Original Article ANESTHESIOLOGY & REANIMATION

North Clin Istanb 2022;9(4):323–330
doi: 10.14744/nci.2021.33407

A randomized controlled trial to study the effect of intratracheal and intravenous lignocaine on airway and hemodynamic response during emergence and extubation following general anesthesia

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ABSTRACT

OBJECTIVE: Intratracheal (IT) and intravenous (IV) lignocaine suppress airway reflex and hemodynamic response during extubation, but studies regarding this are sparse. The primary aim was to compare the effect of IT and IV lignocaine on attenuation of airway reflex to endotracheal extubation and the secondary aim was to compare the hemodynamic responses to extubation, using lignocaine by the two different routes.

METHODS: Seventy-five female patients with comparable age, body mass index, and American Society of Anesthesiologists Physical Status undergoing carcinoma breast surgery were randomized into three groups. Group A received 2% lignocaine 3 mg/kg intratracheally 5 min and Group B received 2% lignocaine 1.5 mg/kg intravenously 3 min before extubation. Group C was control group. The airway and hemodynamic responses were noted in terms of episodes of cough during emergence and extubation. Categorical variables assessed using Fisher's exact test and continuous variables assessed using one-way analysis of variance.

RESULTS: Cough suppression was present in Groups A and B, with better results observed with IT than with IV lignocaine. In the control group, Grade III cough reflex was present predominantly. There was a statistically significant difference ($p<0.001$) in blood pressure and heart rate between Group A versus Group C and in Group B versus Group C, but not between Group A and Group B.

CONCLUSION: IT lignocaine administered before extubation significantly attenuates post-extubation cough reflex than IV lignocaine. Both IT and IV lignocaine can effectively attenuate the airway and hemodynamic response to extubation.

Keywords: Airway reflex; carcinoma breast; cough grade; extubation; hemodynamic stress response; intratracheal; intravenous; lignocaine; randomized controlled trial.

Cite this article as: *Gladston DV, Padmam S, Amma RO, Koshy RC, Krishna KMJ, Vijayan J, et al. A randomized controlled trial to study the effect of intratracheal and intravenous lignocaine on airway and hemodynamic response during emergence and extubation following general anesthesia. North Clin Istanb 2022;9(4):323–330.*

Received: May 03, 2021 *Accepted:* May 29, 2021 *Online:* September 05, 2022

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Tracheal extubation is the removal of endotracheal tube (ETT) from patient's airway [1] and is a stressful situation, associated with 3 times more complication rates than intubation [2, 3]. Complications of extubation include tube entrapment, hemodynamic changes such as tachycardia, hypertension, increased intraocular and intracranial pressure, coughing, breath-holding, tracheal or laryngeal trauma, laryngeal spasm, and pulmonary aspiration [4]. Coughing and hemodynamic responses cause sympathoadrenergic responses due to catecholamine release [5]. Lignocaine is a local anesthetic, causes blockade of the sodium channel [6], and suppresses cough reflex to extubation by its effect on synaptic transmission and hemodynamic response by its central stimulant effect, peripheral vasodilatory effect, and direct myocardial depressant effect [7].

Lignocaine is administered intravenously [8], through laryngotracheal route [9] or in the ETT cuff [5] to blunt reflexes during emergence from general anesthesia (GA) [10]. Emergence is defined as time period between the complete discontinuation of the maintenance anesthetic to 5 min post-extubation [11]. The serum concentration of lignocaine required to suppress the cough reflex has been recorded as >3 mcg/ml, while cough suppression has been achieved at recorded levels <1.63 mcg/ml when the lignocaine is topically applied [12]. Lignocaine is a potent anti-inflammatory and antihyperalgesic agent [13, 14]. Even though cough reflex is protective against aspiration, it can lead to hemodynamic fluctuations in post-operative period. George et al. [15] found that the local mucosal anesthetizing effect of lignocaine is short lived and do not last for 20–30 min for both intratracheal (IT) and intravenous (IV) lignocaine, thereby preventing aspiration risk. Local anesthesia toxicity is a grave complication and requires high levels of alertness and anticipation [16, 17]. The main manifestations of its toxic accident are neurologic signs, with convulsions and no, or slight, cardiac effects on the intact heart [18]. Cardiovascular effects come later, and they include myocardial depression, prolonged conduction interval, bradycardia, hypotension, and heart failure [19]. Administration of IV lignocaine will rise plasma concentration rapidly as compared to IT lignocaine which contributes to such cardiac complications.

