Lidocaine lubricants for intubation-related complications: a systematic review and meta-analysis

Les lubrifiants à base de lidocaïne pour la prévention des complications liées à l'intubation : une revue systématique et méta-analyse

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Received: 21 September 2018 / Revised: 2 April 2019 / Accepted: 6 April 2019 / Published online: 11 June 2019
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Abstract

Purpose Postoperative sore throat (POST) is a relatively common morbidity. Topical lidocaine lubricants have been proposed to prevent POST; however, their effectiveness remains uncertain. This meta-analysis aimed to evaluate the prophylactic effect of lidocaine lubrications against POST, cough, and hoarseness in adult patients after surgery.

Methods Randomized-controlled trials from PubMed, Embase, the Cochrane Library, and the ClinicalTrials.gov registry that were published from

inception until 26 March 2018 were included that compared the effectiveness of lidocaine lubricants with that of controls in preventing the incidence of overall POST and moderate to severe POST (POSTMS) at the first and 24th postoperative hour (POST-1h, POST-24h, POSTMS-1h, and POSTMS-24h). Postoperative cough and hoarseness at the 24th postoperative hour were also studied. Bias assessment and subgroup, sensitivity, and trial sequential analyses were also performed.

Results Fourteen randomized-controlled trials ($n = 2146$) were selected. The incidences of POST-1h and POST-24h were 41.1 % and 22.6 % for the lidocaine group, and 41.9% and 23.5% for the control group, respectively. No effect was found on any of the outcome measurements. The overall risk ratios were 1.11 (95% confidence interval [CI], 0.82 to 1.51) and 1.06 (95% CI, 0.37 to 3.02) for the

Electronic supplementary material The online version of this article (doi:<https://doi.org/10.1007/s12630-019-01408-6>) contains supplementary material, which is available to authorized users.

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incidence of POST-1h and POSTMS-1h, respectively; 0.99 (95% CI, 0.83 to 1.17) and 0.49 (95% CI, 0.16 to 1.50) for POST-24h and POSTMS-24h, respectively; and, 1.09 (95% CI, 0.71 to 1.66) and 0.91 (95% CI, 0.66 to 1.24) for postoperative cough (PC)-24h and postoperative hoarseness (PH)-24h, respectively.

Conclusion Lidocaine lubricants applied on the tips of endotracheal tube are not effective against the morbidities of POST, PC, and PH.

Trial registration PROSPERO (CRD42017073259); registered 26 October, 2017.

Résumé

Objectif Les maux de gorge postopératoires sont une morbidité relativement fréquente. Les lubrifiants topiques à base de lidocaïne ont été proposés pour prévenir les maux de gorge postopératoires, mais leur efficacité demeure incertaine. Cette méta-analyse avait pour objectif d'évaluer l'effet prophylactique des lubrifications de lidocaïne contre les maux de gorge postopératoires, la toux et l'enrouement de la voix chez les patients adultes après une chirurgie.

Méthode Nous avons inclus les études randomisées contrôlées publiées sur PubMed, Embase, la Cochrane Library et le registre de ClinicalTrials.gov entre leur création et le 26 mars 2018 qui comparaient l'efficacité des lubrifiants à base de lidocaïne par rapport à l'absence de traitement pour prévenir l'incidence des maux de gorge postopératoires globaux et des maux de gorge postopératoires modérés à graves à la première et à la vingt-quatrième heure postopératoire (POST-1h, POST-24h, POSTMS-1h, et POSTMS-24h). La toux et l'enrouement à 24 heures postopératoires ont également été étudiés. Des analyses d'évaluation du biais et de sous-groupe, de sensibilité et des analyses séquentielles d'essais ont également été réalisées.

Résultats Quatorze études randomisées contrôlées ($n = 2146$) ont été sélectionnées. Les incidences de POST-1h et de POST-24h étaient de 41,1 % et 22,6 % dans le groupe lidocaïne, et de 41,9 % et 23,5 % dans le groupe témoin, respectivement. Aucun effet n'a été observé pour aucun de nos critères d'évaluation. Les rapports de risque globaux étaient de 1,11 (intervalle de confiance [IC] 95 %, 0,82 à 1,51) et de 1,06 (IC 95 %, 0,37 à 3,02) pour l'incidence de POST-1h et de POSTMS-1h, respectivement; de 0,99 (IC 95 %, 0,83 à 1,17) et de 0,49 (IC 95 %, 0,16 à 1,50) pour les POST-24h et POSTMS-24h, respectivement; et de 1,09 (IC 95 %, 0,71 à 1,66) et 0,91 (IC 95 %, 0,66 à 1,24) pour la toux postopératoire (PC)-24h et l'enrouement postopératoire (PH)-24h, respectivement.

Conclusion Les lubrifiants à base de lidocaïne appliqués sur l'extrémité distale du tube endotrachéal ne sont pas

efficaces pour prévenir les morbidités de maux de gorge, de toux et d'enrouement postopératoires.

Enregistrement de l'étude PROSPERO (CRD42017073259); enregistrée le 26 octobre 2017.

Postoperative sore throat (POST) is a relatively common and distressing adverse effect after adult general anesthesia. Although there is no consensus regarding the actual incidence of POST after orotracheal intubation, it may vary between 14.4% and 50%.¹ The wide variation in the incidence of POST can be attributed to various factors including sex, age, surgical site, timing of surgery, choice of anesthetics, endotracheal tube (ETT) size, ETT cuff design, ETT intracuff pressure, intubator experience, as well as the assessment tool and method.²⁻⁶

Previous prophylactic measures for POST focused mainly on limiting physical trauma from instrumentation and manipulation⁷; however, pharmacological interventions involving topical local analgesics (including lidocaine) have been increasingly used over the past decade.⁸⁻¹⁰ Endotracheal lubrication attenuates airway injuries, improves seal, and reduces pulmonary aspiration.^{11,12} By the combined effect of physical lubrication and pharmacological analgesia, lidocaine lubricants were reported to be effective for POST prevention.¹³ Lidocaine has been used extensively during general anesthesia with ETT intubation and is listed as an anesthetic lubricant for endotracheal intubation by the US Food and Drug Administration.¹⁴ Nevertheless, its routine use under general anesthesia using an ETT has been challenged,^{1,15} and previous studies have generated conflicting results for POST prevention.¹⁶⁻¹⁹ Therefore, we conducted the present systematic review and meta-analysis to assess the currently available studies and to generate the best evidence regarding the use of lidocaine lubricants compared with various controls for prevention of POST, postoperative cough (PC), and postoperative hoarseness (PH).

