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Interventions for prevention of cough reflex during extubation: A protocol for a systematic review and network meta-analysis

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Interventions for prevention of cough reflex during extubation: A protocol for a systematic review and network meta-analysis

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Abstract

Introduction: Coughing during extubation can lead to several postoperative complications, including surgical site bleeding, intracranial hypertension, and high intraocular pressure. Currently, many interventions, both pharmacological and non-pharmacological interventions, are used in clinical practice to reduce coughing at extubation. However, it is unclear which of these interventions has the best preventive effect and 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, Cochrane Central Register of Controlled Trials, CNKI, and Wanfang databases from the date of their inception to March 5, 2023. We will only include RCTs, regardless of publication in any language. The primary outcome is the incidence of cough during extubation. Bias will assess for all included studies using the Cochrane Risk of Bias Risk Assessment Tool Version 2 (ROB 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 (CINeMA).

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 anesthesia.
- Only RCTs will be included in this study, and the primary outcome is the incidence of cough during tracheal extubation.
- We will evaluate the quality and assess the risk of bias of all included studies.
- Although a subgroup analysis is planned, differences in outcomes, such as surgical

type and anesthetics, may still exist, and potential heterogeneity cannot be completely eliminated.

INTRODUCTION

A large proportion of patients require endotracheal intubation for general anesthesia.[1] During recovery from general anesthesia, patients often experience coughing during extubation, which occurs in approximately 15–94% of patients.[2,3] Although it is a protective reflex, coughing can lead to adverse effects such as hypertension, tachycardia, arrhythmias, myocardial ischemia, bronchospasm, surgical site bleeding, intracranial hypertension, high intraocular pressure,[4,5] and even catastrophic outcomes. Hemodynamic changes caused by coughing during extubation in neurosurgery alter the intracranial pressure (ICP), leading to adverse postoperative results.[6]

Many studies have tested pharmacological or non-pharmacological interventions to reduce the incidence or severity of cough during extubation. In one meta-analysis, researchers have compared the effectiveness of local endotracheal anesthesia in reducing cough during extubation and concluded that the use of local endotracheal anesthesia reduced immediate cough during extubation compared to placebo.[7] In addition, a network meta-analysis compared several interventions, including lidocaine, dexmedetomidine, fentanyl and remifentanil, and concluded that dexmedetomidine had the highest cumulative reduction in the incidence of severe cough at extubation.[8] Although the above studies have compared different pharmacological interventions to reduce emergence cough after general anesthesia, the results were still limited. Many other clinical pharmacological interventions, such as alfentanil,[9] tramadol,[10] sulgamonol sodium,[11] oxycodone,[12], as well as other non-pharmacological interventions such as body position adjustment during extubation[13] and nerve block[14] were not included and analyzed.

To identify the treatments with the best preventive effects and the fewest adverse events in clinical practice, we conducted this systematic review and network meta-analysis to compare the effects of all interventions that may reduce the incidence or severity of cough during extubation under general anesthesia.

METHODS AND ANALYSIS

The study protocol (registration number: CRD42023401609) was registered with the International Prospective Register of Systematic Reviews. The study protocol was published in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[15]

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, the Cochrane Central Register of Controlled Trials via OVID, and the Chinese databases CNKI and Wanfang. 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 March 5, 2023. The original keywords are “cough” and “extubation,” and the details of the original search strategy are presented in Supplementary Table 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 ClinicalTrial Registry for ongoing studies. In previous studies, we will re-evaluate unused subject headings or free-text words related to coughing or extubation. 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 RCTs, 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 anesthesia with endotracheal intubation, 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 cough during tracheal extubation. It will be graded using a four-point scale (0 = no cough; 1 = mild, single cough; 2 = moderate, >1 cough lasting <5 s; 3 = severe, lasting >5 s).[16]

The secondary outcomes are: (1) the incidence of other types of postoperative airway complications, such as laryngospasm, apnea, hypoxemia, and sore throat, which will be evaluated within 24 hours after surgery; (2) the side effects related to the interventions, such as bradycardia (heart rate less than 60 BPM), allergic reactions (such as acute rash of skin, mucous membrane, or both, impaired respiratory function, decreased blood pressure, or related symptoms, etc.),[17] which will be evaluated within 24 hours from the start of the drug to the postoperative period; (3) 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 necessary. Two researchers (ZG and YW) independently completed selection forms (Supplementary Table 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 (Supplementary Table 3). A third researcher (LY) 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 (ROB 2)

from the Cochrane Handbook for Systematic Reviews of Interventions[18], which includes the following five domains: bias arising from the randomization 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.