Only a limited number of previous published studies compared the use of IT and IV lignocaine to reduce GA-related complications during emergence and extubation [5, 20–23]. However, the results of these trials were conflicting. Hence, we studied the effect of IT and IV lignocaine on airway reflexes and hemodynamic stress response during extubation to gather more evidence to clear these uncertainties in a randomized controlled trial.

The objective of this study was to compare the effect of IV and IT lignocaine on attenuation of airway reflex to endotracheal extubation and to compare the hemodynamic responses to extubation, using lignocaine by IT versus IV routes.

Highlight key points

- Lignocaine administered intratracheally before extubation significantly attenuates the post-extubation cough reflex than IV lignocaine.
- Both IT and IV lignocaine given before extubation can effectively attenuate the hemodynamic hyper-response to extubation.
- IT lignocaine is cost effective and simple way to suppress the cough as well as adverse hemodynamic reflex responses during extubation.

MATERIALS AND METHODS

Breast cancer patients who underwent modified radical mastectomies (MRM) and breast conserving surgeries (BCS) under GA with ETT at our institution during the period January 2018–December 2018 were included in this study. After obtaining Institutional Review Board approval with IRB No. 10/2017/15 dated October 26, 2017, Regional Cancer Centre Human Ethics Committee No. 32/2017 dated November 22, 2017, CTRI/2020/12/039358, and consent from the participants, those aged more than 18 years belonging to American Society of Anesthesiologists Physical Status (ASA PS) 1, 2, and 3 were included in the study. Patients with known allergy to lignocaine, high risk of aspiration, anticipated difficult airway, history of hypertension on beta-blockers, bronchial asthma, and history of tracheal or laryngeal surgery were excluded from the study. The patients in the study were randomly allocated based on a computer generated random number table, into three groups (A, B, and C). Seventy-five patients were recruited and all of them randomized and allotted into three groups of 25 each and all were followed up by the investigator not involved in providing anesthesia to the study patients. Participants were unaware of the group to which they were allocated. Group A patients received 2% preservative free IT lignocaine 3 mg/kg from a syringe by injection into the ETT's proximal end 5 min before extubation. Group B patients received 2% preservative

