Randomized Double Blind Control Study Comparing the Efficacy of Intracuff Alkalinized Lidocaine to Low Dose Remifentanil Infusion in Attenuating the Endotracheal Tube Induced Emergence Phenomena

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Abstract

Emergence from general anesthesia is often complicated by the endotracheal tube (ETT) induced airway and circulatory reflexes which can lead to potentially dangerous complications. Considerable research has been focused on prevention of these emergence phenomena (EP). Nevertheless, the problem is still far from its final solution.

Objective: To compare the efficacy of intracuff alkalinized lidocaine (ICL) vs low dose remifentanil infusion in attenuating the ETT-induced EP.

Methods: 120 ASA I-III patients, aged 18-65 years, were randomly assigned to receive intracuff alkalinized lidocaine (2% lidocaine mixed 1:1 with 1.4% NaHCO₃) or an intravenous (IV) remifentanil infusion (0.05-0.5 mcg/kg/min) combined with intracuff saline during desflurane-based general anesthesia. At the end of surgery, after desflurane was turned off in the assigned group, low dose remifentanil, or its equivalent placebo was decreased to one-tenth of the mean dose but not less than 0.01 mcg/kg/min and it was continued until extubation. A blinded researcher observed each patient from the time desflurane was discontinued until at least five minutes after extubation. Coughing was evaluated as either present or not, and graded on a point scale based on severity. The patients were also observed for development of any adverse events along with the vital signs during this emergence phase.

Results: The incidence (44% vs 67%, p=0.02) and severity of coughing, overall, was significantly less in the lidocaine group compared to remifentanil group. The lidocaine group also had a lower incidence of significant coughing (2-3 on point scale) (25% vs 49%, p=0.009). The mean arterial pressure (MAP) in the lidocaine group was lower than the remifentanil group at extubation and 5 minutes after extubation.

Conclusions: Intracuff alkalinized lidocaine (ICL) is more effective in reducing the incidence and severity of coughing compared to a low dose remifentanil infusion during emergence from desflurane based anesthesia.

Keywords: Intracuff lidocaine; Remifentanil; Emergence coughing; Emergence phenomena; Lidocaine; Intracuff; ETT

Introduction

Emergence from general anesthesia is often complicated by the ETT-induced EP which includes coughing, sympathetic stimulation, sore throat and dysphonia [1-5]. The reported incidence of patient coughing during emergence is as high as 80-95% [1-3]. Unfortunately, this can result in a number of detrimental side effects including hypertension, tachycardia, increased bleeding from the surgical site and increased intracranial and intraocular pressures [6-9]. Various strategies have been employed to attenuate this response including extubation in a deep plane of anesthesia [10], administration of IV agents like short acting narcotics [11-13], IV lidocaine [14-16] or dexmedetomidine [17] and the topical or intracuff application of lidocaine [1-5]. Each of these methods has its own limitations and a reliable technique which would increase the ETT tolerance while facilitating rapid and complete emergence from general anesthesia has not been proven to date.

Even though, IV lidocaine has shown to suppress both mechanically- and chemically-induced airway reflexes, [14-16] its narrow antitussive window accompanied with the potential for systemic toxicity makes it an unreliable agent as a cough suppressant [18,19]. One of the principal mechanisms for coughing during emergence is irritation of the respiratory mucosa by the ETT and its cuff [1,19,20]. Hence, anesthetizing the mucosa which is in direct contact with the ETT and its cuff should improve ETT tolerance. Lidocaine administered through the Laryngotraheal instilled topical anesthesia (LITA) tube is also effective in suppressing the cough [21,22]. However, the study by Creer et al. demonstrated greater efficacy of intracuff alkalinized lidocaine compared to a LITA tube [22]. Estebe et al showed successful suppression of cough reflex and sore throat with as little as 40 mg of intra cuff alkalinized Lidocaine [23-25]. Encouraged by these reports, we decided to use low dose of alkalinized lidocaine to inflate the ETT cuff.

Acting on the central and peripheral opioid receptors, intravenous opioids have been shown to be successful in suppressing cough during emergence [11-13]. They have also been shown to be effective in attenuating the cardiovascular response to extubation [12,26]. An
advantage of remifentanil over other opioids is its rapid onset and offset of action. It has a short blood-brain equilibration time and rapid elimination which makes it easier to adjust the infusion rate to achieve the desired levels of analgesia [27,28]. Aouad et al. [13] demonstrated that a low-dose infusion of remifentanil during emergence suppresses coughing and provides a smooth emergence from isoflurane-based anesthesia.

