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Is dezocine effective and safe in preventing opioids-induced cough during general anaesthesia induction? A protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Cough is often observed when administrating a bolus of opioids. Opioid-induced cough (OIC) is mostly transient, benign and self-limiting, but could be associated with adverse effects. Numerous pharmacological and non-pharmacological interventions have been used to manage OIC with controversial efficacy and safety. Recent studies suggested that, pretreatment of intravenous dezocine (DZC) could completely suppress OIC during anaesthesia induction. To address this knowledge lack, we will perform a systemic review and meta-analysis to evaluate the efficacy of DZC on OIC and possible complications. We provide here a protocol that will outline the methods and analyses planned for the systematic review.

Methods PubMed, Embase, Cochrane Library, Web of Science as well as Chinese BioMedical Literature & Retrieval System (SinoMed), China National Knowledge Infrastructure, Wanfang Data and VIP Data will be searched from 1978 to 31 December 2019 to identify all randomised controlled trials comparing DZC with placebo on the incidence and severity of OIC. Primary outcomes of interest include the incidence and severity of OIC. Secondary outcomes of interest include possible complications or adverse effects of DZC. Two authors will independently extract relevant variables and outcome data. For continuous variables, treatment effects will be calculated as weighted mean difference and 95% CI. For dichotomous data, treatment effects will be calculated as OR and 95% CI. Each outcome will be tested for heterogeneity, and randomised-effects or fixed-effects model will be used in the presence or absence of significant heterogeneity. Sensitivity analyses will be done by examining the influence of statistical model and individual trial(s) on estimated treatment effects. Publication bias will be explored through visual inspection of funnel plots of the outcomes. Statistical significance will be defined as $p<0.05$.

Ethics and dissemination This study is a protocol of meta-analysis of previously published literatures, ethical approval was not necessary according to the Ethical Committee of Fuwai Hospital. The study will be submitted to a peer-reviewed journal and disseminated via research presentations.

PROSPERO registration number CRD42019141255.

Strengths and limitations of this study

- The protocol describes what will be the first systematic review to conduct a comprehensive assessment of the efficacy of dezocine on opioid-induced cough (OIC) and possible complications.
- The exclusion of trials absent of OIC incidence or placebo control group might leave relevant studies out of the review.
- The main limitation of this review is that varied quality and heterogeneity of included studies may limit the certainty of the findings of meta-analysis.

INTRODUCTION

Cough is often observed when administrating a bolus of opioids (eg, fentanyl,[1–4] sufentanil,[5–7] remifentanil,[8–13] alfentanil[14]), with the reported incidence ranging from 7% to 70%.[1–14] The mechanism of opioid-induced cough (OIC) is complex and remains poorly understood, which may involve pulmonary chemoreflex, enhanced activity of parasympathetic nerve, histamine release, opioid receptor dualism and muscular rigidity.[1–3 15–17] Besides, factors such as age, race, gender and familial inheritance may also play a role in OIC.[3 18] OIC is mostly transient, benign and self-limiting, but could be associated with adverse effects such as hypertension, tachycardia, increased intra-cranial, ocular and abdominal pressures and airway obstruction,[1 2 15–20] which are especially undesirable during the induction of general anaesthesia. Numerous pharmacological interventions including lidocaine, atropine, magnesium sulfate($MgSO_4$), dexamethasone, propofol, midazolam, muscular relaxant, ketamine, pentazocine, tramadol, α_2-agonists, ß2-agonists, sodium cromoglycate, beclomethasone, salbutamol, dextromethorphan and so on; and non-pharmacological interventions such

as priming, dilution and slow injection of opioids, have been used to manage OIC.[1 2 4–9 11–13 15 17 18 20–23] Unfortunately, the efficacy and safety of those antitussive interventions remains controversial.