Methods

In accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses,²⁰ we conducted a meta-analysis of randomized-controlled trials (RCTs) to investigate the prophylactic effect of lidocaine on overall POST, PC, and PH. A review protocol was prepared before conducting the study and was registered with PROSPERO under the registration number CRD42017073259. During our review, we made a minor

alteration to the original PROSPERO registration. In addition to overall POST, the effect of lidocaine lubrication on moderate to severe POST was added to the list of primary outcomes. Control groups were also expanded to include no lubrication in order to reflect all available clinical practices. The PROSPERO registration was kept up-to-date during the review process.

Search strategy and study selection

Two independent reviewers (S.Y. and A.L.) performed a comprehensive literature search using the following search engines: PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), Google Scholar, and the ClinicalTrials.gov registry. Free full text and medical subject heading (MeSH) terms and Supplementary Concepts were searched individually using different combinations of MeSH terms with the following keywords: lidocaine, lignocaine, xylocaine, lubricant, lubrication, sore throat, pharyngitis, cough, hoarseness, dysphonia, dysphagia, and laryngospasm (Appendix). In addition, related citations in the PubMed search tool were used to broaden the search before scrutinizing all abstracts, study reports, and related citations retrieved. No language restrictions were imposed. The final search was performed on March 26 2018.

Inclusion and exclusion criteria

Studies were selected when they were: 1) conducted as an RCT, 2) compared topical lidocaine lubricants with a control (i.e., with or without ingredient-free lubricants) in patients who received an ETT under general anesthesia (ETGA), and 3) reported the incidences and/or the severity of POST, PC, and PH, among other outcomes. Selected studies were then excluded if they met one or more of the following criteria: 1) the control group did not receive ETGA, 2) the study was a pediatric study, 3) the study included emergency surgery, and 4) the design of the ETT used in the study was different from that of the modern, disposable, high-volume low-pressure (HVLP) cuffed ETT. The HVLP cuffed ETT was introduced in the 1970s as a standard to reduce complications such as tracheomalacia and tracheal stenosis associated with the use of ETTs.²¹

Data extraction

The demographic characteristics of participants, choice of anesthetics and anesthesia techniques, design of interventions and controls, measured outcomes, and methodological quality of each study were independently extracted by two reviewers (S.Y. and Y.L.). Disagreements were resolved through discussion between the two reviewers. If no agreement could be reached, the findings

obtained by the two reviewers were compared and arbitrated by a third reviewer (C.C.).

Methodological quality appraisal

The methodological quality of included trials was assessed by guidelines provided in the Cochrane Handbook for Systematic Reviews of Interventions. We assessed the risk of bias in random sequence generation, allocation concealment, blinding (of the patients, personnel, and assessors), incomplete outcome data, selective reporting, and other sources of bias. Two authors (Y.L. and F.L.) independently assessed the risk of bias for each RCT, and disagreements were resolved by a third author (T.C.).

Outcomes and statistical analyses

The primary outcomes were the incidences of intubation-related morbidities—i.e., overall POST and moderate to severe POST at one and 24 hr. Moderate to severe POST were not uniformly defined in the primary studies but a four-point scale (0–3) was commonly used and we elected to choose a threshold of at least two as the definition for moderate to severe POST.^{17,22} The main secondary outcomes were PC and PH at 24 hr, though the occurrence of lidocaine drug-related morbidities such as nausea and vomiting, throat dryness, throat numbness, dry mouth, stridor, or laryngospasm were also collected when available.

The effect sizes of dichotomous outcomes were reported as risk ratios (RR). A pooled estimate of the RR was computed by the DerSimonian and Laird random-effects model.²³ Standard errors were estimated with the confidence interval (CI) set at 95%. The results were subsequently presented as a forest plot to indicate the effects of treatment graphically. Statistical significance was set at 0.10 for Cochrane Q tests. Heterogeneity between studies was quantified using *I*² statistics. Sensitivity analysis was performed by excluding trials with a high risk of other biases (Table 2). All data were computed using the Mantel-Hansel method in Review Manager, version 5.3.5 (Cochrane Collaboration, Oxford, England). Funnel plots and Egger tests were performed to assess potential publication bias in the primary outcomes. We further applied trial sequential analysis (TSA) with the alpha-spending function method on the incidence of POST-24h.²⁴ The TSA was conducted with an overall 5% of a type I error and a power of 80%, and the cumulative z-curve was constructed using a random-effects model. We calculated the alpha-spending adjusted required sample size based on the relative risk reduction of each outcome. TSA software, version 0.9 beta (Copenhagen Trial Unit, Copenhagen, Denmark) was employed to conduct the TSA.

Results

Trial selection

The literature search in PubMed, EMBASE, CENTRAL, and Google Scholar initially returned 3,179 articles. Duplicates and irrelevant articles were identified and excluded by examining titles and abstracts. The full texts of 338 articles were then carefully examined, and 317 of

them were excluded (Fig. 1). Of the selected 21 RCTs,^{13,15-19,22,24-37} a total of seven trials were subsequently excluded because of mixed-aged study subjects,^{32,33} the use of non-HVLP ETTs,^{13,15,30} and the reporting of mixed outcomes.^{25,36} Finally, 14 RCTs with a total of 2,146 patients were included in our meta-analysis (Fig. 1).

As shown in Table 1, the selected RCTs were conducted between 1988 and 2017, and the number of included

