BMJ Open

Effectiveness of different pharmacological or non-pharmacological interventions on preventing coughing during extubation: a protocol for a systematic review and network meta-analysis

Zhichao Gong ,[1,2] Yixuan Wu,[2] Di Yang,[3] Qian Li,[2] Longjun Yang,[1] Lei Yang [2]

To cite: Gong Z, Wu Y, Yang D, *et al*. Effectiveness of different pharmacological or non-pharmacological interventions on preventing coughing during extubation: a protocol for a systematic review and network meta-analysis. *BMJ Open* 2024;**14**:e081592. doi:10.1136/bmjopen-2023-081592

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2023-081592).

ZG and YW contributed equally.

Received 01 November 2023
Accepted 17 October 2024

For numbered affiliations see end of article.

Correspondence to
Dr Lei Yang;
yanglei.wcha@scu.edu.cn and
Dr Longjun Yang;
yljdy1978@sina.com

ABSTRACT

Introduction Coughing during extubation can lead to several postoperative complications, including surgical site bleeding, intracranial hypertension and high intraocular pressure. Currently, various pharmacological and non-pharmacological interventions are employed in clinical practice to reduce coughing during extubation. However, it is unclear which of these interventions has the best preventive effect and the fewest adverse events. Therefore, we plan to conduct a systematic review and network meta-analysis to compare the effects of all interventions.

Methods and analysis We will search MEDLINE, Embase, Web of Science, Cochrane Central Register of Controlled Trials, CNKI and Wanfang databases, as well as reference lists from previously published papers, from the date of their inception to April 2024. We will only include randomised controlled trials, regardless of publication in any language. The primary outcome is the incidence of cough during extubation, using the modified Minogue scales. The secondary outcomes are as follows: (1) the incidence of severe coughing (grade 4); (2) the incidence of other types of postoperative airway complications, such as laryngospasm, apnoea, hypoxaemia and sore throat, which will be evaluated within 24 hours after surgery; (3) the side effects related to the interventions, such as bradycardia (heart rate less than 60 beats per minute), hypotension or allergic reactions, which will be evaluated within 24 hours from the start of the drug to the postoperative period and (4) the time from the end of the surgery to the extubation of the endotracheal tube. The articles meeting the criteria will be independently evaluated by two researchers based on the established screening criteria. The data will then be extracted. Bias will be assessed for all included studies using the Cochrane Risk of Bias Risk Assessment Tool Version 2. We will use the Netmeta package of the R software with a random-effects model to make direct and indirect comparisons through the frequency framework. We will assess the quality of evidence using Confidence in Network Meta-Analysis.

Ethics and dissemination Ethical approval is not required for this protocol, as we will only pool published data. We plan to submit our manuscript for publication in a peer-reviewed academic journal.

PROSPERO registration number CRD42023401609.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We will comprehensively compare pharmacological and non-pharmacological interventions that may reduce or alleviate coughing during extubation after general anaesthesia.
⇒ Only randomised controlled trials will be included in this study, and the primary outcome is the risk of cough during tracheal extubation.
⇒ We will evaluate the quality and assess the risk of bias in all included studies.
⇒ Although a subgroup analysis is planned, the potential heterogeneity cannot be completely eliminated.

INTRODUCTION

A large proportion of patients require endotracheal intubation for general anaesthesia.[1] During recovery from general anaesthesia, approximately 15–94% of patients experienced coughing during extubation.[2 3] The observed wide variation in the incidence of coughing was associated with the different preventive interventions both pharmacological and non-pharmacological employed. Although it is a protective reflex, coughing can lead to adverse effects such as hypertension and tachycardia,[4 5] which can cause haemodynamic changes. The changes can alter the intracranial or intraocular pressure, potentially resulting in adverse postoperative outcomes such as cerebral haemorrhage or herniation.[6 7]

Various techniques have been studied to manage this issue, including pharmacologic (eg, the use of topical or intravenous lidocaine,

dexmedetomidine, remifentanil and fentanyl) and non-pharmacological (eg, extubation in the prone position) methods.[8–12] These techniques work by reducing the local or systemic stress response, thereby minimising the occurrence of cough during extubation. However, they are also associated with certain side effects. For instance, intravenous injection of lidocaine, dexmedetomidine or remifentanil may prolong recovery time.[13 14] Increasing doses of dexmedetomidine can also pose risks of hypotension and bradycardia.[15] A meta-analysis comparing local endotracheal anaesthesia with controls (placebo or no medication) found that local endotracheal anaesthesia significantly reduced immediate cough during extubation compared with placebo.[16] However, the comparison was limited to local anaesthetics for tracheal intubation, and the control group received either a placebo or no treatment at all. This study did not compare differences in the effects of local endotracheal anaesthetic drugs when compared with other pharmaceutical agents. Additionally, a network meta-analysis comparing various interventions (including lidocaine, dexmedetomidine, fentanyl and remifentanil) concluded that dexmedetomidine had the highest cumulative reduction in the incidence of severe cough at extubation.[17] However, dexmedetomidine can cause side effects such as prolonged sedation or bradycardia.