Statistical analysis

We plan to use the relative risk (RR) between the intervention and control groups to estimate the incidence of cough and calculate the 95% confidence intervals (95%CI). For continuous variables, such as the time from the end of surgery to extubation and the severity of the cough, we plan to use the mean difference (MD) and calculate the 95% confidence interval (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.[19]

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 is beyond the range explained by the 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 anesthetics 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 (CINeMA), which includes six domains: (1) within-study bias, (2) between-study bias, (3) indirectness, (4) imprecision, (5) heterogeneity, and (6) inconsistency.[20]

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.

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Authors' contributors

DY and LY conceived and designed the study. LY developed the search strategy. ZG, YX, DY, QL and LY drafted the manuscript. All the authors have agreed to submit this article for publication.

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Competing interests statement

None to declare.

Patient consent for publication

Not applicable.

1.cough/

2.cough.mp

3. 1 or 2

4.extubation.mp

5.((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.

6. 3 and 4 and 5

Study selection form

first author	Journal/Conference Proceedings etc	Year	Study eligibility					NOTE(IN OR EX)	Freehand space for comments on study design and treatment
			RCT	Relevant participants	Relevant interventions	Relevant comparisons	Relevant outcomes		

Data Extraction Form

Paper code:

Participant characteristics	
	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers / %, etc)	
Past medical history（especially trachea or lung disease）	
History of smoking	
Surgery procedure	
Length of surgery	
Anesthetics used during surgery (drug/dose)	
Other	

Trial characteristics	
	Further details
Single centre / Multicentre	
Country / Countries	
How many people were randomized?	
Number of participants in intervention group/control group	/
Number of participants who received intended treatment	
Number of participants who were analysed	
Intervention (name/dose/route)	
Comparison (name/dose/route)	
Trial design (e.g. parallel / cross-over)	
Other	

Data extraction

Outcomes	**Reported in paper (circle)**
Primary outcome	
Outcome 1 – incidence of cough during tracheal extubation.	Yes / No
Secondary outcomes	
Outcome 1 - incidence of other types of postoperative airway complications.	Yes / No
Outcome 2 - The side effects related to the interventions.	Yes / No

Outcome 3 - The time from the end of the surgery to the extubation of the endotracheal tube.	Yes / No
Subgroups	**Reported in paper**
Age	
Sex	
surgical procedure	
anesthetics used during surgery	

For Continuous data							
Paper code	Outcomes	Unit of measurement	Intervention group		Control group		Details if outcome only described in text
			n	Mean (MD)	n	Mean (MD)	
	The time from the end of the surgery to the extubation of the endotracheal tube						

For Dichotomous data			
Paper code	Outcomes	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events
	incidence of cough during tracheal extubation		
	incidence of other types of postoperative airway complications		
	The side effects related to the interventions		

Other information which you feel is relevant to the results Indicate whether the data was obtained from the first author. If the results were estimated by charts or calculated by formulas (as described in the article) and not reported in the article, it should be stated here.