Currently, there are no reports on head-to-head comparison of the remifentanil infusion with intracuff alkalinized lidocaine in suppressing the emergence coughing.

Our primary objective was to measure the incidence of coughing between the ICL vs low dose remifentanil infusion groups. Secondary objectives were to compare the severity of coughing, calculate the mean time to extubation, incidence and severity of sore (or dry) throat, and incidence of other side effects.

**Methods**

We conducted a single-center, prospective, randomized, double-blinded and double-arm trial at The Ohio State University Wexner Medical Center. After obtaining approval from our Institutional Review Board and written informed consent from all patients, we included 120 ASA I-III patients aged 18-65 years who were scheduled to undergo elective surgery under general anesthesia requiring endotracheal intubation for longer than two hours. The types of surgeries are listed in Table 1. Pregnant or breastfeeding patients, those with a history of asthma, chronic obstructive pulmonary disease, chronic cough, recent respiratory infections, active gastrointestinal reflux disease, hiatal hernia, malignant hyperthermia, laryngeal or tracheal surgery or pathology, or patients with allergic to either of the study medications, pathology, or patients with allergic to either of the study medications, were excluded from the study. Additionally, subjects were excluded if they had severe cardiovascular, pulmonary, renal, hepatic, metabolic, psychiatric, endocrine, or neuromuscular disorders and if a nasogastric tube was required after extubation. Lastly, patients with an anticipated difficult intubation as determined by the anesthesiologist or a failure to intubate on the first attempt served as additional exclusion criteria.

Patients were randomly allocated to either remifentanil infusion or ICL group according to a computer-generated random table. All patients received IV induction with lidocaine, propofol, and fentanyl, and the choice of muscle relaxant which was left to the discretion of the anesthesiologist. Endotracheal intubation with a high volume low pressure cuffed ET tube was performed by direct laryngoscopy. Cuff inflation was performed with normal saline for the remifentanil group and with alkalinized 2% lidocaine (2% lidocaine with 1.4% NaHCO₃ in a 1:1 volume ratio prepared immediately before administration) for the lidocaine group. Initial minimal occlusive pressure was established by listening for an audible leak and the cuff pressure was measured and recorded at different times to insure pressures of 25 mmHg or less. Desflurane (0.8-1 MAC) was used for maintenance of general anesthesia. Fentanyl by intermittent boluses was used for analgesia in the lidocaine group, while the continuous infusion of remifentanil at a rate 0.05-0.5 mcg/kg/min was used in the remifentanil group. These were titrated to keep the MAP and HR within 10% of the preoperative baseline values. The normal saline was run as an infusion in the lidocaine group for blinding purposes.

Towards the end of surgery, at the start of closing, neuromuscular blockade was reversed with neostigmine and glycopyrrolate. Mean remifentanil dose was calculated by dividing the total maintenance dose by the patient's weight and duration of surgery. Upon skin closure, desflurane was turned off (T0) and remifentanil was reduced to one tenth of the mean dose but not less than 0.01 mcg/kg/min and was titrated to patient's spontaneous respiratory rate. Similarly fentanyl dosage was titrated to maintain spontaneous respiratory rate between 10-20/min. Tracheal and oral suctioning was done immediately after stopping the desflurane.

During the emergence phase (from T0 to extubation, T1) 100% O₂ was administered at 10 L/min and the patient was intermittently stimulated verbally or with gentle tactile stimulation. The patients were extubated when they met the standardized extubation criteria. The remifentanil or normal saline infusion was stopped at extubation and a longer acting narcotic was administered for post-operative pain control. Once desflurane was discontinued (T0), a blinded observer recorded the mean arterial blood pressure (MAP), heart rate (HR), SpO₂, spontaneous respiratory rate (RR), end tidal CO₂ (ETCO₂) and desflurane concentrations at two minute intervals until 5 minutes after extubation. The number and grading of coughing episodes was also recorded (Table 2).

A second blinded observer evaluated the patient for sore throat in the post anesthesia recovery unit with a visual analog scale (VAS, 0-10 cm) at one hour after extubation. All other side effects that the subjects experienced were recorded as well.