Dezocine (DZC), a mixed opioid agonist/antagonist, was synthesised in 1970s and approved by the Food and Drug Administration of USA for perioperative pain management but was discontinued with the closure of its parent company.[24–28] Although no longer used clinically in western countries, DZC has gained popularity in China and been widely used as a perioperative analgesic for decades.[25 29–33] Recent studies suggested that, pretreatment of intravenous DZC could completely suppress the cough induced by bolus injection of fentanyl or sufentanil during anaesthesia induction. For example, Sun *et al*[4] demonstrated that no fentanyl-induced cough was observed in DZC group. In another randomised controlled trial (RCT), Liu and colleagues[6] shared the same suppressive effect of DZC on sufentanil-induced cough. It is so encouraging that, DZC might be more effective than those above-mentioned antitussive interventions, and could possibly eliminate OIC without causing OIC itself. Therefore, we will perform a systemic review and meta-analysis to evaluate the efficacy of DZC on OIC during general anaesthesia induction, and possible complications.

Objectives

To systematically review the effects of DZC on the incidence and severity of OIC and possible complications during general anaesthesia induction.

METHODS AND ANALYSIS

This protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist.[34] The systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[35]

Patient and public involvement statement

There will be no patient or public involved in this systematic review and meta-analysis.

Inclusion and exclusion criteria

We will include all RCTs comparing DZC with placebo or blank with respect to their effects on OIC. In studies which also included other comparator drugs, only data of DZC and placebo groups will be abstracted. Primary outcomes of interest include the incidence and severity of OIC. The severity of OIC will be graded as mild (1–2 coughs), moderate (3–4 coughs) or severe (≥5 coughs).[18] Secondary outcomes of interest include the incidence of possible complications or adverse effects of DZC such as respiratory inhibition, nausea and emesis, truncal rigidity, dizziness, drowsiness and chill. Exclusion criteria include: (1) studies published as review, case report or abstract; (2) animal or cell studies; (3) duplicate publications; (4) studies lacking information about outcomes of interest. The two authors will independently review the titles and abstracts of all identified studies for eligibility, excluding obviously ineligible ones. The eligibility of those remaining studies for final inclusion will be further determined by reading the full text.

Search strategy

We will conduct a systemic review according to the PRISMA guidelines.[35] The protocol of current meta-analysis was published in PROSPERO. Relevant trials will be identified by computerised searches of PubMed, Embase, Cochrane Library, Web of Science till 31 December 2019, using different combination of search words as follows: (*opioid OR fentanyl OR sufentanil OR remifentanil OR alfentanil) AND cough AND dezocine AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR randomly OR trial*) (table 1). No language restriction will be used. We will also search Chinese BioMedical Literature & Retrieval System (SinoMed), China National Knowledge Infrastructure, Wanfang Data and VIP Data (from 1978 to 31 December 2019). Additionally, we will use the bibliography of retrieved articles to further identify relevant studies.

Study quality assessment

Two authors will independently assess the risk of bias, using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions.[36] The Cochrane collaboration's tool for assessing risk of bias will be used independently by two authors to evaluate the methodological quality of each included trial. The domains considered included: (1) random sequence generation (selection bias), (2) allocation concealment (selection bias), (3) blinding of participants and personnel (performance bias), (4) blinding of outcome assessment (detection bias), (5) incomplete outcome data (attrition bias), (6) selective reporting (reporting bias) and (7) other bias. Each domain will be deemed to be low risk of bias, uncertain risk of bias and high risk of bias and showed as risk of bias summary and graph.

Data abstraction

The following data will be abstracted from the included studies to a data collection form by two authors independently: (1) author, year of publication and journal of included studies; (2) total number of patients, number of patients in the DZC and control groups, gender, age; (3) data regarding outcomes of interest in both groups. Disagreements will be resolved by discussion among all authors during the process of data abstraction. The authors of the included RCTs will be contacted if necessary.