Freehand space for writing actions such as contact with study authors and changes

References to other trials

Did this report include any references to published reports **of potentially eligible trials not already identified for this review?**		
First author	**Journal / Conference**	**Year of publication**
Did this report include any references to unpublished data **from potentially eligible trials not already identified for this review? If yes, give list contact name and details**		

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

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia
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The effectiveness of different pharmacological or non-pharmacological interventions on preventing coughing during extubation : A protocol for a systematic review and network meta-analysis

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Abstract

Introduction: Coughing during extubation can lead to several postoperative complications, including surgical site bleeding, intracranial hypertension, and high intraocular pressure. Currently, many interventions, both pharmacological and non-pharmacological interventions, are used in clinical practice to reduce coughing at extubation. However, it is unclear which of these interventions has the best preventive effect and 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 RCTs, regardless of publication in any language. The primary outcome is the incidence of cough during extubation, using the modified Minogue scales. The literature that meets the inclusion criteria will be independently evaluated by two researchers based on the established screening criteria. The data will then be extracted. Bias will assess for all included studies using the Cochrane Risk of Bias Risk Assessment Tool Version 2 (ROB 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 (CINeMA).

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

anesthesia.

- Only RCTs will be included in this study, and the primary outcome is the incidence of cough during tracheal extubation.
- We will evaluate the quality and assess the risk of bias of 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 anesthesia.[1] During recovery from general anesthesia, patients often experience coughing during extubation, occurring in approximately 15–94% of patients.[2,3] The wide variation observed was associated with the preventive interventions used. Although it is a protective reflex, coughing can lead to adverse effects such as hypertension and tachycardia[4,5], which can cause hemodynamic changes. The changes can alter the intracranial or intraocular pressure, potentially resulting in adverse postoperative outcomes like cerebral hemorrhage or herniation.[6,7]

Various techniques have been studied to manage this issue, including pharmacologic (e.g., use of topical or intravenous lidocaine, dexmedetomidine, remifentanil, fentanyl) and nonpharmacologic (e.g., extubation in the prone position) methods.[8-12] These techniques work by reducing the local or systemic stress response, thereby inhibiting 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 anesthesia with controls found that local endotracheal anesthesia significantly reduced immediate cough during extubation compared to placebo.[16] 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]Although these studies have compared several pharmacologic interventions to reduce emergence cough after general anesthesia, many other clinical pharmacologic interventions, such as alfentanil[18], tramadol[19],sulgamonol sodium[20], oxycodone[21], as well as other non-pharmacological interventions like body position adjustment during extubation[11] and nerve block[12] were not included or analyzed.

To determine the relative efficacies of pharmacological and non-pharmacological interventions, we will conduct this systematic review and network meta-analysis to compare the effects of all interventions that may reduce the incidence or severity of cough during extubation under general anesthesia.

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.

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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 Supplementary 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 ClinicalTrial Registry for ongoing studies. In previous studies, we will re-evaluate unused subject headings or free-text words related to coughing or extubation. 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 RCTs, 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 anesthesia with endotracheal intubation and were extubated in 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)=no coughing or muscular stiffness ; grade 2(mild)=coughing once or twice,or transient cough response to removal of tracheal tube that resolved with extubation; grade 3(moderate)=≤3 coughs lasting 1-2s , or total duration of coughing last ≤5s ; grade 4(severe)=≥4 coughs with each lasting>2s , total duration of coughing last >5s) .[23]

The secondary outcomes are: (1) the incidence of severe coughing (grade 4); (2) the incidence of other types of postoperative airway complications, such as laryngospasm, apnea, hypoxemia, 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 BPM), hypotension or allergic reactions,[24] which will be evaluated within 24 hours from the start of the drug to the postoperative period; (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 (Supplementary 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 (Supplementary file 3). A third researcher (LY) will verify the results.

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Data synthesis

We plan to use the relative risk (RR) between the intervention and control groups to estimate the incidence of coughing or severe coughing, and calculate the 95% confidence intervals (95%CI). For continuous variables, such as the time from the end of surgery to extubation , we plan to use the mean difference (MD) and calculate the 95% confidence interval (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 is beyond the range explained by the 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 anesthetics 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 (CINeMA), which includes six domains: (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.

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Authors' contributors

DY and LY conceived and designed the study. LY developed the search strategy. ZG, YX, DY, QL and LY drafted the manuscript. All the authors have agreed to submit this article for publication.

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Competing interests statement

None to declare.

Patient consent for publication

Not applicable.

