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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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Keywords:	Adult anaesthesia < ANAESTHETICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Meta-Analysis, Systematic Review



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3 4	1	Interventions for prevention of cough reflex during extubation: A
5	2	protocol for a systematic review and network meta-analysis
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7	4	Zhichao Gong ^{1,2#} , Yixuan Wu ^{2#} , Di Yang ^{2,3} , Qian Li ² , Longjun Yang ^{1*} , Lei Yang ^{2*}
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19 20	13	
20	14	Abstract
22	15	Introduction: Coughing during extubation can lead to several postoperative
23	16	complications, including surgical site bleeding, intracranial hypertension, and high
24 25	17	intraocular pressure. Currently, many interventions, both pharmacological and non-
25 26	18	pharmacological interventions, are used in clinical practice to reduce coughing at
27	19	extubation. However, it is unclear which of these interventions has the best preventive
28	20	effect and fewest adverse events. Therefore, we plan to conduct a systematic review
29	21	and network meta-analysis to compare the effects of all interventions.
30 21	22	Methods and analysis: We will search Medline. Embase. Cochrane Central Register
31	23	of Controlled Trials CNKL and Wanfang databases from the date of their incention to
33	24	March 5, 2023. We will only include RCTs regardless of publication in any language
34	27	The primary outcome is the incidence of couch during extubation. Bias will assess for
35	20	The primary outcome is the incidence of cough during exiduation. Dias will assess for
36 27	20	all included studies using the Cochrane Risk of Blas Risk Assessment Tool version 2
38	27	(ROB 2). We will use the Netmeta package of the R software with a random-effects
39	28	model to make direct and indirect comparisons through the frequency framework. We
40	29	will assess the quality of evidence using Confidence in Network Meta-Analysis
41	30	(CINeMA).
42 43	31	Ethics and dissemination: Ethical approval is not required for this protocol, as we
44	32	will only pool published data. We plan to submit our manuscript for publication in a
45	33	peer-reviewed academic journal.
46		
47	34	PROSPERO registration number CRD42023401609.
48 49	35	
50	36	Strengths and limitations of this study
51	37	• We will comprehensively compare pharmacological and non-pharmacological
52	30	• we will complete ensively compare pharmacological and non-pharmacological interventions that may reduce or alleviate coupling during extubation after general
53 54	20	interventions that may reduce of aneviate cougning during extubation after general
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56	40	• Only RC1s will be included in this study, and the primary outcome is the incidence
57	41	of cough during tracheal extubation.
58	42	• We will evaluate the quality and assess the risk of bias of all included studies.
59 60	43	• Although a subgroup analysis is planned, differences in outcomes, such as surgical
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 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 extubation¹³ and nerve block¹⁴ 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 metaanalysis to compare the effects of all interventions that may reduce the incidence or severity of cough during extubation under general anesthesia.

75 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

46
4780Patient and public involvement

81 The patients and the public had no role in the design, conduct, reporting, or

82 dissemination of the study.

83 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) For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

from the Cochrane Handbook for Systematic Reviews of Interventions¹⁸, 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 l^2 statistics. When $l^2 > 50\%$, 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

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ETHICS AND DISSEMINATION

180 181 182 183	Etl pla	hical approval was not required for this study, as we only pooled published data. We an to present our review at academic conferences and in peer-reviewed journals.
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10	250	2020, 17.e 1003062. doi. 10. 137 1/journal.pmed. 1003062.
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12	252	We would like to thank Adham (www.editage.com) for English language editing
13	252	
14	255	
15 16	254	Authors' contributors
10	255	DY and LY conceived and designed the study. LY developed the search strategy. ZG,
18	256	YX, DY, QL and LY drafted the manuscript. All the authors have agreed to submit this
19	257	article for publication.
20	258	
21	200	Funding statement
22	259	
23	260	This research was supported by the Key Research and Development Project of the Ministry
24	261	of Science and Technology of Sichuan Province (No. 2023YFS0139).
25 26	262	
20	263	Competing interests statement
28	264	None to declare
29	265	
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31	266	Patient consent for publication
32	267	Not applicable.
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Page 11 of	14				BMJ Open		jopen-20 1 by cop			
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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 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	
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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	Yes / No				
complications.					
Outcome 2 - The side effects related to the interventions.	Yes / No				