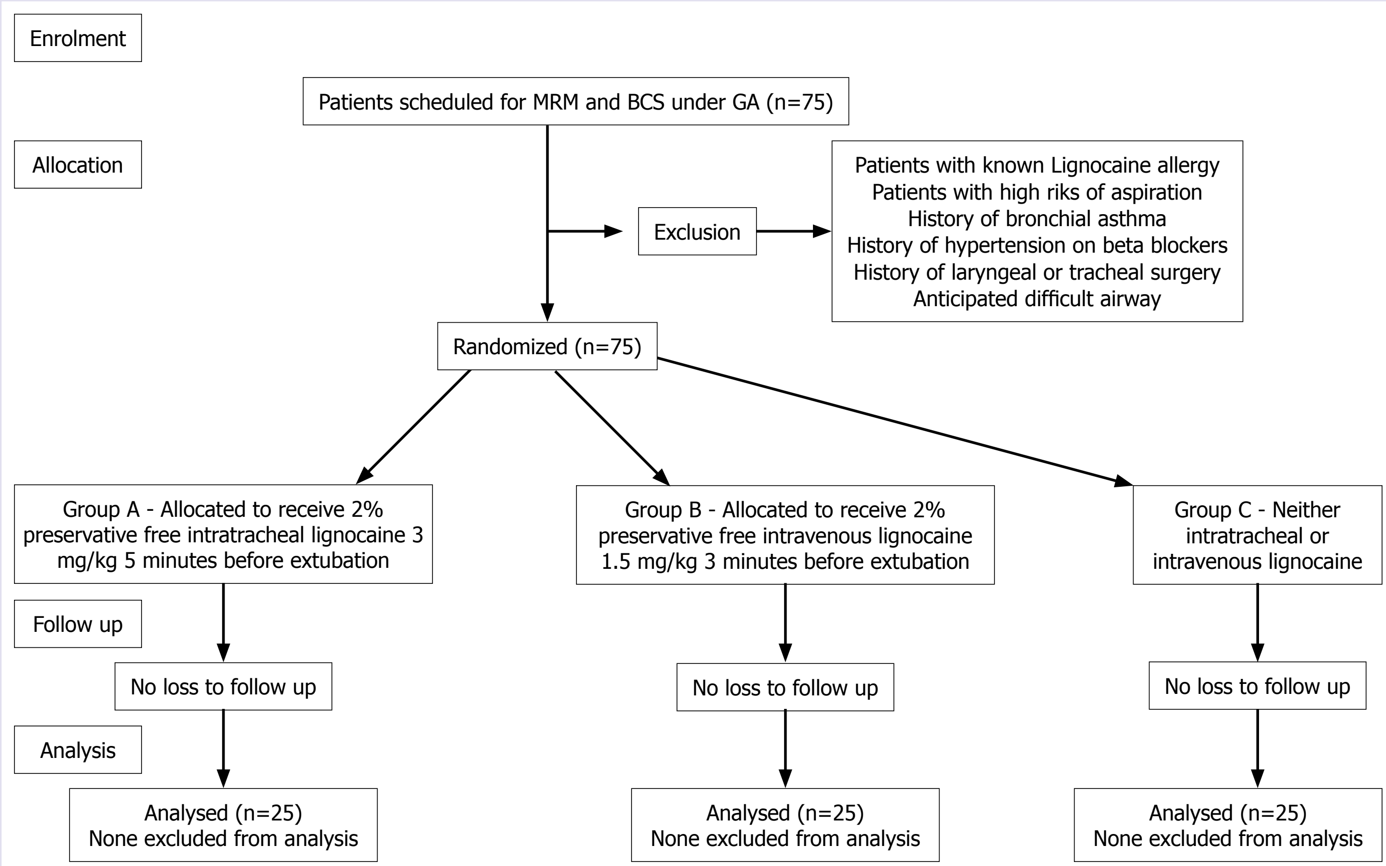

FIGURE 1. CONSORT diagram.

free lignocaine 1.5 mg/kg IV 3 min before tracheal extubation. Group C included control group of patients who received neither IT nor IV lignocaine (Fig. 1).

Breast cancer patients were selected to ensure comparability between the groups and were of comparable age, weight, sex, and ASA PS and these values were recorded before induction of GA and monitored using standard ASA monitors, under a standardized anesthesia protocol. All patients received oral premedication with tab. pantoprazole 40 mg and tab. alprazolam 0.5 mg the previous night and at 7 am on the day of surgery and IV premedication with glycopyrrolate 0.004 mg/kg and midazolam 0.02 mg/kg in the operation theater. GA induced with inj. fentanyl 2 micrograms/kg and inj. propofol 2 mg/kg, inj. vecuronium 0.08 mg/kg was administered to facilitate intubation, maintained with a mixture of air, oxygen, and sevoflurane. No opioids were used 30 min before end of surgery. Patients were reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg. After gentle aspiration of oropharyngeal secretions, extubation was performed when train of four count was >0.9. Oxygen was supplemented through facemask and patients followed in post anesthesia care unit (PACU) for any complications.

The airway responses were noted in terms of cough reflex to assess the smoothness of extubation and hemodynamic effect noted in terms of heart rate (HR) and blood pressure (BP) at extubation, 1 min, 2 min, 3 min, and 5 min before and after extubation in Groups A, B, and C. Mean emergence time noted in three groups and effects on Group A and Group B were compared with Group C. Time to emergence was defined as the period from switching off of anesthetic agents till tracheal extubation [11]. The cough reflex is defined as forceful expiration following inspiration [24].