Search Strategy

1. Search strategy via OVID (MEDLINE, Cochrane and Embase)

(1). cough/

(2). cough.mp

(3). 1 or 2

(4). extubation.mp

(5). ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.

(6). (3) and (4) and (5)

2. CNKI search strategy

(篇关摘：拔管期呛咳 or 苏醒期呛咳 or 呛咳) * （麻醉+拔管）

3. Wanfang search strategy

（主题：（拔管期呛咳 or 苏醒期呛咳 or 呛咳)）and （主题（麻醉 and 拔管）

Study selection form

first author	Journal/Conference Proceedings / Gray Literature/Reference in published papers	Year	Study eligibility					NOTE(IN OR EX)	Freehand space for comments on study design and treatment
			RCT	Relevant participants	Relevant interventions	Relevant comparisons	Relevant outcomes		

Data Extraction Form

Paper code:

Participant characteristics	
	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers / %, etc)	
Past medical history（especially trachea or lung disease）	
History of smoking	
Surgery procedure	
Length of surgery	
Anesthetics used during surgery (drug/dose)	
Other (mentioned in the article and not included in the above content)	

Trial characteristics	
	Further details
Single centre / Multicentre	
Country / Countries	
How many people were randomized?	
Number of participants in intervention group/control group	/
Number of participants who received intended treatment	
Number of participants who were analysed	
Intervention (name/dose/route)	
Comparison (name/dose/route)	
Trial design (e.g. parallel / cross-over)	
Other	

Data extraction

Outcomes	**Reported in paper (circle)**
Primary outcome	
Outcome 1 – incidence of cough during tracheal extubation.	Yes / No
Secondary outcomes	
Outcome 1 - incidence of other types of postoperative airway complications.	Yes / No
Outcome 2 - The side effects related to the interventions.	Yes / No

Outcome 3 - The time from the end of the surgery to the extubation of the endotracheal tube.	Yes / No
Subgroups	**Reported in paper**
Age	
Sex	
surgical procedure	
anesthetics used during surgery	

For Continuous data							
Paper code	Outcomes	Unit of measurement	Intervention group		Control group		Details if outcome only described in text
			n	Mean (MD)	n	Mean (MD)	
	The time from the end of the surgery to the extubation of the endotracheal tube						

For Dichotomous data			
Paper code	Outcomes	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events
	incidence of cough during tracheal extubation		
	incidence of other types of postoperative airway complications		
	The side effects related to the interventions		

Other information which you feel is relevant to the results Indicate whether the data was obtained from the first author. If the results were estimated by charts or calculated by formulas (as described in the article) and not reported in the article, it should be stated here.

Freehand space for writing actions such as contact with study authors and changes

References to other trials

Did this report include any references to published reports **of potentially eligible trials not already identified for this review?**		
First author	**Journal / Conference**	**Year of publication**
Did this report include any references to unpublished data **from potentially eligible trials not already identified for this review? If yes, give list contact name and details**		

BMJ Open

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

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

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Abstract

Introduction: Coughing during extubation can lead to several postoperative complications, including surgical site bleeding, intracranial hypertension, and high intraocular pressure. Currently, many interventions, both pharmacological and non-pharmacological interventions, are used in clinical practice to reduce coughing at extubation. However, it is unclear which of these interventions has the best preventive effect and 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 randomized controlled trials (RCTs) , regardless of publication in any language. The primary outcome is the incidence of cough during extubation, using the modified Minogue scales. And 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, apnea, hypoxemia, 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 BPM), hypotension or allergic reactions,[24] which will be evaluated within 24 hours from the start of the drug to the postoperative period; (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 assess for all included studies using the Cochrane Risk of Bias Risk Assessment Tool Version 2 (ROB 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 (CINeMA).

