Intracuff 160 mg alkalinized lidocaine reduces cough upon emergence from N₂O-free general anesthesia: a randomized controlled trial

Une solution de 160 mg de lidocaïne alcalinisée dans le ballonnet réduit la toux à l'émergence d'une anesthésie générale sans N₂O: une étude randomisée contrôlée

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Abstract

Purpose Chemical and mechanical irritation of the tracheal mucosa influences the incidence of cough at emergence from general anesthesia, potentially leading to significant postoperative complications. This study evaluates the benefits of endotracheal tube (ETT) intracuff alkalinized lidocaine during N₂O-free general anesthesia by 1) assessing the *in vitro* effect of alkalization on lidocaine diffusion kinetics across the cuff's membrane and 2) evaluating, in a randomized controlled clinical trial, the impact of 160 mg of intracuff alkalinized lidocaine on cough upon emergence from anesthesia for surgery lasting > 120 min.

Methods In the *in vitro* study, diffusion kinetics of various intracuff alkalinized lidocaine amounts (40, 80, and 160 mg) were compared to their non-alkalinized

lidocaine controls. In the clinical trial, 80 adult patients (American Society of Anesthesiologists physical status I–III) undergoing urological or gynecological surgery expected to last > 120 min and scheduled for N₂O-free general anesthesia were enrolled. The ETT cuffs (high-volume, low-pressure) were filled with either 160 mg of alkalinized lidocaine or a comparable volume of 0.9% saline. The primary outcome was the incidence of cough upon emergence from anesthesia. Sore throat, hoarseness, and postoperative nausea and vomiting were evaluated as secondary outcomes.

Results Our *in vitro* study confirmed that alkalization increases lidocaine diffusion across the membrane of ETT cuffs and suggested that the lidocaine diffusion rate is associated with the initial intracuff lidocaine quantity. Our clinical trial demonstrated that, compared with the saline group, 160 mg of intracuff alkalinized lidocaine reduced the incidence of cough upon emergence from N₂O-free general anesthesia (76% vs 34%, respectively; difference 42%; 95% confidence interval, 21% to 62%; $P < 0.001$) while having no clinical impact on secondary outcomes.

Conclusions The use of 160 mg of intracuff alkalinized lidocaine is associated with a decreased incidence of cough upon emergence from N₂O-free general anesthesia > 120 min. This trial was registered at www.clinicaltrials.gov (NCT01774292).

The study was registered prior to patient enrolment (clinicaltrials.gov). Registry URL: <https://goo.gl/nOoaTu>. Identifier: NCT01774292.

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Résumé

Objectif L'irritation chimique et mécanique de la muqueuse trachéale influence l'incidence de toux à l'émergence d'une anesthésie générale et peut provoquer

d'importantes complications postopératoires. Cette étude a évalué les avantages de l'application de lidocaïne alcalinisée dans le ballonnet de la sonde endotrachéale (SET) pendant une anesthésie générale sans N₂O, 1) en évaluant l'effet *in vitro* de l'alcalinisation sur la cinétique de diffusion de la lidocaïne à travers la membrane du ballonnet et 2) en évaluant, dans une étude clinique randomisée contrôlée, l'impact de 160 mg de lidocaïne alcalinisée dans le ballonnet sur la toux à l'émergence de l'anesthésie pour une chirurgie durant > 120 min.

Méthode Dans l'étude *in vitro*, la cinétique de diffusion de diverses quantités de lidocaïne alcalinisée (40, 80, et 160 mg) a été comparée aux quantités témoins de lidocaïne non alcalinisée. Dans l'étude clinique, 80 patients adultes (de statut physique I-III selon la classification de l'American Society of Anesthesiologists) subissant une chirurgie urologique ou gynécologique devant durer > 120 min prévue avec une anesthésie générale sans N₂O ont été recrutés. Les ballonnets des SET (volume élevé, basse pression) ont été remplis de 160 mg de lidocaïne alcalinisée ou d'un volume comparable d'une solution saline physiologique 0,9 %. Le critère d'évaluation principal était l'incidence de toux à l'émergence de l'anesthésie. Les critères d'évaluation secondaires étaient les maux de gorge, l'enrouement et les nausées et vomissements postopératoires.