Smoothness of extubation was graded using the degree of cough reflex as [5].

Grade I: No cough or mild cough only during removal of ETT.

Grade II: Coughing while breathing regularly.

Grade III: Bouts of coughing before regular breathing is established.

Table 1. Patient characteristics and baseline cardiorespiratory parameters

	Group A (n=25)	Group B (n=25)	Group C (n=25)	p
Age, years	51.28	52.20	49.60	0.647
BMI	25.47	26.80	25.42	0.374
Emergence from fentanyl	76.20	88	78.80	0.111
Baseline mean SBP (mm of Hg)	134.6	132.84	132.96	0.796
Baseline mean DBP (mm of Hg)	77	79.32	78.2	0.653
Baseline mean HR (beats/ minute)	87.72	80.88	86.64	0.086

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; Group A – 25 patients who received intratracheal lignocaine, Group B – 25 patients who received intravenous lignocaine, Group C – control group, p<0.05 is statistically significant.

Statistical Analysis

The sample size was calculated as 75 with 25 in each group with 80% power and 5% level of significance, based on the study by Jee et al. [21] where the three groups of patients were assessed similarly based on cough reflex. The categorical data used in our study body mass index (BMI), ASA PS, and cough grade were represented using frequencies and percentages. Continuous variables represented using mean and standard deviation. The association between categorical variables assessed using Fisher's exact test and continuous variables with respect to three groups were assessed using one-way analysis of variance. Further, the significance between the pairs of groups for the continuous variables, HR and BP, was compared using Bonferroni multiple comparison test. $P<0.05$ was considered to be statistically significant. Statistical analysis done using Statistical Package for the Social Sciences (SPSS) version 11.0 (SPSS Ltd., Chicago, IL).

RESULTS

The demographic data of the three groups studied during the period January 2018–December 2018 were comparable (Table 1) and there was no significant difference in ASA PS (p=0.206). In our study, Group A and Group B had cough suppression. We observed that in Group A, 80% of patients had Grade I cough and 20% had Grade II cough with no event of Grade III cough. In Group B, 28% of patients had Grade I cough and 72% had Grade II cough with no events of Grade III cough. There is statistically significant cough suppression with IT lignocaine than with IV lignocaine. The patients in Group C had no events of Grade I cough reflex but had 12% of Grade II cough and 88% of Grade III cough reflex, which is predominant. Table 2 shows that the difference in cough reflex grade is statistically significant (p=0.001).

Table 2. Comparison of cough reflex grade in IT, IV, and control group with P value

Groups		Cough reflex grade			p
		I	II	III	
A	% within group	80.0	20.0	0.0	0.001
B	% within group	28.0	72.0	0.0	
C	% within group	0.0	12.0	88.0	
Total	% within group	36.0	34.7	29.3	

Grade I: No cough; Grade II: Mild cough; Grade III: Bouts of coughing; p<0.05 is statistically significant.

The mean systolic BP (SBP) in Group A (136.6 mm of Hg) and B (132.12 mm of Hg) showed attenuation of BP variation on extubation, when compared to patients in Group C (150.48 mm of Hg). Three groups did not show statistically significant difference in the mean baseline SBP and mean SBP 5 min, 3 min, and 2 min before extubation. When compared to Groups A and B, Group C showed statistically significant (p=0.001) difference in mean SBP recorded at 1 min pre-extubation, at extubation, and 1 min, 2 min, 3 min, and 5 min post-extubation (Fig. 2). However, the difference in mean SBP recorded during the periextubation period between Group A and Group B was not significant statistically.