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Outcome 3 - The time from the end of the surgery to the extubation of	Yes / No
the endotracheal tube.	
Subgroups	Reported in paper
Age	
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For Continuous data							
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Paper	Outcomes	Intervention group (n)	Control group (n)
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		n = number of	n = number of
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	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.

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References to other trials

Did this report include any references to published reports of potentially eligible trials not					
already identified for	already identified for this review?				
First author	Journal / Conference Year of publication				
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The effectiveness of different pharmacological or nonpharmacological interventions on preventing coughing during extubation : A protocol for a systematic review and network meta-analysis

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SCHOLARONE[™] Manuscripts

1	The effectiveness of different pharmacological or non-pharmacological
2	interventions on preventing coughing during extubation : A protocol for
3	a systematic review and network meta-analysis
4	
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14	
15	Abstract
16	Introduction: Coughing during extubation can lead to several postoperative
17	complications, including surgical site bleeding, intracranial hypertension, and high
18	intraocular pressure. Currently, many interventions, both pharmacological and non-
19	pharmacological interventions, are used in clinical practice to reduce coughing at
20	extubation. However, it is unclear which of these interventions has the best preventive
21	effect and fewest adverse events. Therefore, we plan to conduct a systematic review
22	and network meta-analysis to compare the effects of all interventions.
23	Methods and analysis: we will search Mediline, Embase, web of Science, Cochrane
:4)5	central Register of Controlled Thats, CINRI, and Walliang databases, as well as
20	April 2024 We will only include PCTs, regardless of publication in any language. The
<u>-0</u> 27	primary outcome is the incidence of cough during extubation using the modified
28	Minoque scales. The literature that meets the inclusion criteria will be independently
29	evaluated by two researchers based on the established screening criteria. The data
30	will then be extracted. Bias will assess for all included studies using the Cochrane Risk
31	of Bias Risk Assessment Tool Version 2 (ROB 2). We will use the Netmeta package
32	of the R software with a random-effects model to make direct and indirect comparisons
33	through the frequency framework. We will assess the quality of evidence using
34	Confidence in Network Meta-Analysis (CINeMA).
35	Ethics and dissemination: Ethical approval is not required for this protocol, as we
36	will only pool published data. We plan to submit our manuscript for publication in a
37	peer-reviewed academic journal.
38	PROSPERO registration number CRD42023401609.
39	
40	Strengths and limitations of this study
.5 41	• We will comprehensively compare pharmacological and non-pharmacological
	- win comprehensivery compare pharmacological and non-pharmacological

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2		
3	43	anesthesia.
4 5	44	• Only RCTs will be included in this study, and the primary outcome is the incidence
6	45	of cough during tracheal extubation.
7	46	• We will evaluate the quality and assess the risk of hias of all included studies
8	47	Although a subgroup analysis is planned, the notantial betargeneity segret be
9	47	Annough a subgroup analysis is planned, the potential neterogeneity cannot be
10	48	completely eliminated.
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lidocaine.

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

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

dexmedetomidine had the highest cumulative reduction in the incidence of severe

cough at extubation. ¹⁷Although these studies have compared several pharmacologic

interventions to reduce emergence cough after general anesthesia, many other clinical

pharmacologic interventions, such as alfentanil¹⁸, tramadol¹⁹, sulgamonol sodium²⁰,

oxycodone²¹, as well as other non-pharmacological interventions like body position

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

adjustment during extubation¹¹ and nerve block¹² were not included or analyzed.