Résultats Notre étude *in vitro* a confirmé que l'alcalinisation augmente la diffusion de la lidocaïne à travers la membrane des ballonnets de SET et suggère que le taux de diffusion de la lidocaïne est associé à la quantité initiale de lidocaïne dans le ballonnet. Notre étude clinique a démontré que, par rapport au groupe avec solution saline physiologique, une quantité de 160 mg de lidocaïne alcalinisée dans le ballonnet a réduit l'incidence de toux à l'émergence d'une anesthésie générale sans N₂O (76 % vs 34 %, respectivement; différence 42 %; intervalle de confiance 95 %, 21 % à 62 %; $P < 0,001$) tout en n'ayant aucun impact clinique sur les critères d'évaluation secondaires.

Conclusion L'utilisation de 160 mg de lidocaïne alcalinisée dans le ballonnet est associée à une réduction de l'incidence de toux à l'émergence d'une anesthésie générale sans N₂O > 120 min. Cette étude a été enregistrée au www.clinicaltrials.gov (NCT01774292).

Cough upon emergence from general anesthesia has an estimated incidence of 38% to 96%.¹ Contributing factors such as smoking status, pharyngeal secretions, and chemical irritation due to volatile anesthetics are known to have an impact on cough at emergence and extubation.²⁻⁴ Moreover,

endotracheal tube (ETT) cuff inflation to prevent air leaks during controlled ventilation produces significant mechanical irritation of the tracheal mucosa.⁵ Although intubation-induced sore throat and hoarseness occur upon emergence, cough has important clinical relevance because it is often accompanied by hemodynamic alterations, arrhythmias, increased intraocular and intracranial pressures, and bronchospasm.⁶ These complications can lead to hypoxemia, cardiac ischemia, bleeding, and extension of brain injury.^{7,8}

Various strategies aimed at reducing adverse effects associated with mucosal irritation caused by ETT insertion have been studied. Potential solutions suggested by investigators include ETT cuff lubrication, fluticasone inhalation before intubation, intravenous lidocaine, opioid administration during emergence and extubation, or extubation under deep anesthesia.⁹⁻¹⁴ Of particular interest, filling the ETT cuff with alkalinized lidocaine to serve as a reservoir that allows continuous diffusion of local anesthetic over the tracheal mucosa has been proposed.^{15,16} This strategy is attractive because of its high safety margins, ease of application, and reproducibility.¹ However, the vast majority of studies designed to assess the effect of intracuff alkalinized lidocaine (compared with intracuff saline or air) on cough at emergence from general anesthesia were performed in situations in which nitrous oxide (N₂O) was used.^{4,16-20} Because using N₂O as an anesthetic adjuvant is a matter of debate concerning patient safety issues and environmental toxicity,^{21,22} evaluation of the efficacy of alkalinized lidocaine on cough at emergence from N₂O-free general anesthesia is relevant and has yet to be tested in a clinical trial. Furthermore, there is no consensus regarding the safest, most efficacious amount of intracuff alkalinized lidocaine necessary to provide overall clinical benefit.

In the present study, we aimed to assess the *in vitro* effect of alkalinization on lidocaine diffusion kinetics across the cuff membrane of high-volume, low-pressure ETTs at various clinically safe lidocaine doses. The principal objective of this study, however, was to evaluate, in a randomized clinical trial, the potential benefits of intracuff alkalinized lidocaine on cough upon emergence from N₂O-free general anesthesia for operations scheduled to last > 120 min. We also aimed to evaluate the incidence of sore throat, hoarseness, and postoperative nausea and vomiting (PONV) as secondary outcomes. We hypothesized that sufficient diffusion of lidocaine across the cuff membrane would lead to a decreased incidence of cough upon emergence from N₂O-free general anesthesia, potentially leading to fewer severe postoperative complications.

