**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 67927

**Manuscript Type:** META-ANALYSIS

**Intracuff alkalinized lidocaine to prevent postoperative airway complications: A meta-analysis**

Chen ZX *et al*. A meta-analysis for lidocaine

Zhen-Xing Chen, Zhou Shi, Bin Wang, Ye Zhang

**Zhen-Xing Chen, Zhou Shi, Bin Wang,** Department of Anesthesiology and Perioperative Medicine, The Second Affiliated Hospital of Anhui Medical University, Hefei 230601, Anhui Province, China

**Ye Zhang,** Department of Anesthesiology, The Second Affiliated Hospital of Anhui Medical University, Hefei 230601, Anhui Province, China

**Author contributions:** Chen ZX, Wang B and Zhang Y participated in the design; Chen ZX and Shi Z extracted the data; Chen ZX, Wang B and Shi Z performed the quality assessment; Chen ZX performed the statistical analysis; Zhang Y wrote the manuscript.

**Corresponding author: Ye Zhang, PhD, Doctor, Full Professor,** Department of Anesthesiology, The Second Affiliated Hospital of Anhui Medical University, No. 678 Furong Road, Hefei 230601, Anhui Province, China. zhangye\_hassan@sina.com

**Received:** May 8, 2021

**Revised:** June 6, 2021

**Accepted:** August 17, 2021

**Published online:**

**Abstract**

BACKGROUND

Post-extubation cough is a common phenomenon in surgical patients undergoing general anesthesia, which can lead to potentially dangerous complications. In this meta-analysis, we evaluated the efficacy and safety of intracuff alkalinized lidocaine in patients with tracheal intubation to prevent cough and other airway complications during the perioperative period.

AIM

To perform a systematic review and meta-analysis of intracuff alkalinized lidocaine for the prevention of postoperative airway complications.

METHODS

Pubmed, Embase, Cochrane, and Web of Science were searched for randomized controlled trials (RCTs) that compared intracuff alkalinized lidocaine to placebo. We used risk-of-bias assessment to assess the RCTs, and the quality of evidence was assessed using the grading of recommendations, assessment, development, and evaluations.

RESULTS

Twelve randomized trials (1175 patients) were analyzed. Meta-analysis showed that intracuff alkalinized lidocaine was associated with less cough compared to that produced by placebo [risk ratio (RR): 0.38; 95% confidence interval (CI): 0.23-0.63]. Similarly, intracuff alkalinized lidocaine was more effective than the control in reducing postoperative sore throat at 24 h (RR: 0.19; 95%CI: 0.09-0.41) and postoperative hoarseness (RR: 0.38; 95%CI: 0.21-0.69).

CONCLUSION

Intracuff alkalinized lidocaine is an effective adjuvant that can decrease airway complications, such as coughing, hoarseness, and sore throat.

**Key Words:** Cough; Hoarseness; Lidocaine; Sore throat; Airway complication; Intracuff; Meta-analysis

Chen ZX, Shi Z, Wang B, Zhang Y. Intracuff alkalinized lidocaine to prevent postoperative airway complications: A meta-analysis. *World J Clin Cases* 2021; In press

**Core Tip:** Our study is different to previous systematic reviews and meta-analysis. We focused on adult patients and included relevant literature on alkalinized lidocaine in the analysis. In addition, this is the first systematic review and meta-analysis to analyze lubrication of the cuff before intubation in order to eliminate the influence of confounding factors on the results.

**INTRODUCTION**

Tracheal intubation is the most commonly used airway management method in general anesthesia. Due to its high safety, simple operation, and convenient management, it has become the most important airway management method in most operations[1]. However, this approach has been associated with some problems, such as postoperative airway complications[2], which are common phenomena and adverse reactions in patients who underwent elective general anesthesia. Under normal physiological conditions, cough serves as a protective mechanism, which can clear sputum and foreign matter from the airway and prevent aspiration that may cause pneumonia[3]. However, after the operation, during recovery from general anesthesia, coughing may cause potentially dangerous complications[4]. Coughing may lead to increased intracranial pressure[5,6], which may cause re-bleeding after the evacuation of intracranial hematoma and even lead to brain hernia. High blood pressure induced by cough can also result in the risk of cerebral hemorrhage and bleeding from surgical wounds. Furthermore, cough itself may also cause severe complications such as tracheospasm and bronchospasm[7]. Also, sore throat[8] and hoarseness[9] are common adverse events after general anesthesia. Although pharyngeal pain and hoarseness are mostly mild and self-limited, they may result in strong adverse emotional experiences in patients, reduce patients' satisfaction with the surgical process, and ultimately result in a poor medical experience. To reduce the occurrence of postoperative airway-related complications, many interventions have been proposed, such as intravenous injection of fentanyl, remifentanil, dextromethopyrimidine[10], and other drugs[11], extubation under deep anesthesia[12], local application of local anesthetics[13,14], filling of lidocaine in the tracheal catheter cuff[15-17], intratracheal administration of lidocaine[18], intravenous injection of lidocaine[19-21] and so on. Among these, intracuff lidocaine can be used as local anesthesia, to reduce complications during extubation, and to avoid the side effects of lidocaine on the circulation and central nervous system during general application. Nevertheless, lidocaine is not easy to diffuse in the cuff, and adding sodium bicarbonate can greatly enhance the diffusion ability of lidocaine, so as to achieve better action on the tracheal mucosa[22]. Therefore, it is necessary to perform a systematic review and meta-analysis to summarize the efficacy of intracuff alkalinized lidocaine in the prevention of postoperative airway-related complications.