Although these meta-analyses have compared several pharmacological interventions to reduce emergence cough after general anaesthesia, a considerable number of other clinical pharmacological interventions were excluded from the analysis. These exclusive interventions included such drugs (ie, alfentanil,[18] tramadol,[19] sulgamonol sodium,[20] and oxycodone[21] and non-pharmacological interventions (ie, body position adjustment during extubation[11] and nerve block.[12] We do not have sufficient evidence to show whether these measures have similar or better effects on the reduction of coughing during extubation.

To find an optimal method for reducing cough during extubation and determine the comparative efficacies of pharmacological and non-pharmacological interventions, we will conduct this systematic review and network meta-analysis to compare all interventions found by our analysis that may reduce the incidence or severity of cough during extubation under general anaesthesia.

METHODS

The study protocol (registration number: CRD42023401609) was registered with the International Prospective Register of Systematic Reviews. The study protocol will be published in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[22]

Patient and public involvement

The patients and the public had no role in the design, conduct, reporting or dissemination of the study.

Data sources and searches

We will search the following databases: MEDLINE, Embase, Web of Science, the Cochrane Central Register of Controlled Trials via OVID, the Chinese databases CNKI and Wanfang, as well as reference lists from previously published papers. The language of retrieval is not limited. The search period for all databases will be limited to the period from the date of database establishment to April 2024. The original keywords are 'cough' and 'extubation', and the details of the original search strategy are presented in online supplemental file 1. In addition, we will search for conference papers via SCOPUS by restricting the 'source type' to 'conference proceedings'. At the same time, we will search ClinicalTrials.gov and the Chinese Clinical Trial Registry for ongoing studies. A reassessment of the subject headings and free-text terms related to coughing or extubation, which have not been used, will be conducted. Newly identified subject headings and free-text words will be added to the modified search strategy. The final version of the search strategy will be reported in our review.

Eligibility criteria

Types of study

We will include only randomised controlled trials, regardless of language or publication status. Conference abstracts will also be included if they have sufficient data.

Types of participants

We will include all adult patients (≥18 years old) who received general anaesthesia with endotracheal intubation and were extubated in the operating room, regardless of the type of surgery performed.

Types of interventions

We will include all interventions to prevent postoperative cough including pharmacological treatments such as intravenous medications and local medications and non-pharmacological treatments such as adjustment of body position during extubation.

Types of comparisons

We will compare the different interventions or placebo.

Types of outcomes

The primary outcome is the incidence of coughing during tracheal extubation. We will define the incidence of cough using the modified Minogue scale (grade 1 (none cough) means no coughing or muscular stiffness; grade 2 (mild cough) means coughing once or twice; grade 3 (moderate cough) means ≤3 coughs lasting 1–2 s, or total duration of coughing last ≤5 s; grade 4 (severe cough) means ≥4 coughs with each lasting ≥2 s, total duration of coughing last >5 s).[23] If no direct data related to the modified Minogue scale can be extracted from the study, we will attempt to interpret the data from the original source using the descriptions provided or other related measures of cough severity. The secondary outcomes are as follows: (1) the incidence of severe coughing (grade 4); (2) the

incidence of other types of postoperative airway complications, such as laryngospasm, apnoea, hypoxaemia and sore throat, which will be evaluated within 24 hours after surgery; (3) the side effects related to the interventions, such as bradycardia (heart rate less than 60 beats per minute), hypotension or allergic reactions,[24] which will be evaluated within 24 hours from the start of the drug to the postoperative period and (4) the time from the end of the surgery to the extubation of the endotracheal tube.

Study selection

All abstracts will be independently reviewed by two researchers (ZG and YW) to determine their eligibility. The full text will be reviewed if the abstract does not provide sufficient information to determine eligibility. In the event that two researchers diverge in their opinions regarding the suitability of including literature in the review, the full text will be re-reviewed by a third researcher, who will then make the decision on the inclusion of literature. Two researchers (ZG and YW) independently completed selection forms (online supplemental file 2). Disagreements after discussion will be decided by a third person (DY). Finally, we will show all eligible studies that were included in the review.

