

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: Intra cuff lidocaine; Remifentanil; Emergence coughing; Emergence phenomena; Lidocaine; Intra cuff; 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 Laryngotracheal instilled topical anesthesia (LITA) tube is also effective in suppressing the cough [21,22]. However, the study by Crerar 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

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advantage of remifentanyl 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 remifentanyl 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 remifentanyl 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 remifentanyl 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, as well as prisoners, 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 remifentanyl 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

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

Table 1: Types of Surgery included per group.

Observation	Grade
No cough	0
Single cough O ₂ Sat ≥ 95%	1
More than one episode of unsustained cough (≤ 5 sec)	2
Sustained bouts of coughing (≥ 5 secs)	3

Grade 1: Mild cough. Grade 2 and 3: Significant cough.

Table 2: Coughing Point Scale.

the anesthesiologist. Endotracheal intubation with a high volume low pressure cuffed ETT was performed by direct laryngoscopy. Cuff inflation was performed with normal saline for the remifentanyl 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 remifentanyl at a rate 0.05-0.5 mcg/kg/min was used in the remifentanyl 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 remifentanyl 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 remifentanyl 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 remifentanyl 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 remifentanyl 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 remifentanyl 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.

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 remifentanyl 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 remifentanyl patient groups. Incidentally, the mean duration of surgery and intubation in the lidocaine group was significantly longer than in the remifentanyl group (Table 3). However, there was no difference in mean extubation time between the groups:

6.6 ± 2.8 minutes vs 7.1 ± 2.8 minutes, p=0.39. The patients in lidocaine group had a significantly lower incidence of cough compared to remifentanyl 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 remifentanyl 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). Subjects 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 remifentanyl 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 remifentanyl 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