**MATERIALS AND METHODS**

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for the reporting of meta-analyses of randomized controlled trials (RCTs)[23]. The protocol was registered in the International Prospective Register of Systematic Reviews (trial registration number: CRD42020178143).

***Search strategy***

A comprehensive literature search of Pubmed (until May 2020), Embase (until May 2020), Cochrane (until May 2020), and Web of Science (until May 2020) was performed. We used a combination of free text and database-specific subjects (*i.e.*, MESH or EMTREE headings) to describe ‘lidocaine'. The search strategy is shown in Supplementary material: Appendix A. No language restrictions were placed on inclusion. Non-English studies were translated using online translation. Finally, the references of all articles retrieved from the search were manually scrutinized for any relevant trials not identified using the strategy described above.

***Inclusion and exclusion criteria***

Studies were selected if they were: (1) Conducted as an RCT; (2) Compared intracuff alkalinized lidocaine fills with a control (*i.e.*, with air or saline fills) in patients ≥ 18 years old who received tracheal intubation under general anesthesia; and (3) Reported the incidence of cough, hoarseness, sore throat and/or visual analogue scale (VAS) of sore throat, among other outcomes. Selected studies were then excluded if they met one or more of the following criteria: (1) The trial included emergency surgery; (2) It was a small-scale preliminary pilot study; (3) The necessary data could not be extracted or calculated from the published results; (4) Other lidocaine administration methods were included in the experimental group; and (5) There were other intervention measures in the experimental group.

***Outcomes***

The primary outcome was the incidence of post-extubation cough. Secondary outcomes included the following: Incidence of postoperative hoarseness, the incidence of a postoperative sore throat within 24 h, VAS of a postoperative sore throat at 1 h and 24 h.

***Screening and data extraction***

Two independent reviewers (Chen ZX and Shi Z) screened the retrieved titles and abstracts for potential inclusion, reviewed the full text of potential studies, and extracted the data from studies that met the inclusion criteria. Any discrepancies between the reviewers were resolved through a consensus process. When the two reviewers failed to reach an agreement, the final decision was made by the third reviewer (Wang B). Data extraction was completed by two coauthors (Chen ZX and Shi Z) using a predesigned piloted data extraction form. The data extraction form collected information regarding the year of publication; primary author; country of origin; types of surgery; participant characteristics (gender, age, number, inclusion and exclusion criteria); intervention; lidocaine and placebo group events; severity of postoperative sore throat. Dichotomous data were converted to incidences for data synthesis, and continuous data were recorded using mean ± SD. Any disagreement was resolved through the consensus process discussed previously.

***Assessment risk of bias***

The risk of bias was assessed in duplicate using the method outlined in the Cochrane Risk of Bias Tool for Non-Randomized Studies. The risk of bias was assessed as low, moderate, high, for each selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Any disagreement was resolved by consensus.

***Statistical analysis***

The meta-analysis was performed using RevMan 5.3 software (Cochrane Collaboration, Oxford, England). The level of evidence quality of each study was estimated according to the guidelines of the grading of recommendations, assessment, development, and evaluation (GRADE). We examined the following five categories: Risk of bias, consistency, directness, imprecision, and reporting bias. RCTs began as high-quality evidence and were rated down based on the described criteria. The evidence grades were classified as high quality (further research is unlikely to change the confidence in the estimate of effect), moderate quality (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low quality (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low quality (we are very uncertain about the estimate).

If necessary, standard deviations from the confidence interval (CI) limits, the standard error, or the range values provided in the past studies were estimated. The effect sizes of dichotomous outcomes were reported as risk ratios (RR), and the mean difference (MD) was reported for continuous outcomes.

Heterogeneity was assessed using the Cochrane *Q* test and *I*2 statistic. *I*2 < 50% was considered low heterogeneity, *I*2 = 50% to 75% as moderate, and *I*2 = 75% to 100% as high. *P* values < 0.05 were considered statistically significant. A fixed-effect model was used if heterogeneity was considered low. If *I*2 statistic ≥ 50% and *P* < 0.05, a random-effects model was applied to the data. The statistical methods of this study were reviewed by Peng Z fromthe Department of Maternal, Child, and Adolescent Health, School of Public Health, Anhui Medical University, Hefei, China.