Data extraction and quality assessment

We will obtain and extract data from the full texts of all eligible studies. Two researchers (ZG and YW) will independently extract the data from the studies and enter them into a data extraction form (online supplemental file 3). A third researcher (LoY) will verify the results.

Two researchers (ZG and YW) will independently assess the quality of all included studies using the Cochrane Risk of Bias Risk Assessment Tool Version 2 from the Cochrane Handbook for Systematic Reviews of Interventions,[25] which includes the following five domains: bias arising from the randomisation process, bias due to deviations from the intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of reported results. Each domain will be assigned a risk of bias level, which is one of the following: low risk of bias, some concerns or high risk of bias. Disagreements will be resolved through discussion. In this review, we will report the risk of bias table and the risk of bias summary figure.

Data synthesis

We plan to use the relative risk between the intervention and control groups to estimate the incidence of coughing or severe coughing and calculate the 95% CI. For continuous variables, such as the time from the end of surgery to extubation, we plan to use the mean difference and calculate the 95% CI.

We will use the Netmeta package of R software with a random-effects model to make direct and indirect comparisons through the frequency framework. A network diagram and rank probabilities will be generated and presented. We will use different imputation methods (low risk of bias and large sample size studies) and statistical methods (including fixed-effect models) for the sensitivity analyses. We will also generate a funnel plot to assess publication bias.[26]

We will use statistical methods (Q statistics and I^2 statistics) to test the heterogeneity between studies. When the p value is <0.05, the variation between studies exceeds what can be explained by sampling error, and the existence of heterogeneity should be considered. We will quantify the heterogeneity by calculating I^2 statistics. When I^2>50%, it is considered that there is a high degree of heterogeneity between the studies. When significant statistical heterogeneity exists, we will investigate the clinical heterogeneity using a subgroup analysis, which will be performed based on the patient's age, sex, surgical procedure and anaesthetics used during surgery. When patient characteristics, interventions and outcomes are similar, the transitivity between the study results will be considered. Based on previous studies and preliminary screenings, the number of studies is sufficient. We will draw a network diagram using nodes to represent different research interventions and edges to represent head-to-head comparisons between network nodes. If there is an inconsistency among three or more nodes in the loop, we will use the node-splitting method for evaluation. If the p value is >0.05, the difference between the direct and indirect comparisons will not be statistically significant. When the results are inconsistent, the results of direct comparison will be used as the estimated effect quantity.

Assessing the quality of evidence

We will grade the quality of evidence for network meta-analysis based on Confidence in Network Meta-Analysis, which includes six domains, namely (1) within-study bias, (2) between-study bias, (3) indirectness, (4) imprecision, (5) heterogeneity and (6) inconsistency.[27]

ETHICS AND DISSEMINATION

Ethical approval was not required for this study, as we only pooled published data. We plan to present our review at academic conferences and in peer-reviewed journals.

Author affiliations
[1]Department of Anesthesiology, Dongying People's Hospital, Dongying, China
[2]Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China
[3]Department of Anesthesiology, Sichuan Provincial People's Hospital, School of Medicine,University of Electronic Science and Technology of China, Chengdu, China

Acknowledgements We would like to thank Adham (www.editage.com) for English language editing.

Contributors DY and LoY conceived and designed the study. LeY developed the search strategy. ZG, YW, DY, QL and LeY drafted the manuscript. All the authors have agreed to submit this article for publication. LeY is the guarantor.

Funding This research was supported by the Key Research and Development Project of the Ministry of Science and Technology of Sichuan Province (No. 2023YFS0139) and Sichuan Science and Technology Program (No. 2023ZYD0168).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Zhichao Gong http://orcid.org/0009-0007-3417-9036
Lei Yang http://orcid.org/0000-0003-0232-7915