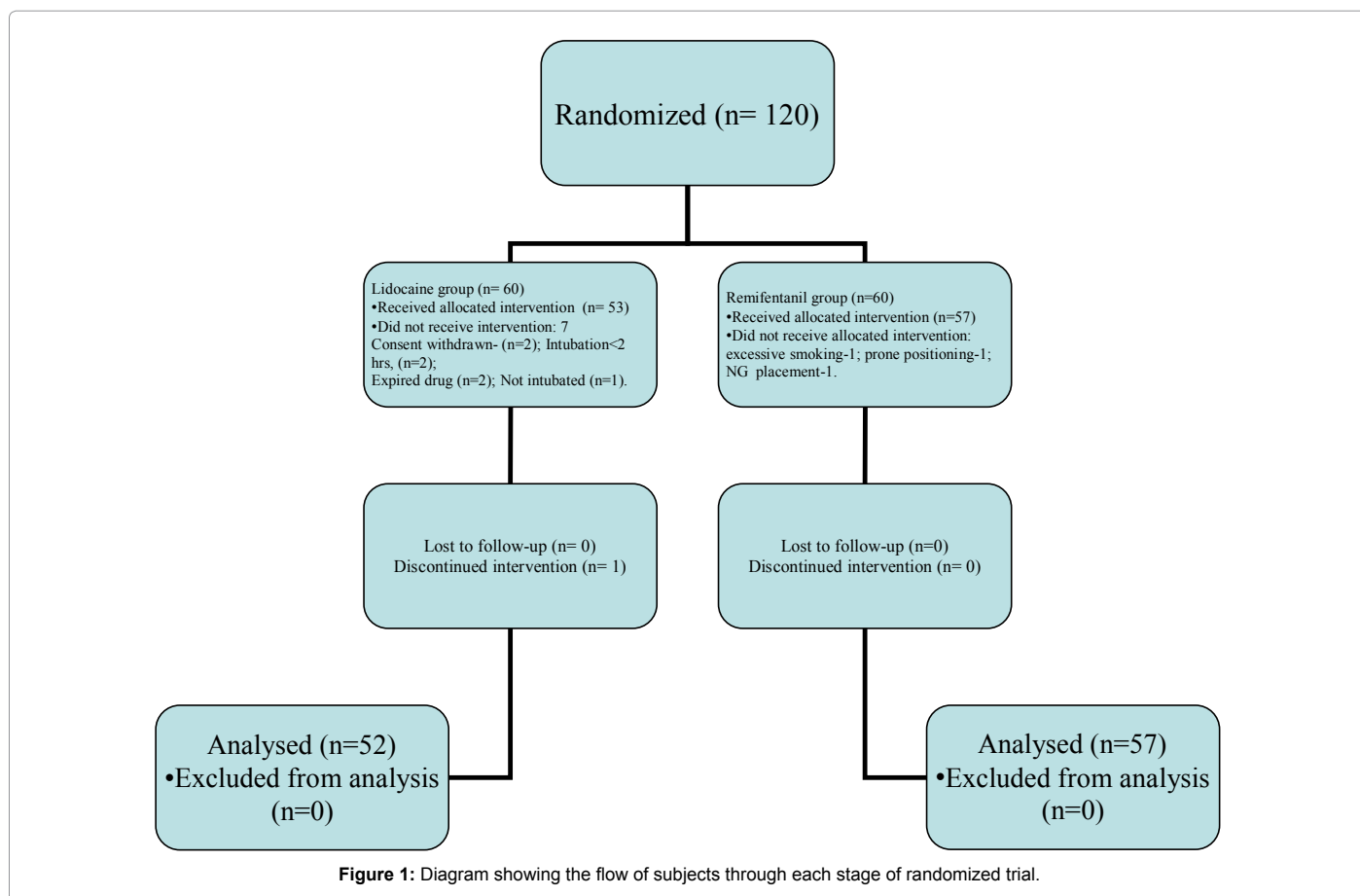


Figure 1: Diagram showing the flow of subjects through each stage of randomized trial.

Characteristic/Measurement	Lidocaine group (N=52)	Remifentanyl group (N=57)	p-value
Age (mean ± sd) years	48 ± 10	49 ± 11	0.58
Female	42 (81%)	40 (70%)	0.20
BMI (mean ± sd)	28.7 ± 6.3	28.4 ± 5.3	0.81
Smokers	41 (79%)	48 (84%)	0.47
HTN	15 (29%)	18 (32%)	0.76
Duration of surgery (mean ± SD) in minutes	181 ± 83	130 ± 56	0.0002
Duration of intubation (mean ± SD) in minutes	217 ± 87	162 ± 62	0.0002

Table 3: Patient Characteristics.

Cough incidence	Lidocaine group (N=52)	Remifentanyl group (N=57)	OR (95% CI)	P-value
Pre extubation	18 (35%)	37 (65%)	3.5 (1.6, 7.7)	0.002
Post extubation	10 (19%)	8 (14%)	0.7 (0.2, 1.9)	0.47
Overall Cough	23 (44%)	38 (67%)	2.5 (1.2, 5.5)	0.02
Significant Cough (Grade 2 and 3)	13 (25%)	28 (49%)	2.9 (1.3, 6.5)	0.009

The odds ratio and its 95% confidence intervals have been listed.

Table 4: Incidence of cough.

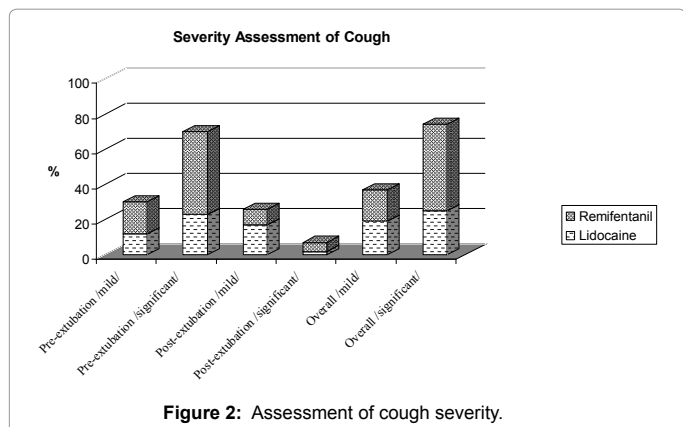


Figure 2: Assessment of cough severity.