Statistical analysis

All data will be analysed by using RevMan V.5.3 (Cochrane Collaboration, Oxford, UK). Pooled OR and 95% CI will be estimated for dichotomous data, and weighted mean difference and 95% CI for continuous data, respectively. Each outcome will be tested for heterogeneity, and randomised-effects or fixed-effects model will be used in the presence or absence of significant heterogeneity (Q-statistical test

Table 1 Search strategy

PubMed

No.	Search items
#1	"dezocine"(Supplementary Concept) OR dezocine(Title/Abstract)
#2	((((((((((((((((Analgesics, Opioid(MeSH Terms)) OR Opioid(Title/Abstract)) OR Fentanyl(MeSH Terms)) OR Fentanyl(Title/Abstract)) OR Phentanyl(Title/Abstract)) OR Fentanyl Citrate(Title/Abstract)) OR Sufentanil(MeSH Terms)) OR Sufentanil(Title/Abstract)) OR Sulfentanyl(Title/Abstract)) OR Sulfentanil(Title/Abstract)) OR Sufentanil Citrate(Title/Abstract)) OR Remifentanil(MeSH Terms)) OR Remifentanil(Title/Abstract)) OR Remifentanil Hydrochloride(Title/Abstract)) OR Alfentanil(MeSH Terms)) OR Alfentanil(Title/Abstract)) OR Alfentanyl(Title/Abstract)) OR Alfentanil Hydrochloride(Title/Abstract)
#3	((((Cough(MeSH Terms)) OR Cough(Title/Abstract)) OR Coughs(Title/Abstract)) OR Antitussive(Title/Abstract)) OR Anti-tussive(Title/Abstract)
#4	((((((Randomized Controlled Trial(Publication Type)) OR Randomized Controlled Trial) OR Controlled Clinical Trial(Publication Type)) OR Controlled Clinical Trial) OR Randomized) OR Placebo) OR randomly
#5	#1 AND #2 AND #3 AND #4

Embase

('dezocine'/exp OR dezocine:ab,ti) AND ('opiate agonist'/exp OR opioid:ab,ti OR 'fentanyl derivative'/exp OR fentanyl:ab,ti OR 'fentanyl citrate':ab,ti OR sufentanil:ab,ti OR 'sufentanil citrate':ab,ti OR remifentanil:ab,ti OR alfentanil:ab,ti) AND ('coughing'/exp OR coughing:ab,ti OR cough:ab,ti OR antitussive:ab,ti OR anti-tussive:ab,ti) AND ('randomized controlled trial'/exp OR 'randomized controlled trial':it OR 'randomized controlled trial':ab,ti OR randomized OR placebo OR randomly)

Cochrane Library

No.	Search items
#1	(dezocine): ti, ab, kw
#2	(Analgesics, Opioid)explode all trees OR (opioid): ti, ab, kw OR [Fentanyl] explode all trees OR (fentanyl): ti, ab, kw OR (fentanyl citrate): ti, ab, kw OR (phentanyl): ti, ab, kw OR [Sufentanil] explode all trees OR (sufentanil): ti, ab, kw OR (sufentanil citrate): ti, ab, kw OR (sulfentanyl): ti, ab, kw OR [Remifentanil] explode all trees OR (remifentanil): ti, ab, kw OR (remifentanil monohydrochloride): ti, ab, kw OR (remifentanil hydrochloride): ti, ab, kw OR [Alfentanil] explode all trees OR (alfentanil): ti, ab, kw OR (alfentanil hydrochloride): ti, ab, kw OR (alfentanyl): ti, ab, kw
#3	(Cough) explode all trees OR (cough): ti, ab, kw OR (coughs): ti, ab, kw OR (antitussive):ti, ab, kw OR (anti-tussive):ti, ab, kw
#4	(Randomised Controlled Trial) explode all trees OR (Randomized Controlled Trial): ti, ab, kw OR [Randomised Controlled Trials as Topic] explode all trees OR [Controlled Clinical Trial] explode all trees OR (Controlled Clinical Trial): ti, ab, kw OR [Controlled Clinical Trial as Topic] explode all trees
#5	#1 AND #2 AND #3 AND #4