Fig. 1 Flowchart of trial selection

Table 1 Characteristics of the selected randomized-controlled trials

First author, year	ETT size (M/F)/intubator	Surgery/ASA physical status/age range (yr)	Anesthetic technique	Intervention	Patient number (male %)
Basaranoglu, 2004	Unclear/unclear	ATH/unknown / adult unknown	Unclear	Lubricated on the distal end of ETT L _G : 2% lidocaine gel L _O : 5% lidocaine pomade C _N : no lubrication at all	L _G : 25 (0) L _O : 25 (0) C _N : 25 (0)
Doukumo, 2011	8/7.5 mm/experience anesthetist	All elective/I-II /adult unknown	Induced by thiopental, succinylcholine, pentazocine 0.5 mg·kg ⁻¹ , tramadol 0.5-1 mg·kg ⁻¹ ; maintenance method unspecified	Lubricated from the ETT distal-end to the 15-cm mark L _G : 2.5 mL of 2% lidocaine jelly C _G : 2.5 mL of KY jelly®	L _G : 43 (33) C _G : 43 (37)
Hung, 2010	7.5/7 mm/2nd year resident to anesthesiologist	All elective/I-III /18-84	Induced with fentanyl 2-3 µg·kg ⁻¹ , propofol 2-2.5 mg·kg ⁻¹ , rocuronium 0.6 mg·kg ⁻¹ /maintenance method unspecified	Lubricated on the ETT cuff L _{SL} : 20 mg of 2% lidocaine spray L _{SH} : 100 mg of 10% lidocaine spray C _{NS} : 1 mL of normal saline B _S : 1.5 mg benzydamine hydrochloride spray	L _{SL} : 92 (50) L _{SH} : 93 (52) C _{NS} : 93 (52) B _S : 94 (48)
Klemola, 1988	9 mm/8 mm/unclear	Otolaryngological (excluded mouth, pharynx, larynx)/unclear / adult unknown	Induced by thiopental, d-tubocurarine, succinylcholine/fentanyl 3-4 µg·kg ⁻¹ ·hr ⁻¹ , maintenance method by ND-NMBA, N ₂ O, halothane, nitroprusside (elective hypotension)	Lubricated by pulling the ETT cuff through lubricants on a swab L _G : 2% lidocaine gel L _{Lrx} : 5 doses of 10% spray on larynx, ETT with no lubrication L _G +L _{Lrx} : combination of the above 2 methods	L _G : 31 (55) L _{Lrx} : 27 (41) L _G +L _{Lrx} : 26 (42) C _N : 30 (50)
Kori, 2009	8.5 mm/7.5 mm/unclear	All elective/I-II /adult unknown	Unclear	C _N : no lubrication at all Lubricated on the distal end of ETT L _G : 2% lidocaine jelly L _T : 4% lidocaine spray into the trachea C _N : no lubrication at all	L _G :20 (9) L _T :20 (10) C _N :20 (10)
Lee, 2017	7.5 mm/7 mm	LC/I-II / 18-80	Induced by propofol 2 mg·kg ⁻¹ , sufentanil 0.5 µg·kg ⁻¹ , rocuronium 0.6-0.8 mg·kg ⁻¹ , maintenance method by desflurane, boluses of sufentanil 0.3 µg·kg ⁻¹ , meperidine 1 mg·kg ⁻¹ at skin closure	Lubricated on the distal end of ETT L _G : 2% lidocaine jelly C _{NS} : normal saline	L _G : 104 (33) C _{NS} : 104 (42)

Table 1 continued

First author, year	ETT size (M/F)/intubator	Surgery/ASA physical status/age range (yr)	Anesthetic technique	Intervention	Patient number(male %)
Lin, 1996	8mm/7mm/anesthesiologist	Unclear/unknown / adult unknown	Induced by thiopental 4-5 mg·kg ⁻¹ , atracurium 0.5 mg·kg ⁻¹ or vecuronium 0.1 mg·kg ⁻¹ or pancuronium 0.1 mg·kg ⁻¹ (non-depolarizing group), or succinylcholine 1 mg·kg ⁻¹ (polarizing group); maintained by enflurane 2-3%, O ₂ /N ₂ O mixture at 2 L·min ⁻¹	Lubrication site on ETT unspecified L _G : 2% lidocaine jelly (both non-depolarizing & polarizing) C _{WG} : KY jelly (both non-depolarizing & polarizing) C _N : no lubrication at all (both non-depolarizing & polarizing)	L _G : 101 (50) C _{WG} : 102 (57) C _N : 99 (59)
Mekhemar, 2016	Unclear/unclear	Lumbar fixation surgery/I-II / 35-61	Induced by fentanyl 2-3 µg·kg ⁻¹ , propofol 2-3 mg·kg ⁻¹ , rocuronium 0.6 mg·kg ⁻¹ ; maintained by 1.2 MAC isoflurane with increments of fentanyl and rocuronium	Lubricated on the ETT cuff L _G : 5% lidocaine gel L _{SH} : 10% lidocaine spray B _G : benzidine hydrochloride gel C _{NS} : normal saline	L _G :31 (58) L _S :31 (61) B _G :31 (68) C _{NS} :31 (58)
Muhammad, 2015	7.5mm/7mm/unclear	All elective/I-II / 18-60	Induced by fentanyl 2 µg·kg ⁻¹ , propofol 2 mg·kg ⁻¹ , atracurium 0.5 mg·kg ⁻¹ ; maintained by 50% N ₂ O with isoflurane; tramadol 2 mg·kg ⁻¹ and ketorolac 0.5 mg·kg ⁻¹ during skin closure, followed by tramadol drip 200 mg/24 hr	Lubricated on the ETT cuff L _G : lidocaine gel (unspecified concentration) B _S : benzidine hydrochloride spray C _{NS} : normal saline spray	L _G : 30 B _S : 30 C _{NS} : 30
Selvaraj, 2002	8.5mm/7.5 mm/unclear	Unclear/I-II / adult unknown	Maintenance by fentanyl 2-3 µg·kg ⁻¹ , N ₂ O, halothane and ND-NMBA	Lubricated from the ETT cuff to the 15-cm mark L _G : 2~2.5 mL lignocaine jelly (unspecified concentration) S _G : 2~2.5 mL 0.05% betamethasone dipropionate C _N : No lubrication at all	L _G : 30 S _G : 30 C _N : 30
Soltani, 2002	8-8.5mm/7-7.5 mm/unclear	Cataract/I-II / 63-64	Induced by lidocaine 1.5 mg·kg ⁻¹ , alfentanil 10 µg·kg ⁻¹ , thiopental 5 mg·kg ⁻¹ , gallamine 20 mg, succinylcholine 1.5 mg·kg ⁻¹ ; maintenance by 50% N ₂ O, 1-2 % halothane	Lubricated on the distal end of ETT L _G : 2.5 mL (50 mg) of 2% lidocaine jelly L _{SH} : 3 puffs (30 mg) of 10% lidocaine spray L _{IV} : 1.5 mg·kg ⁻¹ intravenous lidocaine L _{LTX} : 3 puffs (30 mg) of 10% lidocaine spray on laryngopharyngeal structures L _{IC} : 7-8 mL of 2% lidocaine prefilled in cuff C _{NS} : normal saline spray	L _G : 34 L _S : 34 L _{IV} : 34 L _{LTX} : 34 L _{IC} : 34 C _{NS} : 34