Methods

In vitro lidocaine diffusion across the ETT cuff

To assess the effect of alkalization and dosing on lidocaine diffusion across the cuff membrane, six 7.5-mm ETTs were used (model # 86111; Mallinckrodt Inc., St. Louis, MO, USA). These ETTs are high-volume, low-pressure, thin-walled, barrel-shaped cuffs made of polyvinylchloride (PVC). All ETTs were immersed in beakers filled with 90 mL of physiological release medium (phosphate-buffered saline, pH 7.4). The medium was maintained at 37°C and gently agitated with a magnetic stirrer (100 rpm). The ETT cuffs were filled with 1, 2, or 4 mL of 4% lidocaine (AstraZeneca Canada Inc., Mississauga, ON, Canada), corresponding to 40, 80, and 160 mg, respectively. A final intracuff volume of 12 mL was achieved by adding either 0.9% saline or 8.4% sodium bicarbonate (NaHCO_3 8.4%, injectable USP, Hospira, Montreal, QC, Canada). Each beaker was covered with a paraffin membrane to avoid evaporative losses. For all experimental conditions, the diffusion of lidocaine across the PVC membrane was monitored every 60 min during eight consecutive hours by sampling a 100- μL aliquot of release medium. A digital pH meter was used to measure the pH of the intracuff solution and the release medium before and after the procedure. Samples were kept at -20°C until analysis. The integrity of each ETT cuff was confirmed by visual inspection at the end of the experiment.

Lidocaine concentrations were then measured using a high-performance liquid chromatography system coupled to a mass spectrometer (Waters Acquity H Class equipped with an Acquity UPLC BEH C18 column; 1.7 μm particle size; 2.1 $\times$ 50 mm). The gradient of the mobile phase was the following: water with 0.1% formic acid and acetonitrile (0–0.2 min: 5% acetonitrile; 0.2–1.5 min: 5%–95%; 1.5–1.8 min: 95%; 1.8–2.0 min: 95%–5%; 2.0–2.5 min: 5%). To quantify the amount of diffused lidocaine, 90 μL of each sample were injected with 10 μL of a 4.85 mM aqueous solution of Sensorcaine 0.25% (AstraZeneca Canada Inc., Mississauga, ON, Canada) as a reference standard. Lidocaine concentrations for each condition across time were calculated as the ratio between the area under the curve (AUC) of the sample and the AUC of the reference standard, when compared to the same ratio in a sample with a known concentration of lidocaine. All measures were performed in duplicate. Release profiles of lidocaine were plotted over time and graphically displayed for all experimental conditions.

Clinical trial

Design overview

This clinical trial was registered on clinicaltrials.gov (NCT01774292). The study protocol was approved by the

local institutional review board (*Comité d'éthique de la recherche en santé chez l'humain du CHUS*) and was conducted in accordance with institutional and Good Clinical Practice guidelines. Between February 2013 and May 2014, a total of 80 participants recruited in our tertiary care centre were randomly assigned, using computer-generated random numbers, to receive intracuff alkalized lidocaine (lidocaine group) or intracuff 0.9% saline (saline group). Written informed consent was obtained from all participants prior to the intervention. A staff anesthesiologist administered standard anesthesia, and a research assistant was charged with evaluating the incidence of cough at emergence from general anesthesia. All patients, staff members, and researchers involved in this study were blinded to group assignment.

Study population

Adult (≥ 18 yr) American Society of Anesthesiologists physical status I–III patients requiring general anesthesia with endotracheal intubation for elective gynecological or urological surgeries were approached for consent. Exclusion criteria included an anticipated difficult airway or a history of difficult intubation (Cormack-Lehane grade 3 or 4), previous upper airway surgery (except tonsillectomy), uncontrolled asthma, upper respiratory tract infection within the last month, chronic obstructive pulmonary disease, chronic cough, symptomatic gastric reflux despite medication, pregnancy, and allergy to any of the study medications. Additional perioperative exclusion criteria were the following: more than one laryngoscopy, endotracheal tube lubrication, local anesthetic administration, use of a volatile agent other than desflurane, gastric tube insertion, and dexamethasone administration.