One hundred and twenty patients underwent 1:1 randomization into remifentanil infusion and intracuff alkalinized lidocaine groups. To test the primary hypothesis, a sample size of 60 per group was required to achieve a power of 80% to detect a difference of 24% between the two groups, assuming 40% cough incidence in the remifentanil group [13] and 16% in the ICL group [1] The sample size was calculated by a 2-sided Pearson Chi-square test at α=0.05. This sample size took into account a 10% dropout rate.

<table>
<thead>
<tr>
<th>Operation</th>
<th>Lidocaine(L) Group (n)</th>
<th>Remifentanil(R) Group (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robotic nephrectomy</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Robotic ovarian cystectomy</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Open total abdominal hysterectomy</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Robotic hysterectomy</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Laparoscopic nephrectomy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Robotic myomectomy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Robotic prostatectomy</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Partial mastectomy</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Laparoscopic hysterectomy</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Total mastectomy</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Robotic salpingoophorectomy</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Robotic pyeloplasty</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Hernia repair</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Removal breast tissue expander</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>57</td>
</tr>
</tbody>
</table>

**Table 1**: Types of Surgery included per group.

<table>
<thead>
<tr>
<th>Observation</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>No cough</td>
<td>0</td>
</tr>
<tr>
<td>Single cough O₂ Sat ≥ 95%</td>
<td>1</td>
</tr>
<tr>
<td>More than one episode of unsustained cough (≤ 5 sec)</td>
<td>2</td>
</tr>
<tr>
<td>Sustained bouts of coughing (≥ 5 secs)</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild cough</td>
</tr>
<tr>
<td>2</td>
<td>Significant cough</td>
</tr>
</tbody>
</table>

| Table 2: Coughing Point Scale. |
Statistical Analysis

First, the cough score was dichotomized to 0 and 1. A score of 1-3 was treated as an event occurrence (1=cough) while 0=no occurrence. The proportion of patients with coughing episodes was compared between the two groups by the Pearson's Chi-square test. Odds ratio and its 95% confidence interval was calculated as well. Results were summarized using descriptive statistics (means, standard deviations for continuous variables and frequencies for discrete data). The continuous variables were compared between treatment groups using the two-tailed T-test, and the categorical variables were compared using the Chi-square test, or Fisher's exact test, as indicated. Bonferroni method has been used to adjust the multiple comparisons at different time point for both MAP and HR values. A P value<0.05 was considered as statistically significant.

Results

A total of 120 patients were enrolled: 60 subjects for each group. 10 subjects were excluded from analysis because of screening failures and one patient was excluded because of missing data. Thus, the total number of patients analyzed was 57 subjects for the remifentanil group and 52 for the ICL group (Figure 1).

There was no statistically significant difference with regards to age, gender, BMI, smoking history, or history of hypertension between the lidocaine and remifentanil patient groups. Incidentally, the mean duration of surgery and intubation in the lidocaine group was significantly longer than in the remifentanil group (Table 3). However, there was no difference in mean extubation time between the groups:

\[ 6.6 \pm 2.8 \text{ minutes} vs 7.1 \pm 2.8 \text{ minutes}, \ p=0.39 \]

The patients in lidocaine group had a significantly lower incidence of cough compared to remifentanil group: 44% vs 67%, \( p=0.02 \) (Table 4 and Figure 2). The lidocaine group also had significantly lower rates of cough before extubation: 35% vs. 65%, \( p=0.002 \). However there was no significant difference in post-extubation cough rates: 19% vs. 14%, \( p=0.47 \). The lidocaine group also had lower incidence of significant coughing (grade 2 and 3), when compared to the remifentanil group: 25% vs 49%, \( p=0.009 \).

A post-hoc subgroup analysis was performed in order to readjust the mean duration of surgery between both groups (Table 5). Patients taken into consideration on this analysis were those who had surgeries lasting between 120 and no more than 300 minutes. From these, 35 subjects remained in the lidocaine group and 29 in the remifentanil group. Duration of surgery did not show any statistical significance (\( p=0.14 \)). Nonetheless, significant coughing before extubation and overall coughing remained higher in the remifentanil group when compared to the lidocaine group: 55% vs. 20% (OR=4.9); \( p \) value=0.004 and 55% vs. 23% (OR=3.1); \( p \) value=0.008.

