person undergoing general anaesthesia, which could be detrimental to patients with cardiac problems. Tachycardia and hypertension induced by TI decrease myocardial perfusion and increase oxygen consumption, both of which disrupt myocardial function.

Heart rate variability is a more advanced noninvasive measurement of autonomic regulation than simpler parameters such as HR and blood pressure changes; spectral powers of different frequency bands of HRV are capable of reflecting parasympathetic and sympathetic regulation. Therefore, HRV can be an ideal parameter with which to investigate autonomic effects during TI. Heart rate variability analysis has also been used to assess the autonomic effects of pharmacological agents, including beta-blockers, calcium blockers, antiarrhythmics, psychotropic agents, and cardiac glycosides.^{15,16)} Owing to the fact that

HRV measurements are quite stable over the short- and long-term, drug effects on HRV can be established with a relatively small number of study participants.^{17,18)}

The different results obtained in studies using simple parameters are difficult to compare because of variations in the route of lidocaine administration,^{7,19)} speed of injection, dose, interval between administration and TI,^{6,20)} duration of TI, patient population, premedication,²¹⁾ additional use of opioids,⁶⁾ method of data collection, and statistical analysis.

In previous studies, measurements of QTd and HRV have provided important prognostic information after myocardial infarction. Both increased QTd and reduced HRV have been shown to be associated with vulnerability to life-threatening ventricular arrhythmias in patients with previous myocardial infarction.^{22,23)} Low HRV is specifically related to susceptibility to ventricular fibrillation but not to stable monomorphic ventricular tachycardia, suggesting that the autonomic nervous system modifies the presentation of life-threatening ventricular arrhythmias.⁹⁾

The greatest variation of heart rate occurs with circadian changes mediated by complex and poorly understood neurohormonal rhythms. All subjects in the present study were female. Past clinical and experimental studies have showed that the female gender demonstrates differences in the ECG pattern of ventricular repolarisation in humans and animal species and is also associated with a longer QTc interval at baseline than males.^{24,25)}

The effects of sevoflurane anaesthesia on QTcd and HRV parameters have not been well established. Although the present study did not aim to evaluate the effects of sevoflurane in different types of surgery, it has been demonstrated that sevoflurane anaesthesia increased the QTc interval in laparotomic gynaecological surgery²⁶⁾ but had no effect on the main haemodynamics during minor gynaecological surgeries.²⁷⁾ Moreover, some have suggested that QTd and the QTcd are not affected²⁸⁾ regardless of the severity and type of surgery. On the other hand, there are reports showing that all QT parameters (QT, QTc, QTd, and QTcd)³⁾ or 2 parameters such as QT and QTc²⁹⁾ or QTd and QTcd³⁾ increased. Further study is needed to resolve these conflicting results.

Tracheal intubation is essential for maintaining the airway passage in most surgeries and must be performed under general anaesthesia. Therefore, it is most important to determine the effect of lidocaine on the detrimental effects of TI and anaesthetic agents on cardiac functions. The only trial evaluating the effects of TI on QTcd under sevoflurane anaesthesia was performed by Gurkan, *et al.*²⁸⁾ Similarly, in the present study the QTcd was also unchanged. One distinctive feature between the 2 studies is that they conducted their trial in paediatric patients.

Studies examining the cardiac effects of sevoflurane using HRV parameters arrived at different conclusions. It was determined that the usage of sevoflurane-

N₂O anaesthesia had a decreasing effect on LF and HF power,³⁰⁾ whereas, another study showed an attenuation in LF power but no effect on HF power.¹²⁾

Although there were no significant differences in LF and HF powers as they moved in opposite directions, with LF increasing and HF decreasing, a significant increase in the LF/HF ratio immediately after TI under sevoflurane anaesthesia was observed in the present trial. There was also a significant increase in SDNN power but no significant increase in QTcd. As the LF/HF ratio and also SDNN are usually regarded as indices of the balance between the sympathetic and parasympathetic systems,¹⁰⁾ these results suggest that autonomic nervous system balance is the main factor affected by TI with sevoflurane anaesthesia. The LF/HF ratio is more sensitive than LF power as an indicator of sympathetic nervous system activation.³¹⁾ The increase in the LF/HF ratio immediately after intubation indicates that the sympathetic nervous system activation after intubation was not totally blocked by sevoflurane anaesthesia.