and

remifentanil)

concluded

that

fentanyl

Various techniques have been studied to manage this issue, including

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outcomes like cerebral hemorrhage or herniation.6,7

dexmedetomidine,

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

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94	language of retrieval is not limited. The search period for all databases will be limited
95	to the period from the date of database establishment to April, 2024. The original
96	keywords are "cough" and "extubation," and the details of the original search strategy
97	are presented in Supplementary file 1. In addition, we will search for conference papers
98	via SCOPUS by restricting the "source type" to "conference proceedings." At the same
99	time, we will search ClinicalTrials.gov and the Chinese ClinicalTrial Registry for
100	ongoing studies. In previous studies, we will re-evaluate unused subject headings or
101	free-text words related to coughing or extubation. Newly identified subject headings
102	and free-text words will be added to the modified search strategy. The final version of
103	the search strategy will be reported in our review.
104	Eligibility criteria
105	Types of study
106	We will include only RCTs, regardless of language or publication status. Conference
107	abstracts will also be included if they have sufficient data.
108	Types of participants
109	We will include all adult patients (≥18 years old) who received general anesthesia
110	with endotracheal intubation and were extubated in operating room, regardless of the
111	type of surgery performed.
112	Types of interventions
113	We will include all interventions to prevent postoperative cough, including
114	pharmacological treatments such as intravenous medications and local medications
115	and non-pharmacological treatments such as adjustment of body position during
116	extubation.
117	Types of comparisons
118	We will compare the different interventions or placebo.
119	Types of outcomes
120	The primary outcome is the incidence of coughing during tracheal extubation. We will
121	define the incidence of cough using the modified Minogue scale (grade 1(none)=no
122	coughing or muscular stiffness ; grade 2(mild)=coughing once or twice,or transient
123	cough response to removal of tracheal tube that resolved with extubation; grade
104	2(moderate)=<2 equate leating 1.2e = extend duration of equation leat <5 + extends
124	3(moderate)=53 coughs lasting 1-2s, or total duration of coughing last 55s; grade
125	4(severe)=≥4 coughs with each lasting>2s , total duration of coughing last >5s) $.^{23}$
126	The secondary outcomes are: (1) the incidence of severe coughing (grade 4); (2)
127	the incidence of other types of postoperative airway complications, such as
128	laryngospasm, apnea, hypoxemia, and sore throat, which will be evaluated within 24
129	hours after surgery; (3) the side effects related to the interventions, such as
130	bradycardia (heart rate less than 60 BPM), hypotension or allergic reactions, ²⁴ which
131	will be evaluated within 24 hours from the start of the drug to the postoperative period;
132	(4) The time from the end of the surgery to the extubation of the endotracheal tube.
133	Study selection
	Δ

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.

15 143 Data extraction and quality assessment

16
 144 We will obtain and extract data from the full texts of all eligible studies. Two researchers
 145 (ZG and YW) will independently extract the data from the studies and enter them into
 146 a data extraction form (Supplementary file 3). A third researcher (LY) will verify the
 147 results.

Two researchers (ZG and YW) will independently assess the guality 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 Interventions²⁵, 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.

34
35158Data 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 I² 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 l^2 statistics. When $l^2 > 50\%$, 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

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3	178	during surgery. When patient characteristics, interventions, and outcomes are similar.
4	170	the transitivity between the study results will be considered. Based on previous studies
5	100	and proliminary acrossings, the number of studies is sufficient. We will draw a network
7	100	dia many science and a descent different as a sub-interneting, and a descent
8	181	diagram using nodes to represent different research interventions and edges to
9	182	represent head-to-head comparisons between network nodes. If there is an
10	183	inconsistency among three or more nodes in the loop, we will use the node splitting
11	184	method for evaluation. If the p-value is >0.05, the difference between the direct and
12	185	indirect comparisons will not be statistically significant. When the results are
13	186	inconsistent the results of direct comparison will be used as the estimated effect
14 15	100	
15	107	
10	188	Assessing the quality of evidence
18	189	We will grade the quality of evidence for network meta-analysis based on confidence
19	190	in Network Meta-Analysis (CINeMA), which includes six domains: (1) within-study bias,
20	191	(2) between-study bias. (3) indirectness. (4) imprecision. (5) heterogeneity, and (6)
21	192	inconsistency ²⁷
22	102	
23	193	
24 25	194	ETHICS AND DISSEMINATION
26	195	Ethical approval was not required for this study, as we only pooled published data. We
27	196	plan to present our review at academic conferences and in peer-reviewed journals.
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59 60	299	Acknowledgment
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6	302	Authors' contributors
7 9	303	DY and LY conceived and designed the study. LY developed the search strategy. ZG,
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16	310	and Technology Program (No. 2023ZYD0168).
17 19	311	
10	312	Competing interests statement
20	313	None to declare
21	314	
22 23	315	Patient consent for publication
23	316	Not applicable
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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)