The mean diastolic BP (DBP) in Group A (87 mm of Hg) and Group B (88.72 mm of Hg) showed attenuation of BP variation on extubation, when compared to patients in Group C (97.44 mm of Hg). The mean base-

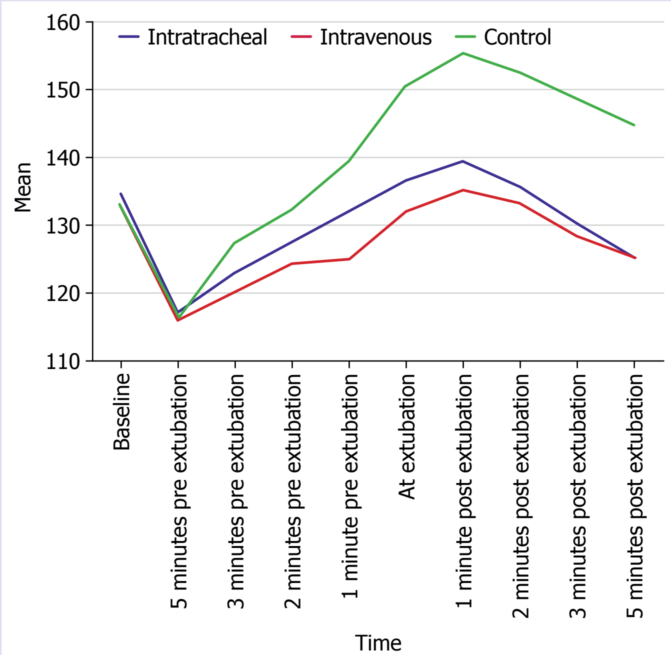

FIGURE 2. Graph comparing mean SBP among IT, IV, and control group.

SBP: Systolic blood pressure; IV: Intravenous; IT: Intratracheal.

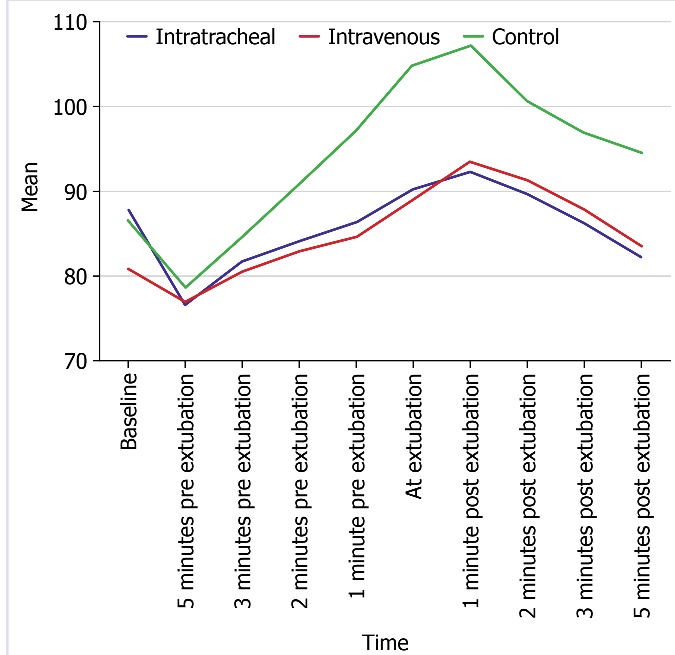

FIGURE 4. Graph comparing mean HR among IT, IV, and control group.

HR: Heart rate; IV: Intravenous; IT: Intratracheal.