There was no significant difference between the groups with regard to incidence of sore throat, postoperative nausea, or desaturation after extubation. Additionally, there were no differences between the groups in the incidence or severity of sore throat in the PACU. The majority of patients experienced no significant adverse effects (Table 6). Baseline MAP and HR values were comparable between the two groups. Both groups had some sympathetic stimulation during emergence evidenced by raise in the HR and MAP compared to baseline. Between the two
groups, mean HR was similar during emergence however MAP was significantly higher in the remifentanil group at extubation and at 5 minutes after extubation (Figure 3).

**Discussion**

The effects of intra cuff lidocaine and remifentanil infusion in suppressing cough during emergence from general anesthesia have been thoroughly investigated [3,11-13,23-25]. However, no study has directly compared the two agents to demonstrate a greater efficacy of one over the other. Comparison between different studies is limited due to variation in the protocol design and anesthetic agents (inhaled anesthetics, narcotics). Our results indicate that ICL is more effective in reducing emergence coughing compared to low dose remifentanil infusion in patients receiving desflurane anesthesia.

Repeated success has been demonstrated with the ETT cuffs filled with lidocaine in suppressing the cough reflex [1-3]. The quantity of lidocaine that diffuses through the cuff was found to be directly related to the concentration of lidocaine and time [29,30]. Hence, earlier studies [1] used large doses of concentrated solution of lidocaine (200-500 mg) despite the possible adverse reactions if the cuff would rupture. Later studies [23,24] found that alkalization of lidocaine increased the rate of diffusion as much as 65 to 100 times which allowed reduction in the lidocaine dose while achieving the same results. One of the drawbacks of using 8.4% NaHCO₃ for alkalization of Lidocaine was the potential for tracheal irritation if the cuff ruptures. Estebe et al. [25] has shown 1.4% NaHCO₃ to be as effective as 8.4% NaHCO₃. They showed successful attenuation of cough reflex and sore throat with as little as 40 mg of lidocaine alkalized with 1.4% NaHCO₃. The incidence of coughing in their study was only 5%, however, they used continuous infusion of sufentanil in all the patients. The anti-tussive effect of narcotics needs to be considered while reviewing their results. Fagan et al. [1] used 4% plain lidocaine with a mean dose of 244 ± 36 mg. The incidence of coughing in the lidocaine group in their study was 16%. Another study by Navarro et al. [31], also showed successful attenuation of emergence coughing and sore throat among smokers by using intra cuff alkalized 2% lidocaine (28% in ICL vrs 80% in control). The mean dosage of lidocaine was 138 ± 52 mg. However, study by Wetzel et al. [32], didn’t show any decrease in the emergence coughing by ICL when used for procedures lasting less than 1.5 hours.
According to the authors, the incidence of coughing in remifentanil groups. One group also received 4% lidocaine through the LITA tube. At 0.1 μg/kg/min was continued at the end of the surgery in both when combined with remifentanil. In that study, remifentanil infusion such a goal can be difficult to achieve by manually controlled infusion.

Conclusions

Remifentanil is an ultra-short acting opioid analgesic which has been shown to facilitate the smooth emergence from general anesthesia [11-13]. The dose of remifentanil used in our study was based on previous investigation by Aouad et al. [12], who demonstrated that a low-dose infusion of remifentanil attenuates coughing and hemodynamic stimulation during emergence from isoflurane-based anesthesia. The authors of that publication maintained remifentanil at one tenth of the patient's weight and the duration of surgery. The mean remifentanil concentration of 2.0-2.5 ng/ml. Thus reiterates the importance of showing that maintaining the predicted effect-site concentration (Ce) of remifentanil at 1.5 ng/ml during emergence from sevoflurane infusion, because it is very easy to use, doesn't require any property of different inhalational agents also needs to be considered.

Conclusion

The intra cuff alkalized lidocaine is more effective than low dose remifentanil infusion in suppressing coughing during emergence from Desflurane based anesthesia in patients undergoing surgeries lasting for longer than 2 hours. ICL was also more effective than remifentanil for reducing severity when coughing did occur. Moreover, ICL is advantageous when compared with several other techniques including remifentanil infusion, because it is very easy to use, doesn't require any special infusion device, is inexpensive, and has an established excellent safety profile.

Acknowledgement

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References