Page 13 of	16				BMJ Open		ijopen∹ d by co		
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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	
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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 Yes / No				
complications.				
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	Yes / No
the endotracheal tube.	
Subgroups	Reported in paper
Age	
Sex	
surgical procedure	
anesthetics used during surgery	

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	The time from the end	I					
	of the surgery to the						
	extubation of the						
	endotracheal tube						

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

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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.

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References to other trials

References to other trial	ls	
Did this report include	any references to published reports o	f potentially eligible trials not
already identified for t	this review?	
First author	Journal / Conference	Year of publication
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Did this report include	any references to unpublished data fr	om potentially eligible trials not
already identified for t	this review? If yes, give list contact na	me and details
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The effectiveness of different pharmacological or nonpharmacological interventions on preventing coughing during extubation : A protocol for a systematic review and network meta-analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-081592.R2
Article Type:	Protocol
Date Submitted by the Author:	29-Aug-2024
Complete List of Authors:	GONG, ZHICHAO; Dongying People'Hospital, Anesthesiology; West China Hospital of Sichuan University, Anesthesiology Wu, Yixuan; Sichuan University, Department of Anesthesiology Yang, Di; Sichuan Academy of Medical Sciences and Sichuan People's Hospital, Anaesthesiology Li, Qian; Sichuan University, Yang, Longjun; Dongying People's Hospital, Department of Anesthesiology Yang, Lei; Sichuan University, Department of Anesthesiology
Primary Subject Heading :	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Adult anaesthesia < ANAESTHETICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Meta-Analysis, Systematic Review

SCHOLARONE[™] Manuscripts

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4	1	The effectiveness of different pharmacological or non-pharmacological
5 6	2	interventions on preventing coughing during extubation : A protocol for
7	3	a systematic review and network meta-analysis
8 9	4	
10	5	Zhichao Gong ^{1,2#} , Yixuan Wu ^{2#} , Di Yang ^{2,3} , Qian Li ² , Longjun Yang ^{1*} , Lei Yang ^{2*}
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17 18	11	*Contributed equally
19	12	*Correspondence to:
20	13	Dr Lei Yang yanglei.wcha@scu.edu.cn and Longjun Yang yljdy1978@sina.com
21	14	
22	15	Abstract
24	16	Introduction: Coughing during extubation can lead to several postoperative
25	17	complications, including surgical site bleeding, intracranial hypertension, and high
26 27	18	intraocular pressure. Currently, many interventions, both pharmacological and non-
28	19	pharmacological interventions, are used in clinical practice to reduce coughing at
29	20	extubation. However, it is unclear which of these interventions has the best preventive
30 21	21	effect and fewest adverse events. Therefore, we plan to conduct a systematic review
32	22	and network meta-analysis to compare the effects of all interventions.
33	23	Methods and analysis: We will search Medline, Embase, Web of Science, Cochrane
34	 24	Central Register of Controlled Trials, CNKI, and Wanfang databases, as well as
35 36	25	reference lists from previously published papers, from the date of their inception to
37		
38	26	April, 2024. We will only include randomized controlled trials (RCTs), regardless of
39 40	27	publication in any language. The primary outcome is the incidence of cough during
40	28	extubation, using the modified Minogue scales. And the secondary outcomes are as
42	29	follows: (1) the incidence of severe coughing (grade 4): (2) the incidence of other types
43	30	of postoperative airway complications, such as larvngospasm, appea, hypoxemia, and
44 45	31	sore throat, which will be evaluated within 24 hours after surgery: (3) the side effects
46	32	related to the interventions, such as bradycardia (heart rate less than 60 BPM).
47	33	hypotension or allergic reactions ²⁴ which will be evaluated within 24 hours from the
48 40	34	start of the drug to the postoperative period: (4) The time from the end of the surgery
49 50	35	to the extubation of the endotracheal tube. The articles meeting the criteria will be
51	36	independently evaluated by two researchers based on the established screening
52	37	criteria. The data will then be extracted. Rias will assess for all included studies using
53 54	38	the Cochrane Risk of Rias Risk Assessment Tool Version 2 (ROR 2). We will use the
55	30	Netmeta nackage of the R software with a random-effects model to make direct and
56	<u>4</u> 0	indirect comparisons through the frequency framework. We will assess the quality of
57 58	 ⊿1	evidence using Confidence in Network Meta-Analysis (CINeMA)
59	יד 10	Ethics and dissemination: Ethical approval is not required for this protocol, as we
60	42	Lines and dissemination. Ethical approval is not required for this protocol, as we