Table 1 continued

First author, year	ETT size (M/F)/intubator	Surgery/ASA physical status/age range (yr)	Anesthetic technique	Intervention	Patient number(male %)
Sumathi, 2008	8.0/7.0 mm/trainee (> 2 years)	Unclear/I-II / 18-50	Induced by meperidine 0.75 mg·kg ⁻¹ , thiopental 5 mg·kg ⁻¹ , vecuronium bromide 0.1 mg·kg ⁻¹ ; maintenance by N ₂ O 66%, 0.5-1% halothane, vecuronium bromide	Lubricated from the ETT tip to the 15-cm mark L _G : 2.5 mL 2% lidocaine jelly S _G : 2.5 mL 0.05% betamethasone gel C _N : No lubrication at all	L _G : 50 (56) S _G : 50 (54) C _N : 50 (54)
Teoh, 2014	7.5-8/7-7.5 mm/experienced trainee (>5 years)	All elective/I-II / 18-60	Induced by fentanyl 2 µg·kg ⁻¹ , propofol 2 mg·kg ⁻¹ , and rocuronium 0.6 mg·kg ⁻¹ , sevoflurane in 100% O ₂ at 1-1.2 MAC for 3 min; maintenance by sevoflurane 1-1.2 MAC, morphine 0.1-0.2 mg·kg ⁻¹	Lubricated on the ETT tip and cuff L _G : 3 mL 2% lidocaine gel C _G : 3 mL KY jelly	L _G : 80 (66) C _G : 71 (63)
Thapa, 2017	7.5/7.0 mm/unclear	All elective/I-II / 18-65	Induced by titrated dose of propofol and vecuronium 0.1 mg·kg ⁻¹ , maintenance by titrated isoflurane in 100% O ₂ , vecuronium 1mg intermittently	Lubricated from the ETT tip to the 15-cm mark L _G : 2.5 mL of 2% lidocaine gel S _G : 2.5 mL of 0.05% betamethasone gel C _N : no lubrication at all	L _G : 40 (35) S _G : 40 (38) C _N : 40 (33)

ASA = American Society of Anesthesiologists; B = benzylamine hydrochloride; C = control group; C_N = no lubrication; C_{NS} = normal saline; ETT = endotracheal tube; GYN = gynecologic surgery; L = lidocaine; L_G = lidocaine gel/jelly; L_{IC} = intracuff lidocaine; L_{IV} = intravenous route; L_O = lidocaine ointment/pomade; Lrx = larynx/laryngopharyngeal structures; L_{SL} = lidocaine spray of low concentration; L_{SH} = lidocaine spray of high concentration; L_T: trachea; MAC = minimal alveolar concentration; ND-NMBA = non-depolarizing neuromuscular blocking agent; NMBA = neuromuscular blocking agent; S_G = steroid gel

participants ranged from 60 to 372. The ETT size, intubator experience, surgery type, American Society of Anesthesiologists physical status, anesthetic agents, and interventions varied among the included trials. All the 14 trials investigated the effect of lidocaine-containing lubricants. In addition, three trials compared the effects of steroid-containing lubricants,^{22,34,37} and one trial compared the effects of different concentrations of a lidocaine-containing spray²⁶ with that of a control. All of the included studies were published in English except those reported by Kori *et al.*,²⁸ Lim *et al.*,²⁹ and Muhammad *et al.*³¹

Quality assessment of included trials

The overall risk of bias in all 14 selected studies is depicted in Fig. 2. Most studies had unclear selection bias as no details of their randomization were disclosed in the text. Eight studies were assessed to have a low performance risk as they were double-blinded.^{16,18,19,26,27,34,35,37} Most studies had unclear detection biases and low reporting biases, while half of the studies had low attrition biases. One trial had two loss-to-follow-ups.¹⁶ Other biases identified included unspecified gender, surgery types, smoking history, and intubator experience, and the use of premedication or succinylcholine, among others.^{17-19,27,29} These were further analyzed in the sensitivity analysis.

Defining intervention and control groups

Intervention groups were defined as those in which patients: 1) underwent intubation using an ETT lubricated with lidocaine-containing lubricants, and 2) received no treatment of the larynx or vocal cord before intubation (i.e., lidocaine spray). Among the ten interventions listed in Table 1, four were selected for analyses, these were the water-based lidocaine gel/jelly (L_G), oil-based lidocaine ointment/pomade (L_O), lidocaine spray of low concentration (L_{SL}) and lidocaine spray of high concentration (L_{SH}). Two concentrations of lidocaine sprays (2% and 10%) used in Hung *et al.*²⁶ were combined as a common intervention group in our analyses.

Control groups were defined as those in which patients were intubated using an ETT: 1) with no lubrication (C_N),^{22,24,27,29,34,37} 2) lubricated with ingredient-free jelly (C_G),^{18,19,29} and 3) normal saline as a form of lubrication (C_{NS}).^{16,17,26,31,35} All three categories of control groups did not receive any treatment of the larynx, pharynx, or the trachea.

Lidocaine lubricants on POST incidence and POST severity

Statistical analyses of the primary outcomes were: 1) sore throat at the first postoperative hour (POST-1h),^{16-19,22,24,26,34,35,37} 2) moderate to severe sore throat at first postoperative hour (POSTMS-1h),^{16,17,22,24,34} 3) sore throat at the 24th postoperative hour (POST-24h),^{16-19,22,24,26-29,31,34,35,37} and 4) moderate to severe sore throat at 24th postoperative hour (POSTMS-24h).^{16,17,22,24,31,34} We elected to analyze our primary outcomes according to the three different control groups in order to assess the individual as well as the overall effects. The overall incidences of POST-1h and POST-24h were 41.1% and 22.6% for the lidocaine group, and 41.9% and 23.5% for the control group. (Figs 3 and 4) The overall incidences of POSTMS-1h and POSTMS-24h were 9.8% and 2.8% for the lidocaine group, and 10.4% and 5.8% for the control group (Figs 5 and 6).

The results of our analysis showed no difference between the lidocaine lubricants and their corresponding control group for POST-1h, POSTMS-1h, and POST-24h, POSTMS-24h, with the overall RR being, 1.11 (95% CI, 0.82 to 1.51), 1.06 (95% CI, 0.37 to 3.02), and 0.99 (95% CI, 0.83 to 1.17), 0.49 (95% CI, 0.16 to 1.50), respectively.

Lidocaine lubricants on PC, PH, and other secondary outcomes

Secondary outcomes analyzed included cough at the 24th postoperative hour (PC-24h)^{16,18,19,24,27,34,37} and hoarseness at the 24th postoperative hour (PH-24h)^{16,18,19,24,27,28,34,37}; the overall RR were 1.09 (95% CI, 0.71 to 1.66) and 0.91 (95% CI, 0.66 to 1.24), respectively (Fig. 7).