A sensitivity analysis was performed to assess the potential influence in our analysis. We attempted to exclude RCTs with: (1) A high risk of bias; (2) Only female subjects; and (3) Cuff prefilling.

**RESULTS**

***Study selection***

A total of 580 articles were identified from the primary electronic databases (PubMed: 188, Embase: 194, Cochrane: 109, Web of Science: 89. After removing duplicates, we screened 416 studies based on the abstracts, among which 62 full-text articles were assessed for eligibility. Finally, 12 studies were included in the analysis (Figure 1).

***Study characteristics/participants***

The 12 included studies involved a total of 1175 participants with an average age ranging from 36.71 years to 52.00 years, and gender ratios ranging from 0-1.96. All studies were RCTs with placebo or no treatment control arms. Seven trials included patients with an ASA status of I and II[24-30]. Five trials included patients with an ASA status of I, II, and III[31-35]. The included surgeries were: One gynecological surgery[30]; two lumbar surgeries[33,34]; one orthopedic, spine and general surgery[25]; one gynecological, orthopedic, or plastic surgery[26]; one gynecological or plastic surgery[28]; one thyroidectomy surgery[29]. Four studies did not report the type of surgery[24,27,32,35]. Opioids were used in all studies except one which did not report on the use of anesthetics[24]. Saline and air were used in the control group in three and seven experiments[24,25,28,29,33-35], respectively. Two experiments used both saline and air[27,31]. One of the experiments using air in the control group also used 1.4%NaHCO3 as an intervention[29]. In addition, 5 studies lubricated the cuff of the tracheal tube with sterile water or water-soluble gel or normal saline spray before intubation[26,29,30,33,34], and 2 studies performed prefilled at least 90 min before tracheal intubation[32,35] (Table 1).

***Risk-of-bias and GRADE assessment***

Six trials were judged to be a low risk of bias in all domains. Six trials had an unclear risk of bias, mostly related to random sequence generation and allocation concealment. Two trials had a high risk of bias. The domain that was judged to have a high risk of bias was performance bias and detection bias (Figure 2). The GRADE assessment demonstrated an overall high quality of evidence for the incidence of post-extubation cough and hoarseness. The quality of evidence for the following outcomes was considered moderate: incidence of a postoperative sore throat at 24 h, VAS of a postoperative sore throat at 1 h and 24 h (Supplementary material: Appendix B).

***Incidence of post-extubation cough***

The aggregate effect of the 7 studies (*n* = 629) evaluating the effect of intracuff alkalinized lidocaine on the incidence of post-extubation cough was in favor of lidocaine over the control (RR: 0.38; 95%CI: 0.23-0.63). Subgroup analysis revealed that the use of intracuff alkalinized lidocaine could also result in a large reduction in post-extubation cough regardless of the lubricated cuff. Concerning subgroup analysis, a significant effect in the reduction of the post-extubation cough was found in the lubricated group (RR: 0.30; 95%CI: 0.13, 0.68) compared with the non-lubricated group (RR: 0.53; 95%CI: 0.37-0.75). However, there was no subgroup difference in relation to lubrication of the cuff (*P* = 0.21) (Figure 3).

***Incidence of postoperative hoarseness***

Based on the data pooled from 5 trials (*n* = 370), the use of intracuff alkalinized lidocaine demonstrated a large reduction in postoperative hoarseness (RR: 0.38; 95%CI: 0.21-0.69) (Figure 4).

***Incidence of a postoperative sore throat within 24 h***

The data from four trials (*n* = 290) indicated that intracuff alkalinized lidocaine reduced the incidence of a postoperative sore throat within 24 h (RR: 0.19; 95%CI: 0.09-0.41) (Figure 5).

***VAS of a postoperative sore throat at 1 h and 24 h***

Five trials that included 476 participants demonstrated a large reduction in the VAS of a postoperative sore throat at 1 h with the use of intracuff alkalinized lidocaine (MD: -18.30; 95%CI: -22.79, -13.82) (Figure 6). Similarly, in the 5 studies (*n* = 476) that evaluated intracuff alkalinized lidocaine on the VAS of a postoperative sore throat at 24 h, a significant benefit of alkalinized lidocaine compared with the control was identified (MD: -14.86; 95%CI: -15.75, -13.98) (Figure 7).

***Assessment of publication bias***

The funnel plot for the included studies showed an asymmetrical characteristic, which suggested a possible publication bias (Figure 8).