Intervention

All patients received a standardized anesthetic consisting of pre-oxygenation with 100% oxygen and induction with fentanyl 2–3 $\mu\text{g}\cdot\text{kg}^{-1}$ *iv*, propofol 2–3 $\text{mg}\cdot\text{kg}^{-1}$ *iv* with lidocaine 40 mg *iv* (to reduce pain during propofol administration), and rocuronium 0.6 $\text{mg}\cdot\text{kg}^{-1}$ *iv*. Laryngoscopy was performed with a Macintosh blade (#3 or #4) by a senior resident or a certified anesthesiologist. High-volume low-pressure PVC ETTs (model #86111, Mallinckrodt Inc., St. Louis, MO, USA) were used in this study. Their internal diameters were 7 mm and 8 mm for women and men, respectively. Thirty minutes before general anesthesia induction, a sealed envelope containing a computer-generated randomization code indicating the treatment assignment was provided to the

anesthesiologist (otherwise not involved in the study). Patients were stratified by smoking status (i.e., smoker or non-smoker) and randomly assigned in a 1:1 ratio to the lidocaine group or the saline group. A block design with a permuted block size of four was used.

After intubation, the ETT cuff was filled with either 4 mL of 4% lidocaine (160 mg total; lidocaine group) or 4 mL of 0.9% saline (saline group). In the lidocaine group, 8.4% sodium bicarbonate, the alkalinizing agent, was added to the ETT cuff to obtain a seal at a positive ventilation pressure of 30 cm H₂O. In the saline group, 0.9% saline was used to attain a similar seal.

Anesthesia was maintained with desflurane in an oxygen/air mixture (1:1). If required, fentanyl 1 µg·kg⁻¹ and/or rocuronium 0.15 mg·kg⁻¹ was permitted. Fentanyl was the only long-acting opioid used during the surgical procedure prior to emergence. Thirty minutes before the end of surgery, all patients were given ondansetron (4 mg *iv*) to prevent PONV. Residual neuromuscular blockade was reversed with appropriate amounts of neostigmine and glycopyrrolate. Pharyngeal secretions were gently aspirated before the desflurane was stopped. While the patient was still on the operating table, tracheal extubation was performed when all of the following criteria were met: return of neuromuscular function, regular spontaneous ventilation, ability to follow verbal commands.

Primary and secondary outcomes

Our primary outcome was the incidence of cough upon emergence from general anesthesia. Cough was defined as a sudden, forceful, sustained expiration leading to interruption of spontaneous ventilation. Cough incidence (or bucking) was recorded from the moment desflurane was turned off until immediately after extubation. During this period, the patient remained on the operating table without stimulation while breathing spontaneously. The same blinded investigator systematically assessed the presence or absence of cough. Secondary outcomes (incidence of sore throat, hoarseness, PONV) were recorded as present or absent by the same investigator. These secondary outcomes were assessed 15 min, one hour, and 24 hr after extubation at the bedside or, if the patient was sent home, by telephone. The following supplemental variables were recorded in addition to the sociodemographic data: duration of surgery, smoking status, total fentanyl use during surgery and 30 min before extubation, Guedel airway use at induction, cuff volumes (initial, added, final), occurrence of bronchospasm or laryngospasm, occurrence of cuff rupture. All data were collected by the same blinded investigator.