Other outcomes included nausea and vomiting,^{16,17} throat dryness,¹⁸ throat numbness,¹⁶ dry mouth,¹⁷ stridor, and laryngospasm.³⁵ These outcomes were all comparable between the lidocaine and the control group within each respective study or studies (Table 3).

Heterogeneity and subgroup, sensitivity, and trial sequential analyses

The subgroup analysis of the prophylactic effect of non-gel or jelly-type lidocaine lubricants on POST-24h, including two different medium types (i.e., pomade or spray), showed no overall difference (RR, 0.93; 95% CI, 0.60 to 1.45). For the respective subgroups in which lidocaine was sprayed on the larynx and ETT, the RR were 0.84 (95% CI, 0.33 to 2.13) and 0.95 (95% CI, 0.43 to 2.12), respectively (eFig. 1, available as Electronic Supplementary Material [ESM]). Notably, in an extended analysis, steroid jelly was

Fig. 2 Risk of bias assessment for the primary studies

shown to be highly effective in preventing POST-24h (RR, 0.4; 95% CI, 0.29 to 0.54) (eFig. 2, available as ESM).

High heterogeneity was observed for POST-1h and POSTMS-1h among studies ($I^2 = 77\%$ and 59%), but a moderate heterogeneity was noted for POST-24h and

POSTMS-24h ($I^2 = 33\%$ and 28%). For PC-24h and PH-24h, I^2 values were 8% and 1% , respectively.

Sensitivity analysis (Table 2) was performed to evaluate the effect of potential biases and limitations on the overall result. These were categorized into: 1) patient-related bias,

Fig. 3 Forest plot showing the effect of lidocaine lubrication on the incidence of sore throat at the first postoperative hour (POST-1h)

2) surgery-related bias, 3) anesthetic-related bias, 4) intubation-related bias, and 5) lubricant-related bias. The unspecified history of nitrous oxide use had a positive influence on the effectiveness of lidocaine lubricants against POST-1h. On the contrary, the concentrations of lidocaine did not have an impact on POST-1h or POST-24h. No other potential bias changed the overall results. Funnel plots are presented with their respective Egger tests in eFig. 3, available as ESM. Trial sequential analysis on the incidence of POST-24h indicated that the required information size (RIS) was not reached and the cumulative z-curve did not cross the conventional boundary. This was due to a very low effect with homogeneity among the included trials, resulting in almost unachievable RIS. This may support the rejection of the benefit of lidocaine lubrication for POST 24 hr after surgery, irrespective of the TSA result (Fig. 8).

Discussion

Despite previous evidence suggesting that topical lidocaine lubrication may be effective in preventing POST,³⁸ the present meta-analysis showed that lidocaine lubrication was ineffective in preventing intubation-related POST, PC, or PH; furthermore, it also did not alter the incidence of moderate to severe POST. Our sensitivity analyses revealed an increased incidence of POST at 1 hr after the exclusion of studies with N₂O use.

This meta-analysis is a route-specific research that focused exclusively on the prophylactic effect of lidocaine lubricants applied on the end of an ETT and yielded a different result compared with a previous systematic review on lidocaine prophylaxis for POST.³⁹ The meta-analysis conducted by Tanaka *et al.* investigated the prophylactic effects of topical and systemic lidocaine on POST, and concluded that topical lidocaine is effective in reducing POST. They recently updated their work by including four more trials and obtained the same conclusion.³⁸ Nevertheless, at least two methodological

Fig. 4 Forest plot showing the effect of lidocaine lubrication on the incidence of sore throat at the 24th postoperative hour (POST-24h)

concerns may limit that study's applicability. First, their conclusion was derived from lidocaine administered through multiple routes (i.e., intracuff infusion, direct laryngotracheal spray, and ETT lubricant); therefore, the result is at risk of potential interference from the protective effect of intracuff lidocaine, as was found in a recent study.⁹ Second, only three studies that involved smearing lidocaine lubricants on the end of an ETT were included in their comparison.^{38,39} Our meta-analysis included more studies and may provide a more robust and alternative evidence to guide the current practice of POST prevention with prophylactic topical lidocaine.

Physical contact between an ETT and laryngotracheal structures as the direct cause of POST has been the focus of interest and extensively discussed in previous studies.^{1,7,15,40} Nevertheless, although the duration of ETT cuff-tracheal contact and high pressure imposed on the tracheal mucosa were linked with POST, mucosal

abrasions and trauma from cuff movement over the vocal cord and within the trachea have been rarely discussed. There are two possible mechanisms that link airway trauma and POST. First, vocal cord trauma may occur at the time of intubation or extubation.^{1,26} This trauma can theoretically be minimized by an experienced intubator by performing a smooth intubation; however, multiple intubation attempts were not linked to an increase in the incidence of POST in a previous study.⁴¹ Our sensitivity analysis did not indicate a decreased incidence of POST when studies with an unspecified intubator were excluded.^{17,24,27,31,34,35} Second, the movement of the ETT against the vocal cord and trachea, which can occur during patient positioning,⁴² may cause additional trauma that further contributes to POST. Other causative factors, such as the role of a throat pack in POST, were also studied but were reported to be inconclusive.⁴³

Fig. 5 Forest plot showing the effect of lidocaine lubrication on the incidence of moderate to severe sore throat at the first postoperative hour (POST-1h)

Fig. 6 Forest plot showing the effect of lidocaine lubrication on the incidence of moderate to severe sore throat at the 24th postoperative hour (POST-24h)

Theoretically, POST evaluation at the first postoperative hour can be inaccurate because it may be masked by the residual effect of perioperative analgesia that dissipates with time. This may partly explain the pro-lidocaine result observed at POST-1h that lost its statistical significance at POST-24h in the trial of Sumathi *et al.* for lidocaine jelly.