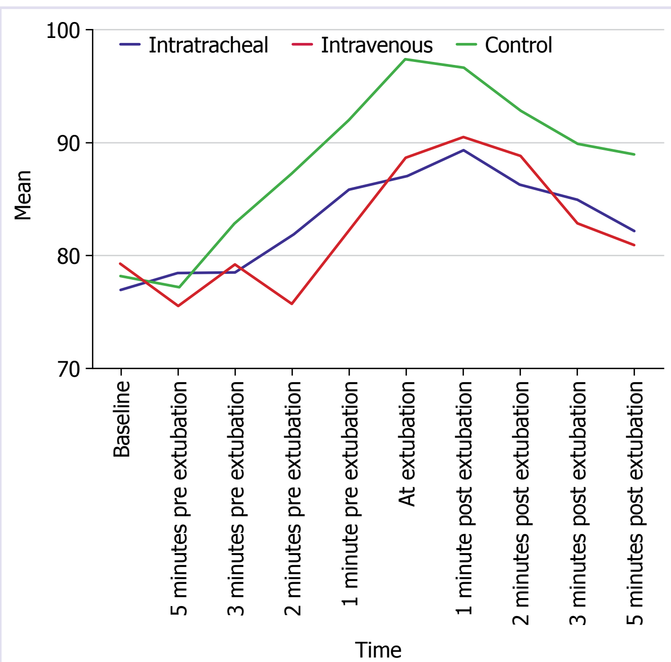

FIGURE 3. Graph comparing mean DBP among IT, IV, and control group.

DBP: Diastolic blood pressure; IV: Intravenous; IT: Intratracheal.

line DBP, DBP 5 min and 3 min pre-extubation in three groups did not show statistically significant difference. There is statistically significant difference (p=0.001) in mean DBP in Group C recorded at 1 min pre-extubation, at extubation and 1 min, 2 min, 3 min, and 5 min post-extubation when compared to that of Group A and Group B (Fig. 3). However, the difference between Group A and Group B in mean DBP recorded during the periextubation period was statistically insignificant. In our study, Group A and Group B had significant attenuation of BP when compared with Group C. Hence, lignocaine was found to be effective in suppressing hypertension at the time of extubation. However, the intergroup comparison of the BP between IV group and IT group was comparable and statistically insignificant.

The mean HR in Group A and Group B showed attenuation of HR variation on extubation when compared to patients in Group C. The mean baseline HR and mean HR recorded 5 min pre-extubation in Groups A, B, and C showed no statistically significant difference. There is statistically significant difference (p=0.001) in mean HR recorded at 1 minute pre-extubation, at extubation and 1 min, 2 min, 3 min, and 5 min post-extubation in Group C, when compared to that of Group A and Group B (Fig. 4). However, the mean HR recorded during the periextubation period in Group A and Group B was insignificant.

The mean emergence time after fentanyl administration in Groups A, B, and C were 76.20, 88.00, and 78.80, respectively. The p=0.111 is statistically insignificant, hence, the effect of fentanyl on ETT tolerance can be ruled out in our study during extubation [12].

Thus, on comparison between Group A and Group B, there was no statistically significant difference in SBP, DBP, and HR. However, there was a statistically significant difference in SBP, DBP, and HR between Group A versus Group C as well as between Group B and Group C.

DISCUSSION

In our study, cough reflex in post-extubation period was well suppressed with IT lignocaine than with IV lignocaine. The predominant attenuation of airway circulatory reflexes is due to local anesthetic effect rather than its systemic absorption of IT lignocaine resulting in anesthesia to tracheal mucosa which was in contact with the ETT and cuff. Due to gravity in the supine position, IT lignocaine will spread distally down the trachea. The wet mucous blanket permits lignocaine to diffuse proximally from the distal end of ETT, thereby blocks the receptors and anesthetize tracheal mucosa in contact with the ETT. We found out that lignocaine given 5 min before extubation through IT was superior to IV as is evident from the cough reflex grading. This is comparable to studies done by Jee and Park et al. [21] who found that IT lignocaine suppressed cough when given approximately 5 min before extubation, and is superior to IV injection given 3 min before extubation. However, our results were contradictory to the studies done by Shabnum et al. [5] and Saghaei et al. [25] The use of IV lignocaine also decreases perioperative airway complications, including coughing and sore throat [17]. Khezri et al. [26] compared 2% injection lignocaine 1.5 mg/kg IV or IT and came to conclusion that the effect of IV or IT lignocaine was similar on bucking, cough, and emergence time at the end of GA till 30 min post-extubation. Suppression of cough reflex during emergence and extubation is effective when plasma concentration of lignocaine is between 2.3 and 3 µg/mL [27, 28]. The administration of IT 2% lignocaine 3 mg/kg would lead to peak plasma concentrations adequate to suppress the reflexes. Hence, from our study, IT lignocaine was superior to IV in cough suppression at extubation.