Statistical analysis

We estimated a 70% incidence of coughing at emergence^{23,24} and aimed for a relative risk reduction of 50% (i.e., 35% incidence of coughing). Therefore, 32 patients in each group were required to provide 80% power for a two-sided 0.05 level of significance. For baseline and descriptive continuous variables, means and standard deviation with two-sided 95% confidence intervals (CI) were used. Categorical data were expressed as frequencies and percentages. For the incidence of cough at emergence, we followed a per-protocol analysis. Pearson Chi-square (expected cell frequency > 5) or Fisher's exact test (expected cell frequency ≤ 5) were used for binary outcomes. Normally distributed continuous data were analyzed with Student's t-test. Non-normally distributed continuous data, as determined by the Shapiro-Wilk test, were compared using the Mann-Whitney test. The number needed to treat was calculated to determine the effectiveness of the experimental treatment on the incidence of cough at emergence. All analyses were performed with IBM SPSS statistics 20.0 (Armonk, NY, USA) and graphs generated with GraphPad Prism 6.00 (San Diego, CA, USA).

Results

Effect of alkalinization of lidocaine on its diffusion across the cuff's membrane

The *in vitro* experiments indicated that lidocaine alkalinization facilitated lidocaine diffusion across the ETT cuff membrane when compared with non-alkalinized lidocaine. Diffusion profiles of all tested quantities of lidocaine were increased by > 20-fold when alkalinized. At the experimental endpoint (i.e., after eight hours), our data show that alkalinization allowed diffusion of 25.2, 40.1, and 49.3 mg of total initial intracuff lidocaine content (for initial quantities of 40, 80, and 160 mg, respectively) (Fig. 1).

Demographic and clinical characteristics

Of the 80 patients enrolled (23 patients undergoing urological surgeries, 57 undergoing gynecological surgeries), five were excluded because of protocol violations (three patients in the saline group and two patients in the lidocaine group). Four patients required more than one laryngoscopy (or Eschmann bougie), and one was on chronic oral steroid treatment. The demographic and clinical characteristics were similar in the two groups (Table 1). Guedel airway use (at induction)

Fig. 1 Diffusion profiles of lidocaine across polyvinylchloride cuffs of 7.5-mm endotracheal tubes (ETT) over time as measured using a high-performance liquid chromatography system coupled to a mass spectrometer. Solid lines represent diffusion profiles of the various quantities of intracuff alkalized lidocaine (alk-lid; 40, 80, and 160 mg). Dotted lines represent diffusion profiles of the non-alkalinized lidocaine quantities (lid; 40, 80, and 160 mg). Final diffused quantities of lidocaine across the ETT cuff after 480 min (8 hr) under each condition are displayed on the right side of the curves. Vertical dotted lines represent intermediate diffused quantities for the 160-mg intracuff alkalized lidocaine condition at 120 and 180 min. ETT cuffs were filled with 1, 2, or 4 mL of lidocaine 4%, corresponding to initial quantities of 40, 80, and 160 mg, respectively. A final intracuff volume of 12 mL was achieved by adding either saline 0.9% or 8.4% sodium bicarbonate

was increased only for patients in the lidocaine group (42% vs 11% in the saline group). Importantly, no significant differences between the two groups were found during the anesthetic procedure. Initial volumes needed to inflate ETT cuffs and the proportion of patients who required an additional volume during surgery were similar in the two groups (Table 1). No cuff ruptures or respiratory complications (bronchospasm, laryngospasm) were reported in the study.

Primary and secondary outcomes

The primary outcome of this study was the incidence of cough upon emergence from general anesthesia. Compared to the saline control group, the incidence of cough was less with intracuff alkalized lidocaine (76% [13/38] vs 34% [28/37], respectively; absolute difference 42%; 95% CI 21% to 62%; $P < 0.001$) (Fig. 2). For the intracuff alkalized lidocaine treatment, the number needed to treat to avoid coughing was 2.4. No clinically significant differences between the two groups were observed for sore throat, hoarseness, or PONV at the evaluated time points (15 min, one hour, and 24 hr after emergence) (Table 2).