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 anesthesia.
- Only RCTs 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 of 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 anesthesia.[1] During recovery from general anesthesia, patients often experience coughing during extubation, occurring in approximately 15–94% of patients.[2,3] The wide variation observed was associated with the different preventive interventions (pharmacologic or nonpharmacologic) used. Although it is a protective reflex, coughing can lead to adverse effects such as hypertension and tachycardia[4,5], which can cause hemodynamic changes. The changes can alter the intracranial or intraocular pressure, potentially resulting in adverse postoperative outcomes like cerebral hemorrhage or herniation.[6,7]

Various techniques have been studied to manage this issue, including pharmacologic (e.g., use of topical or intravenous lidocaine, dexmedetomidine, remifentanil, fentanyl) and nonpharmacologic (e.g., extubation in the prone position) methods.[8-12] These techniques work by reducing the local or systemic stress response, thereby minimizing 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 anesthesia with controls (placebo or no medication) found that local endotracheal anesthesia significantly reduced immediate cough during extubation compared to placebo.[16] However, the comparison was limited to local anesthetics for tracheal intubation, and the control group received either a placebo or no treatment at all. It is impossible to discern any differences in the effects of the drug when compared to 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] As previously mentioned, dexmedetomidine has the capability to induce prolonged sedation or bradycardia.

Although these meta-analysis have compared several pharmacologic interventions to reduce emergence cough after general anesthesia, a considerable number of other clinical pharmacological interventions were excluded from the analysis. These exclusive interventions included such drugs as alfentanil[18], tramadol[19],sulgamonol sodium[20], oxycodone[21],.As well as a number of non-pharmacological interventions such as body position adjustment during extubation[11] and nerve block[12] were not included in the analysis. 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, 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 anesthesia.

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 Supplementary 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 ClinicalTrial Registry for ongoing studies. A reassessment of the subject headings and free-text terms related to coughing or extubation, which have not been utilised, 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 RCTs, 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 anesthesia with endotracheal intubation and were extubated in 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 1-2s , or total duration of coughing last ≤5s ; grade 4(severe cough) means ≥4 coughs with each lasting≥2s , total duration of coughing last >5s) .[23]

The secondary outcomes are: (1) the incidence of severe coughing (grade 4); (2) the incidence of other types of postoperative airway complications, such as laryngospasm, apnea, hypoxemia, 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 BPM), hypotension or allergic reactions,[24] which will be evaluated within 24 hours from the start of the drug to the postoperative period; (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 (Supplementary 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 (Supplementary file 3). A third researcher (LY) 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 (ROB 2) from the Cochrane Handbook for Systematic Reviews of Interventions[25], which includes the following five domains: bias arising from the randomization 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 (RR) between the intervention and control groups to estimate the incidence of coughing or severe coughing, and calculate the 95% confidence intervals (95%CI). For continuous variables, such as the time from the end of surgery to extubation , we plan to use the mean difference (MD) and calculate the 95% confidence interval (95%CI).

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Authors' contributors

DY and Longjun Yang conceived and designed the study. Lei Yang developed the search strategy. ZG, YX, DY, QL and Lei Yang drafted the manuscript. All the authors have agreed to submit this article for publication. Lei Yang is the guarantor. All the authors have agreed to submit this article for publication.

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Competing interests statement

None to declare.

Patient consent for publication

Not applicable.

Search Strategy

1. Search strategy via OVID (MEDLINE, Cochrane and Embase)

(1). cough/

(2). cough.mp

(3). 1 or 2

(4). extubation.mp

(5). ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.

(6). (3) and (4) and (5)

2. CNKI search strategy

(篇关摘：拔管期呛咳 or 苏醒期呛咳 or 呛咳) * （麻醉+拔管）

3. Wanfang search strategy

（主题：（拔管期呛咳 or 苏醒期呛咳 or 呛咳)）and （主题（麻醉 and 拔管）

Study selection form

first author	Journal/Conference Proceedings / Gray Literature/Reference in published papers	Year	Study eligibility					NOTE(IN OR EX)	Freehand space for comments on study design and treatment
			RCT	Relevant participants	Relevant interventions	Relevant comparisons	Relevant outcomes		

Data Extraction Form

Paper code:

Participant characteristics	
	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers / %, etc)	
Past medical history（especially trachea or lung disease）	
History of smoking	
Surgery procedure	
Length of surgery	
Anesthetics used during surgery (drug/dose)	
Other (mentioned in the article and not included in the above content)	