**DISCUSSION**

In this study, 12 RCTs on the prevention of postoperative airway complications with intracuff alkalinized lidocaine were included. This meta-analysis showed that intracuff alkalinized lidocaine could significantly reduce the incidence of post-extubation cough with high quality of evidence, compared with the control group, and many surgical patients may benefit from the application of intracuff alkalinized lidocaine in clinical practice. At the same time, subgroup analysis showed that saline lubrication before intubation reduced the incidence of post-extubation cough; nonetheless, the observed differences were not statistically significant. Therefore, the evidence in this study strongly suggests that intracuff alkalinized lidocaine can prevent post-extubation cough, and further study is unlikely to change this conclusion. Regarding the VAS of a postoperative sore throat at 1 h and 24 h, intracuff alkalinized lidocaine reduced the severity of postoperative sore throat at 1 h or 24 h. Similarly, the use of intracuff alkalinized lidocaine demonstrated a large reduction in postoperative hoarseness.

In terms of safety, there is no doubt that the usage of intracuff alkalinized lidocaine is much safer than the usage of intravenous lidocaine. In terms of the extubation time, no study has shown that intracuff alkalinized lidocaine may prolong the extubation time. None of the trials reported any adverse events directly related to the use of intracuff alkalinized lidocaine.

In the present study, we performed a detailed literature search, which included the main RCTs on the subject of intracuff alkalinized lidocaine. Our methodology followed strict guidelines developed by the Cochrane Collaboration. A bias risk assessment was conducted for each trial. Also, the quality of available evidence was assessed using grading criteria. The robustness of the obtained results was also tested by sensitivity analysis.

Two previous systematic reviews and meta-analyses have also demonstrated the effectiveness of intracuff alkalinized lidocaine for the prevention of airway complications in patients with tracheal intubation; nonetheless, our study is different to these studies. First of all, previous studies did not distinguish between adult and pediatric patients, while the present study focused on adult patients. Secondly, based on the huge difference in diffusion velocity between alkalinized lidocaine and non-alkalinized lidocaine in tracheal intubation, in the present study, we only included the relevant literature on alkalinized lidocaine in the analysis. At the same time, the previous systematic review and meta-analysis were not limited, although they also carried out the corresponding subgroup analysis. Thirdly, regardless of whether lubricating the cuff before intubation may have an important impact on postoperative airway complications in patients undergoing endotracheal intubation, it is necessary to analyze lubrication of the cuff before intubation in order to eliminate the influence of confounding factors on the results. Finally, 12 RCTs were included in this study, while the previous study only included 9 RCTs[36] and 8 RCTs[37] in the alkalized lidocaine subgroup. Additional trials will provide more data and information to support the conclusions of this study.

Our results revealed that intracuff alkalinized lidocaine decreased postoperative airway complications. To achieve a significant therapeutic effect, large doses of lidocaine may be necessary without alkalinization[37]. According to Estebe *et al*[34], plasma lidocaine levels confirmed the increased diffusion of lidocaine through the cuff when lidocaine was alkalinized. Moreover, this increased diffusion did not lead to vocal cord palsy. Therefore, the use of a small dose of alkalinized lidocaine (40 mg) is a relatively easy and safe practice that avoids the use of large doses of lidocaine.

The main limitation and disadvantage of this study is the obvious heterogeneity, although a pre-defined subgroup analysis was performed. Clinically, opioids, inhalational anesthetics, and the depth of anesthesia during extubation may have an impact on cough, hoarseness, and sore throat after extubation. In order to minimize these possible confounding factors, we conducted a special sensitivity analysis. Meta-analysis still showed the effectiveness of intracuff alkalinized lidocaine when we excluded RCTs with: (1) A high risk of bias; (2) Only female subjects; (3) Cuff prefilling **(**Table 2**)**. However, there are still many variables, such as operation time, inflation volume of the tracheal catheter cuff, anesthesiologist's expertise and ability, which were not systematically reported in the selected studies, thus cannot be analyzed. In addition, only 7 studies with primary outcome were eligible for inclusion, and the funnel plot results are not accurate. To sum up, the use of intracuff alkalinized lidocaine after tracheal intubation is a simple, economical and safe choice to prevent postoperative cough, sore throat, and hoarseness in adult patients. Anesthesiologists can use this technique in clinical patients.

**CONCLUSION**

This meta-analysis revealed that intracuff alkalinized lidocaine decreased postoperative airway complications, including coughing, hoarseness, and sore throat. Furthermore, for patients with a post-extubation sore throat, it could also reduce the degree of pain.

**ARTICLE HIGHLIGHTS**

***Research background***

Tracheal intubation is the most commonly used airway management method in general anesthesia. However, this approach has been associated with some problems, such as postoperative airway complications, which are common phenomena and adverse reactions in patients who underwent elective general anesthesia. To reduce the occurrence of postoperative airway-related complications, many interventions have been proposed. Among these, intracuff alkalinized lidocaine can be used as local anesthesia, to reduce complications during extubation, and to avoid the side effects of lidocaine on the circulation and central nervous system during general application.