Cough incidence	Lidocaine group (N=35)	Remifentanyl group (N=29)	OR (95% CI)	P-value
Before extubation	12 (34%)	20 (69%)	4.3 (1.5, 12.2)	0.006
After extubation	7 (20%)	4 (14%)	0.6 (0.2, 2.4)	0.74*
overall	16 (46%)	20 (69%)	2.6 (0.9, 7.4)	0.06
Severe Cough	8 (23%)	16 (55%)	3.1 (1.1, 9.1)	0.008

*P-value is obtained through Fisher's exact test

Table 5: Post hoc analysis with duration of surgery larger than 120 minutes and less than 300 minutes.

groups, mean HR was similar during emergence however MAP was significantly higher in the remifentanyl group at extubation and at 5 minutes after extubation (Figure 3).

Discussion

The effects of intra cuff lidocaine and remifentanyl 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 remifentanyl 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 alkalinization 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 alkalinization 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 alkalinized 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 alkalinized 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.

Side effects	Lidocaine group (N=52)	Remifentanyl group (N=57)	OR (95% CI)	P-value
Incidence of Sore throat	18 (35%)	26 (48%)	1.7 (0.8, 3.7)	0.18
VAS score for sore throat (mean ± sd)	0.66 ± 1.68	1.10 ± 1.91	NA	0.21
Postoperative nausea	1 (2%)	0 (0%)	NA	0.49*
Desaturation	1 (2%)	0 (0%)	NA	0.49*

*P-value is obtained through Fisher's exact test. VAS: Visual Analog Score

Table 6: Incidence of Sore throat and other side effects.

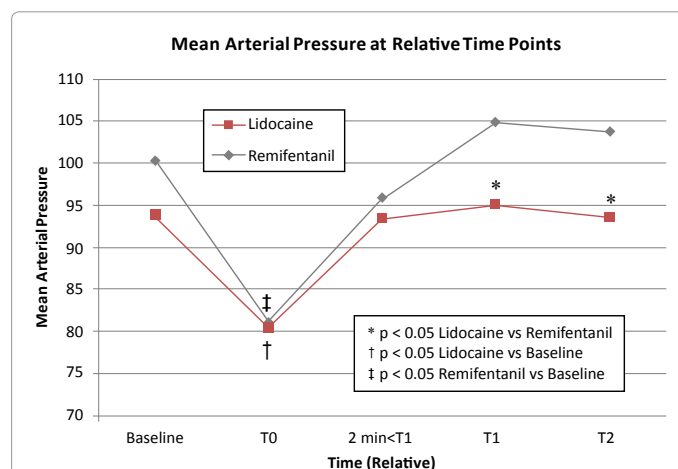


Figure 3: Mean hemodynamic changes during emergence.

T0: Baseline measurement taken from chart; T1: desflurane vaporizer turned off; 2 min<T1: two minutes prior to extubation; T1: at extubation; T2: five minutes after extubation.

This was postulated to be due to inadequate time for the lidocaine to diffuse through the cuff wall.

The overall incidence of coughing in the lidocaine group in our study was 44%. Even though, lidocaine performed better than remifentanyl, it is still not clear how some patients still continue to cough. There are several possible explanations: we used low doses of lidocaine as described by Estebe et al. [23-25]. The mean dose of lidocaine used in our study was only 57.6 mg. Since the amount of drug diffusing through the cuff wall is directly proportional to the concentration of the lidocaine, higher concentration might be more effective in suppressing the cough. The primary mechanism for coughing during emergence is due to irritation of the respiratory mucosa by the ETT and its cuff [1,19] and ICL mainly works by abolishing this reflex. This explains the success of ICL in most of the cases. However, since ICL only anesthetizes the small area in contact with the cuff, any stimulation along the tracheobronchial tree (e.g. irritation with oropharyngeal secretions) can still induce cough. Lastly, ICL might not have a uniform circumferential numbing effect. The diffusion might theoretically be higher on the posterior portion of the trachea (assuming the patient is supine) due to gravity, air collection in the cuff, and other factors. Uneven diffusion may be a probable explanation for uneven numbness and failure to prevent coughing in some patients.