Table 1 Demographic and clinical characteristics

Characteristic	Saline group $n = 37$	Lidocaine group $n = 38$	P value
Demographic data			
Age (yr)	51.6 (13.5)	50.6 (13.1)	-
Sex ratio (M/F)	10/27	12/26	-
BMI ($\text{kg}\cdot\text{m}^{-2}$)	26.5 (5.3)	28.7 (4.2)	-
Smokers ($n/\text{total } n$)	10/37 (27%)	8/38 (21%)	-
Intraoperative data			
Intubation time (min)	154.4 (40.5)	154.6 (34.4)	0.98
Total fentanyl administered (μg)	242 (67)	273 (67)	0.06
Fentanyl administration last 30 min ($n/\text{total } n$)	13/37 (35%)	14/38 (37%)	0.88
NSAID administration ($n/\text{total } n$)	22/37 (59%)	23/38 (61%)	0.93
Guedel airway use ($n/\text{total } n$)	4/37 (11%)	16/38 (42%)	0.002
Cuff volumes			
Initial volume (mL)	6.6 (1.1)	6.9 (1.3)	0.36
Need for additional volume ($n/\text{total } n$)	3/36 (8%)	4/37 (11%)	1.00
Final volume (mL)	6.1 (1.1)	5.7 (1.7)	0.16

Data are expressed as mean (SD), ratio or $n/\text{total } n$ (%)

Total fentanyl: total fentanyl administered during surgery; Fentanyl administration last 30 min: proportion of patient that received fentanyl 30 min before extubation (mean quantity in saline group: 38 ± 13 mg; mean quantity in lidocaine group: 43 ± 14 mg); non-steroidal anti-inflammatory drug administration: proportion of patient that received NSAID (ketorolac 30 mg *iv* or ketoprofen 100 mg via rectal route); Initial volume: volume needed to prevent air leakage at the beginning of the surgery; Need for additional volume: proportion of patients that needed additional volume in endotracheal tube (ETT cuff during surgery (mean added volume in saline group: 1.7 ± 0.6 mL; mean added volume in lidocaine group: 2.5 ± 2.4 mL); Final volume: volume retrieved from ETT cuff at the end of surgery. Denominators that do not equal sample sizes are due to missing data

BMI = body mass index; ETT = endotracheal tube; NSAID = non-steroidal anti-inflammatory drugs

Discussion

In our *in vitro* study, we confirmed that alkalization increases lidocaine diffusion across the PVC membrane of high-volume, low-pressure ETT cuffs, supporting previous findings by others.^{1,16,25,26} Our results also suggest that the lidocaine diffusion rate through the membrane is associated with the initial amount of lidocaine in the intracuff. However, the most important finding in this clinical trial was that 160 mg of intracuff alkalinized lidocaine led to a significant reduction in the incidence of cough upon emergence from N₂O-free general anesthesia, even though the incidence of other side effects associated with tracheal intubation (postoperative sore throat, hoarseness, PONV) were not

Fig. 2 Incidence of cough upon emergence from N₂O-free general anesthesia in the intracuff saline group and the intracuff alkalinized lidocaine (160 mg) group. Data are expressed as a percentage (%) of the number of patients with cough at emergence in each group. *** $P < 0.001$

altered. This result differs from a previous investigation by our group, where a smaller quantity of intracuff alkalinized lidocaine (40 mg) was tested for surgery of shorter duration (87.0 ± 31.6 min) without producing any clinically significant effect on the incidence of cough when compared with control treatment.²⁶

Earlier studies evaluating the efficacy of intracuff lidocaine regarding similar clinical outcomes (i.e., postoperative sore throat and coughing) used larger quantities of non-alkalinized lidocaine (200–500 mg) in an attempt to increase its diffusion^{9,27}—possibly increasing the risk of toxicity in the event of cuff rupture. We now know that alkalization reduces the required amount of intracuff lidocaine needed while maintaining its effectiveness.^{16,20,25,26} Considering our hypothesis that a greater amount of lidocaine on the tracheal mucosa would lead to further cough suppression, we conducted an *in vitro* study where we assessed the impact of alkalization on lidocaine diffusion rates for various clinically safe lidocaine amounts. Our study demonstrated that intracuff lidocaine alkalization (at all tested quantities: 40, 80, and 160 mg) results in higher lidocaine diffusion across the cuff's membrane compared with equivalent amounts of non-alkalinized lidocaine. Moreover, after alkalization, the lidocaine diffusion rate and total amount that diffused across the PVC membrane were superior at the highest tested quantity (i.e., 160 mg). Considering its diffusion dynamics and clinical safety profile, we used 160 mg of alkalinized lidocaine as the cuff-filling medium in the subsequent clinical trial.