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 43 will only pool published data. We plan to submit our manuscript for publication in a44 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.

57 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

61 observed was associated with the different preventive interventions (pharmacologic

62 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 metaanalysis 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.

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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 alfentanil¹⁸, tramadol¹⁹,sulgamonol sodium²⁰, oxycodone²¹,.As well as a number of non-pharmacological interventions such as body position adjustment during extubation¹¹ and nerve block¹² were not

51 91 included in the analysis. We do not have sufficient evidence to show whether these

92 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.

3	98	
4 5	99	METHODS
5 6	100	The study protocol (registration number: CRD42023401609) was registered with the
7	100	International Prospective Register of Systematic Reviews. The study protocol will be
8	107	nublished in accordance with the Preferred Penorting Items for Systematic Peviews
9	102	and Mate Analyzes guidelines 22
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12	104	
13	105	I ne patients and the public had no role in the design, conduct, reporting, or
14	106	dissemination of the study.
15 16	107	Data sources and searches
10	108	We will search the following databases: MEDLINE, EMBASE, Web of Science, the
18	109	Cochrane Central Register of Controlled Trials via OVID, the Chinese databases
19	110	CNKI and Wanfang, as well as reference lists from previously published papers. The
20	111	language of retrieval is not limited. The search period for all databases will be limited
21 22	112	to the period from the date of database establishment to April, 2024. The original
23	113	keywords are "cough" and "extubation," and the details of the original search strategy
24	114	are presented in Supplementary file 1. In addition, we will search for conference papers
25	115	via SCOPUS by restricting the "source type" to "conference proceedings." At the same
26 27	116	time, we will search ClinicalTrials.gov and the Chinese ClinicalTrial Registry for
28	117	ongoing studies A reassessment of the subject headings and free-text terms related
29	118	to coughing or extubation, which have not been utilised will be conducted. Newly
30	110	identified subject headings and free text words will be added to the modified search
31	120	strategy. The final version of the search strategy will be reported in our review
33	120	Eligibility oritorio
34	121	
35	122	Types of study
36 27	123	we will include only RCTs, regardless of language or publication status. Conference
37 38	124	abstracts will also be included if they have sufficient data.
39	125	Types of participants
40	126	We will include all adult patients (≥18 years old) who received general anesthesia
41	127	with endotracheal intubation and were extubated in operating room, regardless of the
42 43	128	type of surgery performed.
44	129	Types of interventions
45	130	We will include all interventions to prevent postoperative cough, including
46	131	pharmacological treatments such as intravenous medications and local medications
47 48	132	and non-pharmacological treatments such as adjustment of body position during
49	133	extubation.
50	134	Types of comparisons
51	135	We will compare the different interventions or placebo.
52 53	136	Types of outcomes
55	137	The primary outcome is the incidence of coughing during tracheal extubation. We will
55	157	The primary outcome is the incidence of coughing during trachear extubation. We will
56	138	define the incidence of cough using the modified Minogue scale (grade 1(none
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59	139	cough)means no coughing or muscular stiffness; grade 2(mild cough) means
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140 coughing once or twice; grade 3(moderate cough) means \leq 3 coughs lasting 1-2s,