REFERENCES

1 Weiser TG, Haynes AB, Molina G, *et al*. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet* 2015;385:S11.
2 Park SY, Kim SH, Lee SJ, *et al*. Application of triamcinolone acetonide paste to the endotracheal tube reduces postoperative sore throat: a randomized controlled trial. *Can J Anaesth* 2011;58:436–42.
3 Thomas S, Beevi S. Dexamethasone reduces the severity of postoperative sore throat. *Can J Anaesth* 2007;54:897–901.
4 Leech P, Barker J, Fitch W. Proceedings: Changes in intracranial pressure and systemic arterial pressure during the termination of anaesthesia. *Br J Anaesth* 1974;46:315–6.
5 Bidwai AV, Bidwai VA, Rogers CR, *et al*. Blood-pressure and Pulse-rate Responses to Endotracheal Extubation with and without Prior Injection of Lidocaine. *Anesthesiology* 1979;51:171–2.
6 Venkatesan T, Korula G. A comparative study between the effects of 4% endotracheal tube cuff lignocaine and 1.5 mg/kg intravenous lignocaine on coughing and hemodynamics during extubation in neurosurgical patients: a randomized controlled double-blind trial. *J Neurosurg Anesthesiol* 2006;18:230–4.
7 Kalfas IH, Little JR. Postoperative hemorrhage: a survey of 4992 intracranial procedures. *Neurosurgery* 1988;23:343–7.
8 Sean C M, James R, Martin J L. Laryngotracheal topicalization with lidocaine before intubation decreases the incidence of coughing on emergence from general anesthesia. *Anesth Analg* 2004;99:1253–7.
9 Saidie S, Modir H, Yazdi B, *et al*. The effect of dexmedetomidine on decrease of cough, hemodynamic parameters and Ramsay score *versus* lidocaine during general anesthesia: a randomized clinical trial. *Med Gas Res* 2021;11:1–5.
10 Aouad MT, Al-Alami AA, Nasr VG, *et al*. The effect of low-dose remifentanil on responses to the endotracheal tube during emergence from general anesthesia. *Anesth Analg* 2009;108:1157–60.
11 Ozden MG, Bakan N, Kocoglu H. The effect of extubation in prone position on emergence and recovery in lumbar spinal surgery. *J Neurosurg Sci* 2023;67:185–90.
12 Zhou Y, Chen B, Xiong Y, *et al*. The Efficacy of Ultrasound-Guided Superior Laryngeal Nerve Block as an Adjuvant to General Anesthesia during Suspension Laryngoscopy Vocal Cord Polypectomy. *Evid Based Complement Alternat Med* 2022;2022:1–8.
13 Gonzalez RM, Bjerke RJ, Drobycki T, *et al*. Prevention of endotracheal tube-induced coughing during emergence from general anesthesia. *Anesth Analg* 1994;79:792–5.
14 Salim B, Rashid S, Ali MA, *et al*. Effect of Pharmacological Agents Administered for Attenuating the Extubation Response on the Quality of Extubation: A Systematic Review. *Cureus* 2019;11:e6427.
15 Panpan F, Lili T, Xuesheng L. Research advances on methods for preventing extubation reaction[J]. *Int J Anesth Resusc* 2021;42:849–53.
16 Sakae TM, Souza RLP, Brand Úo JCM, *et al*. Impact of topical airway anesthesia on immediate postoperative cough/bucking: a systematic review and meta-analysis. *Braz J Anesthesiol* 2023;PMCID:91–100.
17 Tung A, Fergusson NA, Ng N, *et al*. Medications to reduce emergence coughing after general anaesthesia with tracheal intubation: a systematic review and network meta-analysis. *Br J Anaesth* 2020;124:480–95.
18 Mendel P, Fredman B, White PF. Alfentanil suppresses coughing and agitation during emergence from isoflurane anesthesia. *J Clin Anesth* 1995;7:114–8.
19 Lin B-F, Ju D-T, Cherng C-H, *et al*. Comparison between intraoperative fentanyl and tramadol to improve quality of emergence. *J Neurosurg Anesthesiol* 2012;24:127–32.
20 P.s. L, Miskan MM, Y.z. C, *et al*. Staggering the dose of sugammadex lowers risks for severe emergence cough: a randomized control trial. *BMC Anesthesiol* 2017;17:137.
21 Jiang M, Ji J, Li X, *et al*. Effect of intravenous oxycodone on the physiologic responses to extubation following general anesthesia. *BMC Anesthesiol* 2021;21:146.
22 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:71.
23 Tung A, Fergusson NA, Ng N, *et al*. Pharmacological methods for reducing coughing on emergence from elective surgery after general anesthesia with endotracheal intubation: protocol for a systematic review of common medications and network meta-analysis. *Syst Rev* 2019;8:32.
24 Muraro A, Worm M, Alviani C, *et al*. Pharmacological methods for reducing coughing on emergence from elective surgery after general anesthesia with endotracheal intubation: protocol for a systematic review of common medications and network meta-analysis. *Syst Rev* 2021;8:357–77.
25 Higgins JPT, Thomas J, Chandler J, *et al*. *Cochrane handbook for systematic reviews of interventions version*. Cochrane, 2022. Available: https://www.trainingcochraneorghandbook.com
26 Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ* 1997;315:1533–7.
27 Nikolakopoulou A, Higgins JPT, Papakonstantinou T, *et al*. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med* 2020;17:e1003082.