***Research motivation***

Intracuff lidocaine can be used as local anesthesia, to reduce complications during extubation, and to avoid the side effects of lidocaine on the circulation and central nervous system during general application. Nevertheless, lidocaine is not easy to diffuse in the cuff, and adding sodium bicarbonate can greatly enhance the diffusion ability of lidocaine, to achieve better action on the tracheal mucosa.

***Research objectives***

Perform a systematic review and meta-analysis to summarize the efficacy of intracuff alkalinized lidocaine in the prevention of postoperative airway-related complications.

***Research methods***

A comprehensive literature search of Pubmed (until May 2020), Embase (until May 2020), Cochrane (until May 2020), and Web of Science (until May 2020) was performed. Heterogeneity was assessed using the Cochrane *Q* test and *I*2 statistic. A fixed-effect model was used if heterogeneity was considered low. If *I*2 statistic ≥ 50% and *P* < 0.05, a random-effects model was applied to the data.

***Research results***

Twelve randomized trials (1175 patients) met the inclusion criteria. The meta-analysis showed that intracuff alkalinized lidocaine was associated with less cough compared to that produced by placebo. Similarly, intracuff alkalinized lidocaine was more effective than the control in reducing postoperative sore throat at 24 h and postoperative hoarseness. Five trials that included 476 participants demonstrated a large reduction in the visual analogue scale of a postoperative sore throat at 1 h or 24 h with the use of intracuff alkalinized lidocaine.

***Research conclusions***

Intracuff alkalinized lidocaine decreased postoperative airway complications, including coughing, hoarseness, and sore throat. Furthermore, for patients with a post-extubation sore throat, it could also reduce the degree of pain.

***Research perspectives***

The use of intracuff alkalinized lidocaine after tracheal intubation is a simple, economical and safe choice to prevent postoperative cough, sore throat, and hoarseness in adult patients. Anesthesiologists can use this technique in clinical patients.

**REFERENCES**

1 **Weiser TG**, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, Gawande AA. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; **372**: 139-144 [PMID: 18582931 DOI: 10.1016/S0140-6736(08)60878-8]

2 **Asai T**, Koga K, Vaughan RS. Respiratory complications associated with tracheal intubation and extubation. *Br J Anaesth* 1998; **80**: 767-775 [PMID: 9771306 DOI: 10.1093/bja/80.6.767]

3 **Pitts T**. Airway protective mechanisms. *Lung* 2014; **192**: 27-31 [PMID: 24297325 DOI: 10.1007/s00408-013-9540-y]

4 **Thomas S**, Beevi S. Dexamethasone reduces the severity of postoperative sore throat. *Can J Anaesth* 2007; **54**: 897-901 [PMID: 17975234 DOI: 10.1007/BF03026793]

5 **Boes CJ**, Matharu MS, Goadsby PJ. Benign cough headache. *Cephalalgia* 2002; **22**: 772-779 [PMID: 12485201 DOI: 10.1046/j.1468-2982.2002.00439.x]

6 **Mattle HP**, Nirkko AC, Baumgartner RW, Sturzenegger M. Transient cerebral circulatory arrest coincides with fainting in cough syncope. *Neurology* 1995; **45**: 498-501 [PMID: 7898704 DOI: 10.1212/wnl.45.3.498]

7 **Leech P**, Barker J, Fitch W. Proceedings: Changes in intracranial pressure and systemic arterial pressure during the termination of anaesthesia. *Br J Anaesth* 1974; **46**: 315-316 [PMID: 4451611 DOI: 10.1093/bja/46.4.315-a]

8 **El-Boghdadly K**, Bailey CR, Wiles MD. Postoperative sore throat: a systematic review. *Anaesthesia* 2016; **71**: 706-717 [PMID: 27158989 DOI: 10.1111/anae.13438]

9 **Yamanaka H**, Hayashi Y, Watanabe Y, Uematu H, Mashimo T. Prolonged hoarseness and arytenoid cartilage dislocation after tracheal intubation. *Br J Anaesth* 2009; **103**: 452-455 [PMID: 19556269 DOI: 10.1093/bja/aep169]

10 **Tung A**, Fergusson NA, Ng N, Hu V, Dormuth C, Griesdale DEG. Medications to reduce emergence coughing after general anaesthesia with tracheal intubation: a systematic review and network meta-analysis. *Br J Anaesth* 2020 [PMID: 32098647 DOI: 10.1016/j.bja.2019.12.041]

11 **Kuriyama A**, Maeda H, Sun R. Topical application of magnesium to prevent intubation-related sore throat in adult surgical patients: a systematic review and meta-analysis. *Can J Anaesth* 2019; **66**: 1082-1094 [PMID: 31119554 DOI: 10.1007/s12630-019-01396-7]

12 **Neelakanta G**, Miller J. Minimum alveolar concentration of isoflurane for tracheal extubation in deeply anesthetized children. *Anesthesiology* 1994; **80**: 811-813 [PMID: 8024135 DOI: 10.1097/00000542-199404000-00013]