- 141 or total duration of coughing last ≤5s ; grade 4(severe cough) means ≥4 coughs
- 142 with each lasting $\geq 2s$, total duration of coughing last $\geq 5s$).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.

⁾ 150 **Study selection**

All abstracts will be independently reviewed by two researchers (ZG and YW) to 151 determine their eligibility. The full text will be reviewed if the abstract does not provide 152 153 sufficient information to determine eligibility. In the event that two researchers diverge 154 in their opinions regarding the suitability of including literature in the review, the full text 155 will be re-reviewed by a third researcher, who will then make the decision on the 156 inclusion of literature. Two researchers (ZG and YW) independently completed 157 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 158 159 the review.

³ 160 **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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165 Two researchers (ZG and YW) will independently assess the quality of all included 166 studies using the Cochrane Risk of Bias Risk Assessment Tool Version 2 (ROB 2) 167 from the Cochrane Handbook for Systematic Reviews of Interventions²⁵, which 168 includes the following five domains: bias arising from the randomization process, bias 169 due to deviations from the intended interventions, bias due to missing outcome data, 170 bias in the measurement of the outcome, and bias in the selection of reported results. 171 Each domain will be assigned a risk of bias level, which is one of the following: low risk 172 of bias, some concerns, or high risk of bias. Disagreements will be resolved through 173 discussion. In this review, we will report the risk of bias table and the risk of bias 174 summary figure.

175 Data synthesis

176 We plan to use the relative risk (RR) between the intervention and control groups to 55 177 estimate the incidence of coughing or severe coughing, and calculate the 95% 56 178 confidence intervals (95%CI). For continuous variables, such as the time from the end 57 179 58 of surgery to extubation, we plan to use the mean difference (MD) and calculate the 59 180 95% confidence interval (95%CI). 60

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

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

 l^2 statistics. When $l^2 > 50\%$, 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

We will use statistical methods (Q statistics and I² statistics) to test the

generate a funnel plot to assess publication bias.²⁶

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- 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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25 26	319	Authors' contributors
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28	321	strategy, ZG, YX, DY, QL and Lei Yang drafted the manuscript. All the authors have
29	322	agreed to submit this article for publication. Lei Yang is the guarantor. All the authors
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39	330	Competing interests statement
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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)

Page 13 of	16				BMJ Open		ijopen∹ d by co		
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43 44 45 46			Fo	or peer review only - h	ttp://bmjopen.bmj.com/s	ite/about/guidelines.xh	tml d		

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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	
1	

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	Yes / No				
complications.					
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	Yes / No
the endotracheal tube.	
Subgroups	Reported in paper
Age	
Sex	
surgical procedure	
anesthetics used during surgery	

For Continuous data							
			Int	tervention	Сс	ontrol	Details if
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Paper		Unit of					described in
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	extubation of the						
	endotracheal tube						

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

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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

eferences to other trials					
Did this report include any references to published reports of potentially eligible trials not					
already identified for t	this review?				
First author	Journal / Conference	Year of publication			
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Did this report include any references to unpublished data from potentially eligible trials not					
already identified for t	this review? If yes, give list contact na	me and details			
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The effectiveness of different pharmacological or nonpharmacological interventions on preventing coughing during extubation : A protocol for a systematic review and network meta-analysis