Trial characteristics	
	Further details
Single centre / Multicentre	
Country / Countries	
How many people were randomized?	
Number of participants in intervention group/control group	/
Number of participants who received intended treatment	
Number of participants who were analysed	
Intervention (name/dose/route)	
Comparison (name/dose/route)	
Trial design (e.g. parallel / cross-over)	
Other	

Data extraction

Outcomes	**Reported in paper (circle)**
Primary outcome	
Outcome 1 – incidence of cough during tracheal extubation.	Yes / No
Secondary outcomes	
Outcome 1 - incidence of other types of postoperative airway complications.	Yes / No
Outcome 2 - The side effects related to the interventions.	Yes / No

Outcome 3 - The time from the end of the surgery to the extubation of the endotracheal tube.	Yes / No
Subgroups	**Reported in paper**
Age	
Sex	
surgical procedure	
anesthetics used during surgery	

For Continuous data							
Paper code	Outcomes	Unit of measurement	Intervention group		Control group		Details if outcome only described in text
			n	Mean (MD)	n	Mean (MD)	
	The time from the end of the surgery to the extubation of the endotracheal tube						

For Dichotomous data			
Paper code	Outcomes	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events
	incidence of cough during tracheal extubation		
	incidence of other types of postoperative airway complications		
	The side effects related to the interventions		

Other information which you feel is relevant to the results Indicate whether the data was obtained from the first author. If the results were estimated by charts or calculated by formulas (as described in the article) and not reported in the article, it should be stated here.

Freehand space for writing actions such as contact with study authors and changes

References to other trials

Did this report include any references to published reports **of potentially eligible trials not already identified for this review?**		
First author	**Journal / Conference**	**Year of publication**
Did this report include any references to unpublished data **from potentially eligible trials not already identified for this review? If yes, give list contact name and details**		

BMJ Open

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

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

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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 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 randomized controlled trials (RCTs) , regardless of publication in any language. The primary outcome is the incidence of cough during extubation, using the modified Minogue scales. And 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, apnea, hypoxemia, 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 BPM), hypotension or allergic reactions,[24] which will be evaluated within 24 hours from the start of the drug to the postoperative period; (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 assess for all included studies using the Cochrane Risk of Bias Risk Assessment Tool Version 2 (ROB 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 (CINeMA).

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 anesthesia.
- Only RCTs 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 of 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 anesthesia. [1] During recovery from general anesthesia, 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 hemodynamic changes. The changes can alter the intracranial or intraocular pressure, potentially resulting in adverse postoperative outcomes like cerebral hemorrhage or herniation.[6,7]

Various techniques have been studied to manage this issue, including pharmacologic (e.g., use of topical or intravenous lidocaine, dexmedetomidine, remifentanil, fentanyl) and nonpharmacologic (e.g., extubation in the prone position) methods.[8-12] These techniques work by reducing the local or systemic stress response, thereby minimizing 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 anesthesia with controls (placebo or no medication) found that local endotracheal anesthesia significantly reduced immediate cough during extubation compared to placebo.[16] However, the comparison was limited to local anesthetics 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 anesthetic drugs when compared to 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-analysis have compared several pharmacologic interventions to reduce emergence cough after general anesthesia, a considerable number of other clinical pharmacological interventions were excluded from the analysis. These exclusive interventions included such drugs (i.e., alfentanil[18], tramadol[19], sulgamonol sodium[20], and oxycodone[21]) and non-pharmacological interventions (i.e., 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, 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 anesthesia.