13 **Antoniades N**, Worsnop C. Topical lidocaine through the bronchoscope reduces cough rate during bronchoscopy. *Respirology* 2009; **14**: 873-876 [PMID: 19703068 DOI: 10.1111/j.1440-1843.2009.01587.x]

14 **Diachun CA**, Tunink BP, Brock-Utne JG. Suppression of cough during emergence from general anesthesia: laryngotracheal lidocaine through a modified endotracheal tube. *J Clin Anesth* 2001; **13**: 447-451 [PMID: 11578890 DOI: 10.1016/s0952-8180(01)00299-9]

15 **Altintaş F**, Bozkurt P, Kaya G, Akkan G. Lidocaine 10% in the endotracheal tube cuff: blood concentrations, haemodynamic and clinical effects. *Eur J Anaesthesiol* 2000; **17**: 436-442 [PMID: 10964145 DOI: 10.1046/j.1365-2346.2000.00696.x]

16 **Fagan C**, Frizelle HP, Laffey J, Hannon V, Carey M. The effects of intracuff lidocaine on endotracheal-tube-induced emergence phenomena after general anesthesia. *Anesth Analg* 2000; **91**: 201-205 [PMID: 10866913 DOI: 10.1097/00000539-200007000-00038]

17 **Soltani HA**, Aghadavoudi O. The effect of different lidocaine application methods on postoperative cough and sore throat. *J Clin Anesth* 2002; **14**: 15-18 [PMID: 11880016 DOI: 10.1016/s0952-8180(01)00344-0]

18 **Khezri M,** Jalili S, Asefzadeh S, Kayalha H. Comparison of intratracheal and intravenous lidocaine effects on bucking, cough, and emergence time at the end of anesthesia. Pak J Med Sci 2011; 27: 793-796 [DOI: 10.1016/S0041-624X(97)00098-X]

19 **Yang SS**, Wang NN, Postonogova T, Yang GJ, McGillion M, Beique F, Schricker T. Intravenous lidocaine to prevent postoperative airway complications in adults: a systematic review and meta-analysis. *Br J Anaesth* 2020; **124**: 314-323 [PMID: 32000978 DOI: 10.1016/j.bja.2019.11.033]

20 **Minogue SC**, Ralph J, Lampa MJ. Laryngotracheal topicalization with lidocaine before intubation decreases the incidence of coughing on emergence from general anesthesia. *Anesth Analg* 2004; **99**: 1253-1257, table of contents [PMID: 15385385 DOI: 10.1213/01.ANE.0000132779.27085.52]

21 **Tanaka Y**, Nakayama T, Nishimori M, Tsujimura Y, Kawaguchi M, Sato Y. Lidocaine for preventing postoperative sore throat. *Cochrane Database Syst Rev* 2015: CD004081 [PMID: 26171894 DOI: 10.1002/14651858.CD004081.pub3]

22 **Dollo G**, Estebe JP, Le Corre P, Chevanne F, Ecoffey C, Le Verge R. Endotracheal tube cuffs filled with lidocaine as a drug delivery system: *in vitro* and *in vivo* investigations. *Eur J Pharm Sci* 2001; **13**: 319-323 [PMID: 11384855 DOI: 10.1016/s0928-0987(01)00119-1]

23 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

24 **Gaur P**, Ubale P, Khadanga P. Efficacy and Safety of Using Air Versus Alkalinized 2% Lignocaine for Inflating Endotracheal Tube Cuff and Its Pressure Effects on Incidence of Postoperative Coughing and Sore Throat. *Anesth Essays Res* 2017; **11**: 1057-1063 [PMID: 29284875 DOI: 10.4103/aer.AER\_85\_17]

25 **Suma KV,** Bhaskar KU. Prevention of post intubation sore throat by inflating endotracheal tube cuff with alkalinized lignocaine. Indian Journal of Public Health Research and Development 2015; **6**:200-204 [DOI: 10.5958/0976-5506.2015.00227.2]

26 **Navarro LH**, Lima RM, Aguiar AS, Braz JR, Carness JM, Módolo NS. The effect of intracuff alkalinized 2% lidocaine on emergence coughing, sore throat, and hoarseness in smokers. *Rev Assoc Med Bras (1992)* 2012; **58**: 248-253 [PMID: 22569622 DOI: 10.1016/S2255-4823(12)70188-1]

27 **Shroff PP**, Patil V. Efficacy of cuff inflation media to prevent postintubation-related emergence phenomenon: air, saline and alkalinized lignocaine. *Eur J Anaesthesiol* 2009; **26**: 458-462 [PMID: 19445057 DOI: 10.1097/eja.0b013e32832403fa]

28 **Navarro LH**, Braz JR, Nakamura G, Lima RM, Silva Fde P, Módolo NS. Effectiveness and safety of endotracheal tube cuffs filled with air *vs* filled with alkalinized lidocaine: a randomized clinical trial. *Sao Paulo Med J* 2007; **125**: 322-328 [PMID: 18317601 DOI: 10.1590/s1516-31802007000600004]