Journal:	BMJ Open
Manuscript ID	bmjopen-2023-081592.R3
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Date Submitted by the Author:	07-Oct-2024
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Primary Subject Heading :	Anaesthesia
Secondary Subject Heading:	Anaesthesia
Keywords:	Adult anaesthesia < ANAESTHETICS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Meta-Analysis, Systematic Review

SCHOLARONE[™] Manuscripts

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3	4	The offectiveness of different phermacelesical or per phermacelesical
4 5	1	The effectiveness of different pharmacological or non-pharmacological
6	2	interventions on preventing coughing during extubation : A protocol for
7	3	a systematic review and network meta-analysis
8	4	
9 10	5	Zhichao Gong ^{1,2#} , Yixuan Wu ^{2#} , Di Yang ^{2,3} , Qian Li ² , Longiun Yang ^{1*} , Lei Yang ^{2*}
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22	14	
23	15	Abstract
24 25	16	Introduction: Coughing during extubation can lead to several postoperative
25	17	complications, including surgical site bleeding, intracranial hypertension, and high
27	18	intraocular pressure. Currently, various pharmacological and non-pharmacological
28	19	interventions are employed in clinical practice to reduce coughing during extubation.
29	20	However, it is unclear which of these interventions has the best preventive effect and
30 31	21	fewest adverse events. Therefore, we plan to conduct a systematic review and network
32	22	meta-analysis to compare the effects of all interventions.
33	23	Methods and analysis: We will search Medline, Embase, Web of Science, Cochrane
34	24	Central Register of Controlled Trials, CNKI, and Wanfang databases, as well as
35 36	25	reference lists from previously published papers, from the date of their inception to
37		
38	26	April, 2024. We will only include randomized controlled trials (RCTs), regardless of
39	27	publication in any language. The primary outcome is the incidence of cough during
40 41	21	extubation using the modified Minoque scales. And the secondary outcomes are as
42	20	follows: (1) the incidence of severe coughing (grade 4): (2) the incidence of other types
43	29	onows. (1) the incidence of severe coughing (grade 4), (2) the incidence of other types
44	30	or postoperative all way complications, such as laryingospasm, apriea, hypoxemia, and
45 46	31	sore throat, which will be evaluated within 24 hours after surgery; (3) the side effects
40 47	32	related to the interventions, such as bradycardia (heart rate less than 60 BPM),
48	33	hypotension or allergic reactions, ²⁴ which will be evaluated within 24 hours from the
49	34	start of the drug to the postoperative period; (4) The time from the end of the surgery
50 51	35	to the extubation of the endotracheal tube. The articles meeting the criteria will be
52	36	independently evaluated by two researchers based on the established screening
53	37	criteria. The data will then be extracted. Bias will assess for all included studies using
54	38	the Cochrane Risk of Bias Risk Assessment Tool Version 2 (ROB 2). We will use the
55 56	39	Netmeta package of the R software with a random-effects model to make direct and
סכ 57	40	indirect comparisons through the frequency framework. We will assess the quality of
58	41	evidence using Confidence in Network Meta-Analysis (CINeMA).
59	42	Ethics and dissemination: Ethical approval is not required for this protocol, as we
60		

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 43 will only pool published data. We plan to submit our manuscript for publication in a44 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.

57 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 remiferitanil 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., alfentanil¹⁸, tramadol¹⁹, sulgamonol sodium²⁰, and oxycodone²¹) and non-pharmacological interventions (i.e., body position adjustment during extubation¹¹ and nerve block¹²). 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.

100 METHODS

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101 The study protocol (registration number: CRD42023401609) was registered with the 102 International Prospective Register of Systematic Reviews. The study protocol will be 103 published in accordance with the Preferred Reporting Items for Systematic Reviews 104 and Meta-Analyses guidelines.²²

- a 105 Patient and public involvement
- 105 Patient and public involvement 10 106 The patients and the public had no role in the design, conduct, reporting, or
- ¹¹ 107 dissemination of the study.