Nitrous oxide usage during anesthetic management of patients is associated with cuff over-inflation, which in turn is associated with damage to the pharyngeal mucosa and

Table 2 Incidence of secondary outcomes

Secondary outcomes	Saline group	Lidocaine group	Difference (%)	95% CI of difference (%)	<i>P</i> value
Sore throat (<i>n</i> /total <i>n</i>)					
15 min	13/34 (38%)	14/36 (39%)	−1	−24 to 22	0.96
1 hr	16/36 (44%)	13/38 (34%)	10	−12 to 32	0.37
24 hr	9/34 (26%)	13/36 (36%)	−9	−31 to 12	0.39
Hoarseness (<i>n</i> /total <i>n</i>)					
15 min	22/30 (73%)	28/35 (80%)	−7	−27 to 14	0.53
1 hr	29/35 (83%)	29/38 (76%)	7	−12 to 25	0.49
24 hr	22/33 (67%)	21/36 (58%)	9	−14 to 31	0.48
PONV (<i>n</i> /total <i>n</i>)					
15 min	12/36 (33%)	9/37 (24%)	9	−12 to 29	0.44
1 hr	10/37 (27%)	11/38 (29%)	−3	−22 to 18	0.85
24 hr	10/34 (29%)	8/36 (22%)	7	−13 to 28	0.49

Data are expressed as *n*/total *n*

CI = confidence interval; PONV = postoperative nausea and vomiting. 15 min, 1 hr, and 24 hr: time after extubation

Denominators that do not equal sample sizes are due to missing data

recurrent laryngeal nerve palsy.^{28,29} Interestingly, some studies using N₂O during general anesthesia have demonstrated small benefits of intracuff alkalinized lidocaine (20–120 mg; 1–6 mL of 2% lidocaine) over intracuff air in decreasing throat pain scores and/or coughing.^{16–18} It is important to point out, however, that the use of intracuff liquids is known to prevent over-inflation by limiting the diffusion of N₂O inside the cuff.^{19,30} In these specific anesthetic conditions, prevention of over-inflation by any cuff-filling liquids (e.g., saline or alkalinized lidocaine *vs* air in the cuff) may therefore be a more likely mechanism to explain the reduced incidence of sore throat, in contrast to the potential local anesthetic effect of lidocaine. Accordingly, in studies using N₂O, the superiority of alkalinized lidocaine over air in the intracuff is questionable when the cuff's pressure is not continuously monitored and adjusted to a safe range (i.e., < 20–30 cm H₂O).

Most clinical trials that compared the effect of alkalinized lidocaine *vs* saline in the intracuff regarding the incidence of cough were performed in patients undergoing general anesthesia with N₂O. In a study by Shroff *et al.*, 40 mg of intracuff alkalinized lidocaine had no impact on cough at emergence compared with intracuff saline.¹⁹ In contrast, using a larger amount of alkalinized lidocaine (200 mg), Huang *et al.* observed a significant decrease in cough compared to saline.²⁰ Even though it was tested in a population of smokers, similar effects of alkalinized lidocaine (138 ± 52 mg) *vs* saline were subsequently found by another group.⁴ Altogether, these observations suggest that 40 mg of intracuff alkalinized lidocaine may not be better than saline, and that a greater quantity is required to decrease cough at emergence from general anesthesia using N₂O.