29 **Estebe JP**, Gentili M, Le Corre P, Dollo G, Chevanne F, Ecoffey C. Alkalinization of intracuff lidocaine: efficacy and safety. *Anesth Analg* 2005; **101**: 1536-1541 [PMID: 16244028 DOI: 10.1213/01.ANE.0000180995.24211.89]

30 **D'Aragon F**, Beaudet N, Gagnon V, Martin R, Sansoucy Y. The effects of lidocaine spray and intracuff alkalinized lidocaine on the occurrence of cough at extubation: a double-blind randomized controlled trial. *Can J Anaesth* 2013; **60**: 370-376 [PMID: 23370978 DOI: 10.1007/s12630-013-9896-8]

31 **Rizvanović N**, Čaušević S, Hrnčić N, Hatibović H. Effect of intracuff alkalinized 2% lidocaine on endotracheal tube cuff pressure and postoperative throat symptoms in anaesthesia maintained by nitrous oxide. *Med Glas (Zenica)* 2019; **16**: 7-12 [PMID: 30680980 DOI: 10.17392/991-19]

32 **Nath P**, Williams S, Herrera Méndez LF, Massicotte N, Girard F, Ruel M. Alkalinized Lidocaine Preloaded Endotracheal Tube Cuffs Reduce Emergence Cough After Brief Surgery: A Prospective Randomized Trial. *Anesth Analg* 2018; **126**: 615-620 [PMID: 29189279 DOI: 10.1213/ANE.0000000000002647]

33 **Estebe JP**, Delahaye S, Le Corre P, Dollo G, Le Naoures A, Chevanne F, Ecoffey C. Alkalinization of intra-cuff lidocaine and use of gel lubrication protect against tracheal tube-induced emergence phenomena. *Br J Anaesth* 2004; **92**: 361-366 [PMID: 14970135 DOI: 10.1093/bja/aeh078]

34 **Estebe JP**, Dollo G, Le Corre P, Le Naoures A, Chevanne F, Le Verge R, Ecoffey C. Alkalinization of intracuff lidocaine improves endotracheal tube-induced emergence phenomena. *Anesth Analg* 2002; **94**: 227-230, table of contents [PMID: 11772834 DOI: 10.1097/00000539-200201000-00044]

35 **Navarro RM**, Baughman VL. Lidocaine in the endotracheal tube cuff reduces postoperative sore throat. *J Clin Anesth* 1997; **9**: 394-397 [PMID: 9257206 DOI: 10.1016/s0952-8180(97)00068-8]

36 **Lam F**, Lin YC, Tsai HC, Chen TL, Tam KW, Chen CY. Effect of Intracuff Lidocaine on Postoperative Sore Throat and the Emergence Phenomenon: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *PLoS One* 2015; **10**: e0136184 [PMID: 26288276 DOI: 10.1371/journal.pone.0136184]

37 **Peng F**, Wang M, Yang H, Yang X, Long M. Efficacy of intracuff lidocaine in reducing coughing on tube: a systematic review and meta-analysis. *J Int Med Res* 2020; **48**: 300060520901872 [PMID: 32046552 DOI: 10.1177/0300060520901872]

**Footnotes**

**Conflict-of-interest statement:** The authors report no conflict of interest.

**PRISMA 2009 Checklist statement:** The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** May 8, 2021

**First decision:** June 5, 2021

**Article in press:**

**Specialty type:** Anesthesiology

**Country/Territory of origin:** China

**Peer-review report’s scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): 0

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Sikiric P **S-Editor:** Wu YXJ **L-Editor:** Webster JR **P-Editor:**

**Figure Legends**



**Figure 1 Flow diagram of included and excluded studies.** RCT: Randomized controlled trial.



**Figure 2 Risk of bias assessment for the primary studies.**

****

**Figure 3 Forrest plots showing the effects of the intervention.** Incidence of postoperative cough. CI: Confidence interval.

****

**Figure 4 Forrest plots showing the effects of the intervention.** Incidence of postoperative hoarseness. CI: Confidence interval.

****

**Figure 5 Forrest plots showing the effects of the intervention.** Incidence of a postoperative sore throat within 24 h. CI: Confidence interval.

****

**Figure 6 Forrest plots showing the effects of the intervention.** Visual analogue scale of a postoperative sore throat at 1 h. CI: Confidence interval; SD: Standard deviation.

****

**Figure 7 Forrest plots showing the effects of the intervention.** Visual analogue scale of a postoperative sore throat at 24 h. CI: Confidence interval; SD: Standard deviation.