Remifentanyl is an ultra-short acting opioid analgesic which has been shown to facilitate the smooth emergence from general anesthesia [11-13]. The dose of remifentanyl used in our study was based on previous investigation by Aouad et al. [12], who demonstrated that a low-dose infusion of remifentanyl attenuates coughing and hemodynamic stimulation during emergence from isoflurane-based anesthesia. The authors of that publication maintained remifentanyl at one tenth of the mean dose during emergence, which was calculated at the end of the surgery by dividing the total dose administered during maintenance by the patient's weight and the duration of surgery. The mean remifentanyl infusion rate during emergence was 0.014 ± 0.011 mcg/kg/min. The incidence of coughing in the remifentanyl group was significantly lower compared to control (40% vs 80%, $P=0.002$). We followed the same protocol as Aouad et al. in terms of remifentanyl infusion but desflurane instead of isoflurane was used in our study. The incidence of coughing in the remifentanyl group was much higher in our study-67%, and the mean remifentanyl dose during extubation was 0.014 ± 0.005 mcg/kg/min. The failure of remifentanyl to suppress coughing in our study could be related to inadequate effect site concentration of remifentanyl as shown in some of the recent studies [13]. Nevertheless, airway irritant property of different inhalational agents also needs to be considered.

Jun et al. [11] using target controlled infusion device(TCI), showed that maintaining the predicted effect-site concentration (C_e) of remifentanyl at 1.5 ng/ml during emergence from sevoflurane anesthesia resulted in a 50% reduction in the incidence of coughing whereas patients with remifentanyl C_e of 1.0 ng.ml did not show any significant cough suppression In a dose escalation study, Chen et al. [33], also showed successful cough suppression by remifentanyl which was found to be dose dependent and more pronounced at higher concentrations of 2.0-2.5 ng/ml. Thus reiterates the importance of maintaining minimum plasma concentration of remifentanyl, however, such a goal can be difficult to achieve by manually controlled infusion.

Yamasaki et al. [34], showed synergistic effect of topical lidocaine when combined with remifentanyl. In that study, remifentanyl infusion at 0.1 $\mu\text{g}/\text{kg}/\text{min}$ was continued at the end of the surgery in both groups. One group also received 4% lidocaine through the LITA tube. According to the authors, the incidence of coughing in remifentanyl

only group was 61% whereas that in the combined group was 26%. Interestingly, incidence of coughing was still very high in remifentanyl only group even though it was maintained at a very high dose of 0.1 mcg/kg/min indicating that remifentanyl is not a reliable antitussive agent.

In our study, the two treatments did not differ in their recovery profiles. Mean time to extubation after discontinuation of desflurane was similar between the groups. This likely confers no advantage or disadvantage to either intervention from a timing and efficiency perspective. Neither intervention group proved to be more effective than the other in reducing the incidence of other side effects, including postoperative nausea, postintubation desaturation, and dry/sore throat.

Limitations

There are several limitations in our study. First, even though we followed a standardized protocol, we were unable to use the same anesthesiologist or the observer for all the patients, and this could have introduced a bias and inter-observer variability into our study. Second, we used a fixed dose of remifentanyl and didn't measure the plasma concentration. It is important to test if with higher doses of remifentanyl, as opposed to doses used in our study, it will be possible to reach results comparable with ICL. Third, the duration of surgery and intubation was greater in the lidocaine than the remifentanyl group. Given that remifentanyl is an ultra-short acting opioid, it could be assumed to be at steady state after two hours and prolonging the remifentanyl infusion would likely entail a similar conclusion. Finally, we didn't have a control group to compare the effects of remifentanyl.

Conclusion

The intra cuff alkalinized lidocaine is more effective than low dose remifentanyl 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 remifentanyl for reducing severity when coughing did occur. Moreover, ICL is advantageous when compared with several other techniques including remifentanyl infusion, because it is very easy to use, doesn't require any special infusion device, is inexpensive, and has an established excellent safety profile.