The attenuation of hemodynamic response to extubation was present when lignocaine is administered both routes, comparable to the study done by Shabnum et al. [5] Our study did not show difference in hemodynamic in both groups, suggesting the multimodal mechanism of the action of lignocaine on cardiovascular system after systemic administration and due to its local anesthetic effect on tracheal mucosa resulting in suppression of cough and circulatory reflexes. Our study was not in accordance with Jee et al. [21] who showed that IT lignocaine suppresses the hemodynamic reflexes better than IV due to direct local anesthesia rather than from systemic absorption from the airway. The differences in HR, SBP, and DBP variation were statistically insignificant in Groups A and B, but significant difference was present in the control group.

The time of administration of lignocaine in our study was 3 min in patients receiving IV lignocaine and 5 min in patients receiving IT lignocaine. IV lignocaine was administered 3 min before extubation, which was based on the study by Wilson et al. [29] and Tam et al. [30] Similarly, Denlinger et al. [31] stated that topical lignocaine blunted the reflex responses effectively when given 5 min before extubation. A study done by George et al. [15] found that local anesthesia is achieved within 2–3 min of endotracheal lignocaine application due to short-acting local anesthetic effect of lignocaine. We found out that lignocaine given 5 min before extubation through IT was superior to IV as is evident from the cough reflex grading, comparable to a study done by Jee and Park et al. [21] We chose 3 mg/kg IT lignocaine which is twice the IV dose and 1.5 mg/kg lignocaine through IV route based on the above studies [5, 21]. We administered 1.5 mg/kg lignocaine intravenously and found that our results were comparable with Bidwai et al. [32].

The use of opioids intraoperatively increases the tolerance to ETT [33]. This might have interfered with our study results, and therefore, no opioids had been used intraoperatively other than injection fentanyl 2 µg/kg during anesthesia induction. The average duration of surgery was 90 min. Since the duration of the action of 2 microgram/kg of fentanyl is 30–60 minutes, fentanyl effect on ETT tolerance can be ruled out at the time of extubation [34]. In our study, among the three groups, there was no significant statistically difference (p=0.111) in emergence time after fentanyl administration and all patients were observed in PACU following extubation and had no complications.

The limitation of our study was only female patients who underwent BCS and MRM for carcinoma breast was studied and our study did not measure blood levels of lignocaine, epinephrine, and norepinephrine. Large-scale studies in diverse types of surgeries should address these issues.

However, we found that IT instillation of lignocaine has the additive advantage of suppression of cough reflex, thereby attenuating hemodynamic response than IV lignocaine during extubation that clears the previous uncertainty in this area. To avoid unwanted circulatory and airway responses during post-operative period, suppression of cough and hemodynamic reflex response with endotracheal lignocaine during extubation can be practiced more often especially in patients likely to suffer complications due to increased cough on extubation.

Conclusion

IT lignocaine before extubation significantly attenuates the post-extubation cough reflex than IV lignocaine. Both IT and IV lignocaine given before extubation can effectively attenuate the hemodynamic hyper-response to extubation. IT lignocaine is cost effective and simple way to suppress the cough as well as adverse hemodynamic reflex responses during extubation. Hence, it is prudent to administer lignocaine routinely before extubation.

Ethics Committee Approval: The Regional Cancer Centre Human Ethics Committee granted approval for this study (date: 22.11.2017, number: 32/2017).

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

Authorship Contributions: Concept – DVG, SP, ROA, RCK; Design – DVG, SP, ROA, RCK, JKKM; Supervision – SP, ROA, DVG; Fundings – SP, ROA, RCK, DVG, JKKM; Materials – DVG, JV, PR, NG; Data collection and/or processing – DVG, SP, ROA, JV, PR, NG; Analysis and/or interpretation – DVG, SP, ROA, JKKM; Literature review – DVG, SP, ROA, JV, PR; Writing – DVG, SP, NG, ROA, JKKM; Critical review – SP, ROA, RCK, JKKM.

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