The trial conducted by Lee *et al.*¹⁶ favoured the control over lidocaine at POST-1h. All the other trials in our study failed to show a statistical difference between lidocaine lubricants and the control at POST-1h (Figs 3 and 4). All trials showed no statistical difference between the smeared

Fig. 7 Forest plot showing the effect of lidocaine lubrication in the incidence of cough and hoarseness at the 24th postoperative hour (PC-24h, PH-24h). PC = postoperative cough; PH = postoperative hoarseness

lidocaine lubricant and control at POST-24h, except for one study.²⁹

Sore throat is believed to stem from possible trauma-related activation of pain receptors in the trachea,⁴⁴ which intuitively lead to the notion of applying local anesthetics to prevent POST. An array of other pharmacological agents has been proposed to reduce the incidence of POST, including the ketamine gargle,⁴⁵ steroids,⁴⁶ tenoxicam throat packs,⁴⁷ benzydamine gel/gargle,⁴⁶ and magnesium sulfate gargle.⁴⁸ Of note is that steroid lubricants have been shown to be effective against POST.⁴⁶ Nonpharmacological preventative measures for POST were discussed by McHardy *et al.*¹ and included the maintenance of an adequate anesthetic depth, careful insertion of the ETT by an experienced provider, and the use of soft suction catheters; postintubation measures included the use of a smaller tube, maintenance of a small cuff-tracheal contact area, and reduction of cuff pressure.

Perioperative intravenous, sprayed, and nebulized forms of lidocaine have long been used to prevent fentanyl-induced and non-operation-related cough through the reduction of the laryngeal reflex response to stimuli.⁴⁹⁻⁵¹ Nevertheless, lidocaine of either the intravenous or

nebulized form did not appear to have the same prophylactic effect on cough. The fact that topical lidocaine was effective when administered as an intracuff infusion but not when smeared on the ETT implies that the preparation and route of delivery of a drug may be crucial.⁹ Although there was one case of laryngospasm in one study,³⁵ we could not ascertain if it was a direct harmful effect of lidocaine lubricants. Nevertheless, we postulate that the lack of efficacy of lidocaine lubricants in preventing POST can be attributed to the interaction between pharmacological pain suppression of lidocaine and the potential harmful effects of lubricant additives.

Commercially available lubricants (lidocaine-free) caused a wide range of mucosal irritations based on their osmolality in a slug model designed to examine mucus membrane tolerance.⁵² Methylparaben, a preservative commonly added in lidocaine jelly, was also shown to cause pain sensation in mouse sensory neurons.⁵³ In a rabbit model, lidocaine injection promoted muscular contraction and rigidity in masticatory muscles through calcium ATPase inhibition,⁵⁴ which may have contributed to the increased POST through pharyngeal myalgia.

Table 2 Sensitivity analyses: the effect of potential biases on primary and secondary outcomes

Potential bias or limitations excluded	POST within 1 hr RR (95% CI), I^2	POST within 24 hr RR (95% CI), I^2	POSTMT within 1 hr RR (95% CI), I^2	POSTMT within 24 hr RR (95% CI), I^2	Cough within 24 hr RR (95% CI), I^2	Hoarseness within 24 hr RR (95% CI), I^2
Overall	1.11 (0.82 to 1.51), 77%	0.99 (0.83 to 1.17), 33%	1.06 (0.37 to 3.02), 59%	0.49 (0.16 to 1.50), 28%	1.09 (0.71 to 1.66), 23%	0.91 (0.66 to 1.24), 1%
Patient-related						
Unspecified gender ^{28,31,34,35}	1.21 (0.79 to 1.85), 81%	1.00 (0.82 to 1.22), 40%	1.04 (0.21 to 5.21), 69%	0.36 (0.08 to 1.53), 41%	1.04 (0.64 to 1.71), 23%	0.86 (0.60 to 1.24), 9%
Unspecified smoking history ^{16,17,22,24,26-29,31,34,37}	1.30 (0.94 to 1.79), 0%	1.55 (0.63 to 3.78), 0%	N/E	N/E	0.44 (0.15 to 1.33), 0%	1.53 (0.30 to 7.72), 0%
Surgery-related						
Unspecified surgery type ^{18,19,22,26,28,29,31,34,37}	0.87 (0.68 to 1.10), 0%	0.97 (0.61 to 1.54), 0%	0.72 (0.11 to 4.92), 78%	0.36 (0.06 to 2.38), 58%	0.94 (0.50 to 1.80), 0%	0.99 (0.37 to 2.69), 56%
Anesthetics-related						
Premedication ^{18,27,29,35}	1.20 (0.90 to 1.59), 53%	1.12 (0.85 to 1.46), 0%	1.06 (0.37 to 3.02), 59%	0.49 (0.16 to 1.50), 28%	0.84 (0.34 to 2.11), 41%	0.61 (0.33 to 1.14), 0%
Succinylcholine ^{19,27,29,35}	1.16 (0.78 to 1.73), 81%	1.00 (0.96 to 1.04), 0%	1.06 (0.37 to 3.02), 59%	0.49 (0.16 to 1.50), 28%	1.28 (0.84 to 1.97), 0%	0.83 (0.59 to 1.18), 3%
N ₂ O ^{27,29,31,34,35,37}	1.42 (1.16 to 1.75), 0%	1.08 (0.91 to 1.31), 0%	1.04 (0.21 to 5.21), 69%	0.36 (0.08 to 1.53), 41%	0.85 (0.36 to 2.02), 42%	0.68 (0.36 to 1.29), 0%
Intubation-related						
Unspecified ETT intubator ^{17,24,27,28,31,34,35}	1.24 (0.74 to 2.07), 87%	0.94 (0.63 to 1.41), 66%	1.73 (0.73 to 4.13), 0%	0.35 (0.05 to 2.27), 0%	1.10 (0.38 to 3.23), 59%	0.82 (0.56 to 1.18), 0%
Lidocaine lubricant-related						
High concentration (> 2%) ^{17,24,26,35}	1.18 (0.73 to 1.89), 86%	0.94 (0.70 to 1.26), 69%	1.26 (0.66 to 2.41), 0%	0.59 (0.16 to 2.22), 0%	1.12 (0.60 to 2.11), 22%	0.96 (0.68 to 1.35), 4%
Low concentration (< 2%) ^{16,18,19,22,24,27-29,31,34,37}	1.15 (0.69 to 1.90), 0%	1.08 (0.71 to 1.69), 0%	N/E	N/E	N/E	N/E
Lidocaine type (solution) ^{17,26-28,35}	1.19 (0.77 to 1.85), 84%	0.87 (0.54 to 1.39), 79%	1.39 (0.77 to 2.51), 0%	0.77 (0.30 to 1.95), 0%	1.09 (0.71 to 1.66), 8%	0.89 (0.66 to 1.21), 0%

CI = confidence interval; ETT = endotracheal tube; N₂O = nitrous oxide; N/E = not estimable; NG = nasogastric; POST = postoperative sore throat; RCT = randomized-controlled trial; RR = relative risk; TIVA = total intravenous anesthesia