Findings in the present clinical trial support the efficacy of a higher amount of intracuff alkalinized lidocaine (i.e., 160 mg) for reducing the incidence of cough (*vs* intracuff saline) upon emergence from N₂O-free general anesthesia. Although similar findings were previously demonstrated in studies using N₂O during anesthetic management of the patient,^{4,20} this is the first study reporting such benefits during N₂O-free general anesthesia, thus reflecting current Canadian practices with regard to N₂O usage. Nevertheless, because ETT cuffs were filled with fluid in both of our experimental treatment studies, we cannot rule out the fact that under similar circumstances the use of N₂O could have had limited influence on study outcomes. In contrast, lidocaine alkalinization did not change the sore throat frequency in our study. Perhaps, such lack of benefit could be explained by the ETT cuff position (or depth) in the trachea. In fact, lidocaine diffusion from an ETT cuff inflated farther away from the vocal cord may produce a cough suppressant effect without preventing sore throat,

which is likely due to vocal cord irritation. To our knowledge, only Estebe *et al.* investigated the potential clinical impact of alkalinized lidocaine (i.e., 40 mg) as an ETT cuff-filling medium on cough upon emergence using comparable anesthetic parameters.¹ Similar to our findings, their study detected potential beneficial effects (despite being not statistically significant) of intracuff alkalinized lidocaine on cough upon emergence when compared to the control intracuff air treatment. In their study, however, performed in patients undergoing thyroidectomy surgery, the medical staff was allowed to apply local anesthetics (or other vasoconstrictors) to the larynx without restriction, thus constituting a potential bias.

In our clinical trial, only patients whose surgery was estimated to last 120 min or more were enrolled. Our rationale was that this period would provide sufficient diffusion time to obtain an effective local concentration of anesthetic to block the rapidly adapting stretch receptors, located within the tracheal mucosa, that are responsible for the cough reflex.² Animal studies suggest that a lidocaine concentration of 155 mg·mL⁻¹ is necessary to block these receptors.³¹ We have only an approximation of the amount of lidocaine diffusing over time from our *in vitro* experiment (23.6–33.1 mg) (Fig. 1), so predicting the *in vivo* concentration at the tracheal mucosa remains difficult. It is therefore possible to argue that larger quantities (e.g., 200–300 mg) could have led to better diffusion across the cuff's membrane, thus potentially yielding greater clinical benefit while remaining safe in the unlikely event of cuff rupture.

The fact that we did not include a measure of the intracuff pressure over time in the design of this clinical trial may represent a limitation. The mean initial and final intracuff volumes, however, were not statistically different between the two treatment groups. We therefore assumed that the intracuff pressure was similar for the two treatments. Other potentially confounding factors (including narcotics, non-steroidal anti-inflammatory drugs, time under anesthesia) were similar in the two treatment groups. The only significant difference consisted of increased use of the Guedel airway at induction in the lidocaine group. The possible pharyngeal irritation caused by the increased Guedel airway use in this group could theoretically partially explain the lack of a significant difference in sore throat between the groups, unlike what was previously reported.⁴ Although the surgery in this trial was limited to urological and gynecological procedures, our results could be generalized to other N₂O-free surgery of the same average duration for adult patients of both sexes. Smoking status was recorded in our study, but the limited number of smokers did not allow statistical adjustment to control for the impact of smoking on our results. However, the proportion of tobacco users in

Canada (18.1% in 2014)^A was closely represented in our study population. We therefore believe that our clinical trial reflected the current clinical practice in anesthesiology with regard to patients' smoking status. Additional investigations looking at lidocaine alkalization in a predominantly smoking population, as well as surgery in which coughing can be more detrimental to patient outcome, would therefore be of high clinical interest.

This clinical report demonstrates the beneficial effect of using 160 mg intracuff alkalinized lidocaine as a cuff-filling medium to decrease cough as a primary outcome in N₂O-free anesthetic management of patients undergoing surgical procedures lasting more than 120 min. Additional *in vitro* investigations and clinical trials under these specific anesthetic conditions are needed for better characterization of the minimum diffusion time required to achieve such clinical outcomes. They should focus on the initial intracuff quantity of alkalinized lidocaine and define the optimal concentration of sodium bicarbonate needed to allow safe, efficient diffusion. Studies exploring innovative strategies to achieve similar outcomes for surgery of shorter duration are also needed.

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