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References

1. Fagan C, Frizelle HP, Laffey J, Hannon V, Carey M (2009) The effects of intracuff lidocaine on endotracheal-tube-induced emergence phenomena after general anesthesia. *Anesth Analg* 91:201-205.
2. Tanaka Y, Nakayama T, Nishimori M, Sato Y, Furuya H (2009) Lidocaine for preventing postoperative sore throat. *Cochrane Database Syst Rev*: CD004081.
3. Estebe JP, Delahaye S, Le Corre P, Dollo G, Le Naoures A, et al. (2004) Alkalinization of intra-cuff lidocaine and use of gel lubrication protect against tracheal tube-induced emergence phenomena. *Br J Anaesth* 92: 361-366.
4. Kori K, Muratani T, Tatsumi S, Minami T (2009) Influence of endotracheal tube cuff lubrication on postoperative sore throat and hoarseness. *Masui* 58: 342-345.
5. Jee D, Park SY (2003) Lidocaine sprayed down the endotracheal tube attenuates the airway-circulatory reflexes by local anesthesia during emergence and extubation. *Anesth Analg* 96: 293-297, table of contents.
6. Irwin RS (2006) Complications of cough: ACCP evidence-based clinical practice guidelines. *Chest* 129: 54S-58S.

7. Leech P, Barker J, Fitch W (1974) Proceedings: Changes in intracranial pressure and systemic arterial pressure during the termination of anaesthesia. *Br J Anaesth* 46: 315-316.
8. Holden R, Morsman CD, Butler J, Clark GS, Hughes DS, et al. (1991) Intracuff pressure changes using the laryngeal mask airway and tracheal tube. *Anaesthesia* 46: 922-924.
9. Bidwai AV, Bidwai VA, Rogers CR, Stanley TH (1979) Blood-pressure and pulse-rate responses to endotracheal extubation with and without prior injection of lidocaine. *Anesthesiology* 51: 171-173.
10. Neelakanta G, Miller J (1994) Minimum alveolar concentration of isoflurane for tracheal extubation in deeply anesthetized children. *Anesthesiology* 80: 811-813.
11. Jun NH, Lee JW, Song JW, Koh JC, Park WS, et al. (2010) Optimal effect-site concentration of remifentanil for preventing cough during emergence from sevoflurane-remifentanil anaesthesia. *Anaesthesia* 65: 930-935.
12. Aouad MT, Al-Alami AA, Nasr VG, Souki FG, Zbeidy RA, et al. (2009) The effect of low-dose remifentanil on responses to the endotracheal tube during emergence from general anesthesia. *Anesth Analg* 108: 1157-1160.
13. Lee B, Lee JR, Na S (2009) Targeting smooth emergence: the effect site concentration of remifentanil for preventing cough during emergence during propofol-remifentanil anaesthesia for thyroid surgery. *Br J Anaesth*. 102:775-778.
14. Saghaei M, Reisinejad A, Soltani H (2005) Prophylactic vs therapeutic administration of intravenous lidocaine for suppression of post-extubation cough following cataract surgery: a randomized double blind placebo controlled clinical trial. *Acta Anaesthesiol Taiwan* 43:205-209.
15. Gefke K, Andersen LW, Friesel E (1983) Lidocaine given intravenously as a suppressant of cough and laryngospasm in connection with extubation after tonsillectomy. *Anaesthesiol Scand* 27: 111-112.
16. Nishino T, Hiraga K, Sugimori K (1990) Effects of i.v. lignocaine on airway reflexes elicited by irritation of the tracheal mucosa in humans anaesthetized with enflurane. *Br J Anaesth* 64: 682-687.
17. Guler G, Akin A, Tosun Z, Eskitascoglu E, Mizrak A, et al. (2005) Single-dose dexmedetomidine attenuates airway and circulatory reflexes during extubation. *Anaesthesiol Scand* 49: 1088-1091.