Table 3 Other secondary outcomes

First author, year	Intervention / control	Outcomes = number (%)						
		Nausea	Vomiting	Throat numbness	Dry mouth	Stridor	Laryngospasm	Throat dryness
Lee, 2017 ¹⁶	Lidocaine(G)	25/104 (24%)	7/104 (7%)	15/104 (14%)				
	Normal saline	30/104 (29%)	8/104 (8%)	11/104 (11%)				
Mekhemar, 2016 ¹⁷	Lidocaine(G+S)	19/62 (31%)			44/62 (71%)			
	Normal saline	10/31 (33%)			23/31 (73%)			
Soltani, 2002 ³⁵	Lidocaine(G+S)					5/68 (8%)	1/68 (1%)	
	Normal saline					1-2/34 (4%)	0/34 (0%)	
Teoh, 2014 ¹⁸	Lidocaine(G)							0
	KY jelly							0

(G) Lidocaine gel and (S) lidocaine spray forms

Fig. 8 Trial sequential analysis of incidence of POST-24h under lidocaine lubricants in 11 trials. We calculated an alpha-spending adjusted required information size of 7,851,975 patients using $\alpha = 0.05$ (two-sided), $\beta = 0.20$ (power = 80%), diversity (D^2) = 99%, an anticipated relative risk reduction of 4.04% and an event proportion of 23.52% in the control arm. The cumulative z-curve (blue) was

constructed using a random-effects model. The required information size was not reached and the z-curve not crossed the conventional boundary. Trial sequential analysis with adjusted alpha-spending adjusted confidence interval cannot be calculated, due to too little information (0.02%)

The safety profile of topical lidocaine has been evaluated mainly based on its dose-dependent systemic toxicity.⁵⁵ Nevertheless, lidocaine-induced tissue toxicity could not be ruled out entirely. *In vitro* studies have shown that a high lidocaine concentration ($\geq 5\%$) caused cytotoxicity in human oral mucosal fibroblasts by inducing apoptosis.^{56,57} Clinically, lidocaine spray at a concentration of 8–10% has been suggested to increase the incidence of POST through direct airway mucosal irritations caused by its high osmolality and additives.^{17,26,58} Although the relatively low concentration of topical lidocaine lubricants is generally considered safe,⁵⁹ no studies thus far have tested them on the human laryngeal and tracheal mucosa. The cytotoxic properties of both lubricant additives and lidocaine, superimposed on physical trauma caused by intubations, can potentially lead to increased POST, hoarseness, and other common emergence phenomena through local tissue inflammation of the larynx. No reports of lidocaine toxicity were observed in our primary studies because the doses of lidocaine used in the studies were all less than 100 mg. Different lidocaine concentrations did not appear to affect

the incidence of POST in our analyses (Table 2), but this result needs to be interpreted with caution because of potential biases and the low number of total study subjects.

The effect of lidocaine gel on the incidence of PH remains controversial. Although a direct association was not established,⁶⁰ our results showed no prophylactic effect of topical lidocaine on PH. This is not surprising as PH is associated with ETT design, intubation–procedural-related trauma, movement of the tube during surgery, among others.⁶¹ The effect of lidocaine on PC is also controversial. Although intravenous and intracuff lidocaine have been reported to be effective in preventing PC,^{9,44,60} our result on topical lidocaine did not yield the same result. This may be due to lidocaine's protective effect being offset by the possible harmful effects of additives or preservatives present in the lidocaine gel.

The increase in the incidence of POST caused by N_2O is postulated to be due to an increase in ETT cuff pressure.⁶² Nevertheless, an increased risk of POST at 1 hr was observed after the exclusion of N_2O use in our study (Table 2), suggesting that N_2O use might be protective against POST, possibly through its effect on N-methyl-D-

aspartate-type glutamate receptors or the endogenous opioid and γ -aminobutyric acid type A receptor.⁶³

Compared with a previous study,³⁸ the strength of our study is that we have performed more route-specific (endotracheal) analysis of the effect of lidocaine lubrication on POST. Our results do not support the use of endotracheal lidocaine lubrication for POST prevention.

Nevertheless, our study also has some limitations that merit discussion. First, despite conducting a comprehensive search of available databases and imposing no language restriction, some of the included 14 studies still had a relatively small sample size. Second, the lack of a uniform anesthetic regimen, outcome evaluation, and reporting contributed to the overall heterogeneity of our meta-analysis. We attempted to circumvent these limitations by performing sensitivity analyses to determine the possible source of heterogeneity. And to test the robustness of our findings against type I and type II errors, we TSA with the alpha-spending function method on the incidence of POST-24h. Third, methodological flaws in selection, performance, and attrition biases could have potential impact on the results. Fourth, the inability to access raw data for the incidences of POST in one study²⁸ may have contributed to potential bias. Last, we cannot exclude the possibility of potential publication bias with the overestimation of topical lidocaine efficacy (Fig. 6).

In conclusion, the results of our meta-analysis showed that lidocaine lubricants in jelly, ointment, or spray-form, if

not more harmful, did not demonstrate statistically significant effectiveness in preventing POST, PC, and PH. Because of the potential cytotoxic and irritating effects of lidocaine jelly on the human laryngeal mucosa, we do not recommend routine use of lidocaine lubricants for orotracheal intubation. And future trials on this subject need careful consideration as the enormous RIS based on our TSA calculation may be costly to achieve.

Conflicts of interest None declared.

Editorial responsibility This submission was handled by Dr. Hilary P. Grocott, Editor-in-Chief, *Canadian Journal Anesthesia*.

Author contributions Alan Hsi-Wen Liao and Shang-Ru Yeoh contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article. Chien-Yu Chen and Ta-Liang Chen contributed to the conception and design of the study. Yu-Cih Lin contributed to the acquisition of data. Yu-Cih Lin and Fai Lam contributed to the analysis of data. Fai Lam contributed to the interpretation of data.