****

**Figure 8 Funnel plot for evaluation of potential publication bias.** RR: Risk ratio.

**Table 1 Characteristics of the included trials**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Country** | **Age (yr)** | **Male/ Female** | **Sample size** | **ASA status** | **Surgery** | **Intervention/comparator** | **Outcomes** |
|
| Rizvanović *et al*[31], 2019 | Bosnia and Herzegovina | 49.4 (18-65) | 44/46 | 90 | I, II, III | Elective surgery | 1 Alkalinized 2% lidocaine; 2 0.9% saline; 3 Air | IPOST |
|
| Nath *et al*[32], 2018 | USA | 52 (18-80) | 73/127 | 200 | I, II, III | NR | 1 Alkalinized 2% lidocaine; 2 0.9% saline | IPC  |
|
| Gaur *et al*[24], 2017 | Arabia | 44.62 (18-65) | 51/49 | 100 | I, II | NR | 1 Alkalinized 2% lidocaine; 2 Air | IPOST |
|
| Suma *et al*[25], 2015 | India | 37.66 (18-65) | NR | 200 | I, II | Elective orthopedic, spine, and general surgery  | 1 Alkalinized 2% lidocaine; 2 Air | VAS of POST |
|
| Navarro *et al*[26], 2012 | Brazil | NR (≥ 18) | 13/37 | 50 | I, II | Elective gynecological, orthopedic, or plastic surgery  | 1 Alkalinized 4% lidocaine; 2 0.9% saline | IPC, IPH, IPOST |
|
| Shroffand Patil[27], 2009  | UK | 36.71 (18-60) | 51/99 | 150 | I, II | NR | 1 Alkalinized 2% lidocaine; 2 0.9% saline 3 Air | IPC, IPH |
|
| Navarro *et al*[28], 2007 | Brazil | 45.15 (18-65) | NR | 50 | I, II | Gynecological surgery or plastic surgery | 1 Alkalinized 2% lidocaine; 2 Air | IPOST |
|
| Estebe *et al*[29], 2005 | USA | 47.67 ( ≥ 18) | 13/47 | 60 | I, II | Thyroidectomy surgery | 1 Alkalinized 2% lidocaine (8.4%NaHCO3); 2 Alkalinized 2% lidocaine (1.4%NaHCO3); 3 Air | IPC, IPH, VAS of POST |
|
| Estebe *et al*[33], 2004 | UK | 49.67 ( ≥ 18) | 39/21 | 60 | I, II, III | Lumbar spinal surgery | 1 Alkalinized 2% lidocaine (lubricated with sterile water); 2 Alkalinized 2% lidocaine (lubricated with water-soluble gel); 3 Air | IPC, IPH, VAS of POST |
|
| Estebe *et al*[34], 2002 | USA | 46.5 ( ≥ 18） | 27/23 | 50 | I, II, III | Lumbar spinal surgery | 1 Alkalinized 2% lidocaine; 2 2% Lidocaine; 3 Air | IPC, IPH, VAS of POST |
|
| Navarro *et al*[35], 1997 | USA | 40.15 (NR) | 18/88 | 106 | I, II, III | NR | 1 Alkalinized 2% Lidocaine; 2 Air | IPOST, VAS of POST |
|
| D’Aragon *et al*[30], 2013 | Canada | 41.8 ( ≥ 18) | 0/59 | 59 | I, II | Elective gynecological surgery | 1 Alkalinized 2% lidocaine; 2 0.9% saline | IPC |
|

IPC: Incidence of post-extubation cough; IPH: Incidence of postoperative hoarseness; POST: Postoperative sore throat; IPOST: Incidence of postoperative sore throat; VAS: Visual analogue scale; NR: Not reported.

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

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Potential bias or limitations excluded** | **IPC RR (95%CI), *I2*** | **IPH RR (95%CI), *I*2** | **IPOST within 24 h RR (95%CI), *I2*** | **VAS of POST at 1 h RR (95%CI), *I2*** | **VAS of POST at 24 h RR (95% CI), *I2*** |
| Overall | 0.38 (0.23,0.63), 82% | 0.38 (0.21,0.69), 74% | 0.19 (0.09,0.41), 0% | -18.30 (-22.79, -13.82), 73% | -14.86 (-15.75, -13.98), 43% |
| Only females | 0.33 (0.20,0.52), 69% | NE | NE |  |  |
| Cuff prefilling | 0.35 (0.19,0.63), 85% | NE | NE | -17.59 (-18.69, -16.49), 77% | -14.81 (-17.22, -12.41), 54% |
| A high risk of bias | NE | NE | 0.19 (0.08, 0.48), 0% | -18.45(-25.61, -11.29), 77% | -14.37 (-18.31, -10.43), 56% |

IPC: Incidence of post-extubation cough; IPH: Incidence of postoperative hoarseness; POST: Postoperative sore throat; IPOST: Incidence of postoperative sore throat; VAS: Visual analogue scale; CI: Confidence interval; NE: Not estimable; RR: Relative risk.