It was reported that the optimal timing for IV injection of lidocaine to minimize the haemodynamics upheaval induced by TI was 1-5 minutes^{7,20,32)} before TI. In addition, the study by Hamaga, *et al*, supported reasonable evidence that blood levels of subjects administered lidocaine decreased 5 minutes after injection. Administering lidocaine 5 minutes before performing TI should be considered a practical and convenient period of time due to the time span needed for sevoflurane and muscle relaxants to take effect.

In the present study, the administration of 1 mg kg⁻¹ lidocaine 5 minutes prior to TI resulted in a significant reduction of LF and HF power. However, the LH/HF ratio did not change, suggesting that lidocaine reduces the sympathetic dominance caused by TI.

Intravenous lidocaine, a class Ib antiarrhythmic agent, preferentially blocks the sodium channel of the cardiac action potential, which decreases automaticity by reducing the slope of phase 4 depolarization with little effect on the PR interval, QRS complex, or QT interval. If depolarization is altered, cells cannot reach threshold and will therefore not be able to produce an action potential, which in turn, means sensation or feeling cannot be propagated along the nerve fibres.³³⁾

In the past, the cardiac effects of lidocaine under anaesthesia without TI have been investigated. It has been reported that the endotracheal administration of lidocaine inhibits isoflurane-induced tachycardia.³⁴⁾ Furthermore, the results suggest that lidocaine might be the drug of choice for bupivacaine-induced cardiotoxicity predisposing to ventricular fibrillation in pigs.³⁵⁾ Similar to our results, cervical epidural anaesthesia with lidocaine attenuated LF and HF power. However, lumbar epidural lidocaine did not exhibit the same effect¹⁹⁾ and these differences need to be further investigated.

The only study investigating the effect of lidocaine on TI by using HRV parameters was made by Lin, *et al.*⁶⁾ However, their study differed from our study because they were unable to prove that 1.5 mg kg⁻¹ lidocaine, administered 3 and 5 minutes before TI, had any effect on autonomic regulation. In their study, general anaesthesia was induced with thiopental, fentanyl, droperidol, and succinylcholine, followed by TI in all groups. The reason for the conflicting results between our study and their study may be related to the usage of different induction agents, fentanyl and droperidol. The results obtained with regard to HRV in the study groups might have been caused by the effect of opioids. Several reports have demonstrated an increase in parasympathetic nerve activity with fentanyl.^{36,37)} Also, the mild α -adrenergic blocking effects of droperidol decrease arterial blood pressure by peripheral vasodilatation. The α -adrenergic blocking actions may be responsible for an antidysrhythmic effect.³³⁾ This might explain why the results for their study groups were not different from those of the control. Furthermore, they used the depolarizing-muscle relaxant succinylcholine, which has an effect on cardiac autonomic receptors and increases serum potassium levels. Potassium elevation might possibly have some cardiac effects.³³⁾ Sequential lidocaine and potassium infusion shortens the QTc interval in patients with long QT syndrome.³⁸⁾ In the present study, the nondepolarizing-muscle relaxant vecuronium, which does not have any cardiovascular effects, was used.³³⁾ In the study by Lin, *et al.*, it is expected that it would be difficult to determine the lidocaine effect due to sequential usage of agents with cardiac effects administered prior to TI. In their trial, the effects of lidocaine on SDNN were not studied. The present study showed that lidocaine attenuated the SDNN increase induced by TI under sevoflurane induction.

Conclusion: Intravenous administration of 1 mg kg⁻¹ lidocaine 5 minutes prior to tracheal intubation under the influence of sevoflurane seems to prevent an increase in sympathetic autonomic cardiac function due to TI. Based on the present findings, it is concluded that lidocaine administration before TI has beneficial effects in females under sevoflurane anaesthesia.

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