18. Yukioka H, Yoshimoto N, Nishimura K, Fujimori M (1985) Intravenous lidocaine as a suppressant of coughing during tracheal intubation. *Anesth Analg* 64: 1189-1192.
19. Gonzalez RM, Bjerke RJ, Drobycki T, Stapelfeldt WH, Green JM, et al. (1994) Prevention of endotracheal tube-induced coughing during emergence from general anesthesia. *Anesth Analg* 79: 792-795.
20. Sant'Ambrogio G, Widdicombe J (2001) Reflexes from airway rapidly adapting receptors. *Respir Physiol* 125: 33-45.
21. Diachun CA, Tunink BP, Brock-Utne JG (2001) Suppression of cough during emergence from general anesthesia: laryngotracheal lidocaine through a modified endotracheal tube. *J Clin Anesth* 13: 447-451.
22. Crerar C, Weldon E, Salazar J, Gann K, Kelly JA, et al. (2008) Comparison of 2 laryngeal tracheal anesthesia techniques in reducing emergence phenomena. *AANA J* 76: 425-431.
23. Estebe JP, Dollo G, Le Corre P, Le Naoures A, Chevanne F, et al. (2002) Alkalinization of intracuff lidocaine improves endotracheal tube-induced emergence phenomena. *Anesth Analg* 94: 227-230, table of contents.
24. Dollo G, Estebe JP, Le Corre P, Chevanne F, Ecoffey C, et al. (2001) Endotracheal tube cuffs filled with lidocaine as a drug delivery system: in vitro and in vivo investigations. *Eur J Pharm Sci* 13: 319-323.
25. Estebe JP, Gentili M, Le Corre P, Dollo G, Chevanne F, et al. (2005) Alkalinization of intracuff lidocaine: efficacy and safety. *Anesth Analg* 101: 1536-1541.
26. Shajar MA, Thompson JP, Hall AP, Leslie NA, Fox AJ (1999) Effect of a remifentanil bolus dose on the cardiovascular response to emergence from anaesthesia and tracheal extubation. *Br J Anaesth* 83: 654-656.
27. Westmoreland CL, Hoke JF, Sebel PS, Hug CC Jr, Muir KT (1993) Pharmacokinetics of remifentanil (GI87084B) and its major metabolite (GI90291) in patients undergoing elective inpatient surgery. *Anesthesiology* 79: 893-903.
28. Cavaliere F, Antonelli M, Arcangeli A, Conti G, Costa R, et al. (2002) A low-dose remifentanil infusion is well tolerated for sedation in mechanically ventilated, critically-ill patients. *Can J Anaesth* 49: 1088-1094.
29. Sconzo JM, Moscicki JC, DiFazio CA (1990) In vitro diffusion of lidocaine across endotracheal tube cuffs. *Reg Anesth* 15: 37-40.
30. Huang CJ, Tsai MC, Chen CT, Cheng CR, Wu KH, et al. (1999) In vitro diffusion of lidocaine across endotracheal tube cuffs. *Can J Anaesth* 46: 82-86.
31. Navarro LH, Lima RM, Aguiar AS, Braz JR, Carness JM, et al. (2012) The effect of intracuff alkalinized 2% lidocaine on emergence coughing, sore throat, and hoarseness in smokers. *Rev Assoc Med Bras* 58: 248-253.
32. Wetzel LE, Ancona AL, Cooper AS, Kortman AJ, Loniewski GB, et al. (2008) The effectiveness of 4% intracuff lidocaine in reducing coughing during emergence from general anesthesia in smokers undergoing procedures lasting less than 1.5 hours. *AANA J* 76: 105-108.
33. Chen J, Li W, Wang D, Hu X (2010) The effect of remifentanil on cough suppression after endoscopic sinus surgery: a randomized study. *Anaesthesiol Scand* 54: 1197-1203.
34. Yamasaki H, Takahashi K, Yamamoto S, Yamamoto Y, Miyata Y, et al. (2013) Efficacy of endotracheal lidocaine administration with continuous infusion of remifentanil for attenuating tube-induced coughing during emergence from total intravenous anesthesia. *J Anesth* 27:822-826.