12
13108Data 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.

122 Eligibility criteria

123 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.

131 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

- 137 We will compare the different interventions or placebo.
- 138 Types of outcomes
 - 139 The primary outcome is the incidence of coughing during tracheal extubation. We will
- 55 140 define the incidence of cough using the modified Minogue scale (grade 1(none
 - 141 cough)means no coughing or muscular stiffness ; grade 2(mild cough) means

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142 coughing once or twice; grade 3(moderate cough) means ≤3 coughs lasting 1-2s, 143 or total duration of coughing last $\leq 5s$; grade 4(severe cough) means ≥ 4 coughs with each lasting≥2s, total duration of coughing last >5s).²³ If no direct data related 144 to the modified Minogue scale can be extracted from the study, we will attempt to 145 146 interpret the data from the original source using the descriptions provided or other 147 related measures of cough severity. The secondary outcomes are: (1) the incidence 148 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 149 be evaluated within 24 hours after surgery; (3) the side effects related to the 150 151 interventions, such as bradycardia (heart rate less than 60 BPM), hypotension or 152 allergic reactions,²⁴ which will be evaluated within 24 hours from the start of the drug 153 to the postoperative period; (4) The time from the end of the surgery to the extubation of the endotracheal tube. 154 155 Study selection All abstracts will be independently reviewed by two researchers (ZG and YW) to 156 157 determine their eligibility. The full text will be reviewed if the abstract does not provide 158 sufficient information to determine eligibility. In the event that two researchers diverge 159 in their opinions regarding the suitability of including literature in the review, the full text 160 will be re-reviewed by a third researcher, who will then make the decision on the 161 inclusion of literature. Two researchers (ZG and YW) independently completed 162 selection forms (Supplementary file 2). Disagreements after discussion will be decided 163 by a third person (DY). Finally, we will show all eligible studies that were included in 164 the review. 165 Data extraction and quality assessment 166 We will obtain and extract data from the full texts of all eligible studies. Two researchers 167 (ZG and YW) will independently extract the data from the studies and enter them into 168 a data extraction form (Supplementary file 3). A third researcher (LY) will verify the 169 results. 170 Two researchers (ZG and YW) will independently assess the quality of all included 171 studies using the Cochrane Risk of Bias Risk Assessment Tool Version 2 (ROB 2) 172 from the Cochrane Handbook for Systematic Reviews of Interventions²⁵, which 173 includes the following five domains: bias arising from the randomization process, bias 174 due to deviations from the intended interventions, bias due to missing outcome data, 175 bias in the measurement of the outcome, and bias in the selection of reported results. 176 Each domain will be assigned a risk of bias level, which is one of the following: low risk 177 of bias, some concerns, or high risk of bias. Disagreements will be resolved through 178 discussion. In this review, we will report the risk of bias table and the risk of bias 179 summary figure. 180 **Data synthesis**

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181 We plan to use the relative risk (RR) between the intervention and control groups to
 182 estimate the incidence of coughing or severe coughing, and calculate the 95%

183 confidence intervals (95%CI). For continuous variables, such as the time from the end
184 of surgery to extubation, we plan to use the mean difference (MD) and calculate the
185 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 I² 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 l^2 statistics. When $l^2 > 50\%$, 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.

³⁰ 210 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

46 216 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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44	330	No competing interests are present.
45 46	337	
47	338	Patient consent for publication
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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)

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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	
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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	Yes / No		
complications.			
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	Yes / No
the endotracheal tube.	
Subgroups	Reported in paper
Age	
Sex	
surgical procedure	
anesthetics used during surgery	

For Continuous data							
			Int	tervention	Сс	ontrol	Details if
			gr	oup	gr	oup	outcome only
Paper		Unit of					described in
code		measurement					text
	Outcomes		n	Mean	n	Mean	
				(MD)		(MD)	
	The time from the end	ł					
	of the surgery to the						
	extubation of the						
	endotracheal tube						

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

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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

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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				
	6					
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						