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 Supplementary 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 ClinicalTrial Registry for ongoing studies. A reassessment of the subject headings and free-text terms related to coughing or extubation, which have not been utilised, 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 randomized controlled trials（RCTs), 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 anesthesia with endotracheal intubation and were extubated in 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 1-2s，or total duration of coughing last ≤5s；grade 4(severe cough) means ≥4 coughs with each lasting≥2s，total duration of coughing last >5s）.[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: (1) the incidence of severe coughing (grade 4); (2) the incidence of other types of postoperative airway complications, such as laryngospasm, apnea, hypoxemia, 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 BPM), hypotension or allergic reactions,[24] which will be evaluated within 24 hours from the start of the drug to the postoperative period; (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 (Supplementary 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 (Supplementary file 3). A third researcher (LY) 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 (ROB 2) from the Cochrane Handbook for Systematic Reviews of Interventions[25], which includes the following five domains: bias arising from the randomization 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 (RR) between the intervention and control groups to estimate the incidence of coughing or severe coughing, and calculate the 95%

confidence intervals (95%CI). For continuous variables, such as the time from the end of surgery to extubation, we plan to use the mean difference (MD) and calculate the 95% confidence interval (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 is beyond the range explained by the 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 anesthetics 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 (CINeMA), which includes six domains: (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.

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Authors' contributors

DY and Longjun Yang conceived and designed the study. Lei Yang developed the search strategy. ZG, YX, DY, QL and Lei Yang drafted the manuscript. All the authors have agreed to submit this article for publication. Lei Yang is the guarantor. All the authors have agreed to submit this article for publication.

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Competing interests statement

No competing interests are present.

Patient consent for publication

Not applicable.

Search Strategy

1. Search strategy via OVID (MEDLINE, Cochrane and Embase)

(1). cough/

(2). cough.mp

(3). 1 or 2

(4). extubation.mp

(5). ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.

(6). (3) and (4) and (5)

2. CNKI search strategy

(篇关摘：拔管期呛咳 or 苏醒期呛咳 or 呛咳) * （麻醉+拔管）

3. Wanfang search strategy

（主题：（拔管期呛咳 or 苏醒期呛咳 or 呛咳)）and （主题（麻醉 and 拔管）

Study selection form

first author	Journal/Conference Proceedings / Gray Literature/Reference in published papers	Year	Study eligibility					NOTE(IN OR EX)	Freehand space for comments on study design and treatment
			RCT	Relevant participants	Relevant interventions	Relevant comparisons	Relevant outcomes		

Data Extraction Form

Paper code:

Participant characteristics	
	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers / %, etc)	
Past medical history（especially trachea or lung disease）	
History of smoking	
Surgery procedure	
Length of surgery	
Anesthetics used during surgery (drug/dose)	
Other (mentioned in the article and not included in the above content)	

Trial characteristics	
	Further details
Single centre / Multicentre	
Country / Countries	
How many people were randomized?	
Number of participants in intervention group/control group	/
Number of participants who received intended treatment	
Number of participants who were analysed	
Intervention (name/dose/route)	
Comparison (name/dose/route)	
Trial design (e.g. parallel / cross-over)	
Other	

Data extraction

Outcomes	**Reported in paper (circle)**
Primary outcome	
Outcome 1 – incidence of cough during tracheal extubation.	Yes / No
Secondary outcomes	
Outcome 1 - incidence of other types of postoperative airway complications.	Yes / No
Outcome 2 - The side effects related to the interventions.	Yes / No

Outcome 3 - The time from the end of the surgery to the extubation of the endotracheal tube.	Yes / No
Subgroups	**Reported in paper**
Age	
Sex	
surgical procedure	
anesthetics used during surgery	

For Continuous data							
Paper code	Outcomes	Unit of measurement	Intervention group		Control group		Details if outcome only described in text
			n	Mean (MD)	n	Mean (MD)	
	The time from the end of the surgery to the extubation of the endotracheal tube						

For Dichotomous data			
Paper code	Outcomes	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events
	incidence of cough during tracheal extubation		
	incidence of other types of postoperative airway complications		
	The side effects related to the interventions		

Other information which you feel is relevant to the results Indicate whether the data was obtained from the first author. If the results were estimated by charts or calculated by formulas (as described in the article) and not reported in the article, it should be stated here.

Freehand space for writing actions such as contact with study authors and changes

References to other trials

Did this report include any references to published reports **of potentially eligible trials not already identified for this review?**		
First author	**Journal / Conference**	**Year of publication**
Did this report include any references to unpublished data **from potentially eligible trials not already identified for this review? If yes, give list contact name and details**		