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Appendix: Embase search strategy

Embase Session Results (20180326)

#3	'sore throat' OR 'pharyngitis' OR 'hoarseness' OR 'cough' OR 'dysphonia' OR 'dysphagia' OR 'emergence' OR 'laryngospasm' AND ('lidocaine' OR 'lidoderm' OR 'xylocaine' OR 'zingo' OR 'betacaine' OR 'maxilene' OR 'dimecaina' OR 'dynexan' OR 'esracain' OR 'leostesin' OR 'lignocaine' OR 'power gel' OR 'prolong 1000' OR 'solarcaine' OR 'stud 100' OR 'versatis' OR 'xylocain' OR 'xylocaina' OR 'lubricant' OR 'lubrication')	1750
#2	'lidocaine' OR 'lidoderm' OR 'xylocaine' OR 'zingo' OR 'betacaine' OR 'maxilene' OR 'dimecaina' OR 'dynexan' OR 'esracain' OR 'leostesin' OR 'lignocaine' OR 'power gel' OR 'prolong 1000' OR 'solarcaine' OR 'stud 100' OR 'versatis' OR 'xylocain' OR 'xylocaina' OR 'lubricant' OR 'lubrication'	83871
#1	'sore throat' OR 'pharyngitis' OR 'hoarseness' OR 'cough' OR 'dysphonia' OR 'dysphagia' OR 'emergence' OR 'laryngospasm'	271782

Embase Session Results (20170705)

#3	'sore throat' OR 'pharyngitis' OR 'hoarseness' OR 'cough' OR 'dysphonia' OR 'dysphagia' OR 'emergence' OR 'laryngospasm' AND ('lidocaine' OR 'lidoderm' OR 'xylocaine' OR 'zingo' OR 'betacaine' OR 'maxilene' OR 'dimecaina' OR 'dynexan' OR 'esracain' OR 'leostesin' OR 'lignocaine' OR 'power gel' OR 'prolong 1000' OR 'solarcaine' OR 'stud 100' OR 'versatis' OR 'xylocain' OR 'xylocaina' OR 'lubricant' OR 'lubrication')	1658
#2	'lidocaine' OR 'lidoderm' OR 'xylocaine' OR 'zingo' OR 'betacaine' OR 'maxilene' OR 'dimecaina' OR 'dynexan' OR 'esracain' OR 'leostesin' OR 'lignocaine' OR 'power gel' OR 'prolong 1000' OR 'solarcaine' OR 'stud 100' OR 'versatis' OR 'xylocain' OR 'xylocaina' OR 'lubricant' OR 'lubrication'	74368

continued

#1	'sore throat' OR 'pharyngitis' OR 'hoarseness' OR 'cough' OR 'dysphonia' OR 'dysphagia' OR 'emergence' OR 'laryngospasm'	217054
Embase Session Results (20170704)		
#3	'sore throat' OR 'pharyngitis' OR 'hoarseness' OR 'cough' OR 'dysphonia' OR 'dysphagia' OR 'emergence' OR 'laryngospasm' AND ('lidocaine' OR 'lidoderm' OR 'xylocaine' OR 'zingo' OR 'betacaine' OR 'maxilene' OR 'dimecaina' OR 'dynexan' OR 'esracain' OR 'leostesin' OR 'lignocaine' OR 'power gel' OR 'prolong 1000' OR 'solarcaine' OR 'stud 100' OR 'versatis' OR 'xylocain' OR 'xylocaina' OR 'lubricant' OR 'lubrication')	1656
#2	'lidocaine' OR 'lidoderm' OR 'xylocaine' OR 'zingo' OR 'betacaine' OR 'maxilene' OR 'dimecaina' OR 'dynexan' OR 'esracain' OR 'leostesin' OR 'lignocaine' OR 'power gel' OR 'prolong 1000' OR 'solarcaine' OR 'stud 100' OR 'versatis' OR 'xylocain' OR 'xylocaina' OR 'lubricant' OR 'lubrication'	74368
#1	'sore throat' OR 'pharyngitis' OR 'hoarseness' OR 'cough' OR 'dysphonia' OR 'dysphagia' OR 'emergence' OR 'laryngospasm'	217054
Embase Session Results (20151001)		
#42	#40 AND #41	1420
#41	'lidocaine' OR 'lidoderm' OR 'xylocaine' OR 'zingo' OR 'betacaine' OR 'maxilene' OR 'dimecaina' OR 'dynexan' OR 'esracain' OR 'leostesin' OR 'lignocaine' OR 'power gel' OR 'prolong 1000' OR 'solarcaine' OR 'stud 100' OR 'versatis' OR 'xylocain' OR 'xylocaina' OR 'lubricant' OR 'lubrication'	74368
#40	'sore throat' OR 'pharyngitis' OR 'hoarseness' OR 'cough' OR 'dysphonia' OR 'dysphagia' OR 'emergence' OR 'laryngospasm'	217054
Embase Session Results (10 Sep 2015)		
No	Query	Results
#6	#2 AND #3 AND [randomized controlled trial]/lim	223
#5	#2 AND #3 AND [meta analysis]/lim	16
#4	#2 AND #3	1414
#3	'sore throat' OR 'pharyngitis' OR 'hoarseness' OR 'cough' OR 'dysphonia' OR 'dysphagia' OR 'emergence' OR 'laryngospasm'	217054
#2	'lidocaine' OR 'lidoderm' OR 'xylocaine' OR 'zingo' OR 'betacaine' OR 'maxilene' OR 'dimecaina' OR 'dynexan' OR 'esracain' OR 'leostesin' OR 'lignocaine' OR 'power gel' OR 'prolong 1000' OR 'solarcaine' OR 'stud 100' OR 'versatis' OR 'xylocain' OR 'xylocaina' OR 'lubricant' OR 'lubrication'	74233
Embase Session Results (8 Sep 2015)		
No	Query	Results
#9	#7 AND #8 AND [randomized controlled trial]/lim	181
#8	sore throat' OR 'pharyngeal' OR 'pharyngitis' OR 'cough' OR 'hoarseness' OR 'dysphagia' OR 'dysphonia'	154750
#7	'lidocaine gel' OR 'lidocaine lubricants' OR 'lidocaine lubricant' OR 'lidocaine jelly' OR 'lidocaine hydrochloride' OR 'lidocaine'	66160
#6	#4 AND #5 AND [meta analysis]/lim	13
#5	'sore throat' OR 'pharyngeal' OR 'pharyngitis' OR 'cough' OR 'hoarseness' OR 'dysphagia' OR 'dysphonia'	154750
#4	'lidocaine gel' OR 'lidocaine lubricants' OR 'lidocaine lubricant' OR 'lidocaine jelly' OR 'lidocaine hydrochloride' OR 'lidocaine'	66160

continued

#3	#1 AND #2	1178
#2	'sore throat' OR 'pharyngeal' OR 'pharyngitis' OR 'cough' OR 'hoarseness' OR 'dysphagia' OR 'dysphonia'	154750
#1	'lidocaine gel' OR 'lidocaine lubricants' OR 'lidocaine lubricant' OR 'lidocaine jelly' OR 'lidocaine hydrochloride' OR 'lidocaine'	66160

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