Web of Science

TS=dezocine AND TS=(opioid OR opioid OR "Analgesics, Opioid" OR fentanyl OR phentanyl OR "fentanyl citrate" OR sufentanil OR sulfentanyl OR "sufentanil citrate" OR remifentanil OR "remifentanil hydrochloride" OR alfentanil OR alfentanyl OR "alfentanil hydrochloride") AND TS=(cough OR coughs OR coughing OR antitussive OR anti-tussive) AND TS=("randomized controlled trial" OR "controlled clinical trial" OR randomized OR placebo OR randomly)

SinoMed

No.	Search items
#1	"地佐辛"(不加权:扩展) OR "地佐辛"(摘要:智能)
#2	"阿片"(不加权:扩展) OR "阿片"(中文标题:智能) OR "镇痛药,"(不加权:扩展) AND "阿片类"(不加权:扩展) OR "芬太尼"(不加权:扩展) OR "芬太尼"(中文标题:智能) OR "舒芬太尼"(不加权:扩展) OR "舒芬太尼"(中文标题:智能) OR "瑞芬太尼"(中文标题:智能) OR "阿芬太尼"(不加权:扩展) OR "阿芬太尼"(中文标题:智能)
#3	"咳嗽"(不加权:扩展) OR "咳嗽"(中文标题:智能) OR "呛咳"(中文标题:智能) OR "止咳"(不加权:扩展) OR "止咳"(中文标题:智能) OR "镇咳"(不加权:扩展) OR "镇咳"(中文标题:智能)
#4	"随机对照试验"(不加权:扩展) OR "临床对照试验"(不加权:扩展) OR "随机地"(摘要:智能) OR "随机的"(摘要:智能) OR "对照"(摘要:智能) OR "安慰剂"(摘要:智能)
#5	#1 AND #2 AND #3 AND #4

CNKI

(SU='地佐辛' OR AB='地佐辛') AND (SU=('阿片'+'阿片类镇痛药'+'芬太尼'+'舒芬太尼'+'瑞芬太尼'+'阿芬太尼') OR TI=('阿片'+'阿片类镇痛药'+'芬太尼'+'舒芬太尼'+'瑞芬太尼'+'阿芬太尼')) AND (SU=('咳嗽'+'呛咳'+'止咳'+'镇咳') OR TI=('咳嗽'+'呛咳'+'止咳'+'镇咳')) AND (SU=('随机对照试验'+'临床对照试验'+'随机的'+'随机地'+'安慰剂'+'对照') OR AB=('随机对照试验'+'临床对照试验'+'随机的'+'随机地'+'安慰剂'+'对照'))

Wanfang Data

(主题:地佐辛+摘要:地佐辛)*(主题:(阿片+阿片类镇痛药+芬太尼+舒芬太尼+瑞芬太尼+阿芬太尼)+题名:(阿片+阿片类镇痛药+芬太尼+舒芬太尼+瑞芬太尼+阿芬太尼))*(主题:(咳嗽+呛咳+止咳+镇咳)+题名:(咳嗽+呛咳+止咳+镇咳))*(主题:(随机对照试验+临床对照试验+随机的+随机地+安慰剂+对照)+ 摘要:(随机对照试验+临床对照试验+随机的+随机地+安慰剂+对照))

VIP Data

(M=地佐辛 OR R=地佐辛) AND (M=阿片 OR 阿片类镇痛药 OR 芬太尼 OR 舒芬太尼 OR 瑞芬太尼 OR 阿芬太尼 OR R=阿片 OR 阿片类镇痛药 OR芬太尼 OR 舒芬太尼 OR 瑞芬太尼 OR 阿芬太尼) AND (M=咳嗽 OR 呛咳 OR 止咳 OR 镇咳 OR R=咳嗽 OR 呛咳 OR 止咳 OR 镇咳) AND (M=随机对照试验 OR 临床对照试验 OR 随机的 OR 随机地 OR 安慰剂 OR 对照 OR R=随机对照试验 OR 临床对照试验 OR 随机的 OR 随机地 OR 安慰剂 OR 对照)

$p<0.05$). Sensitivity analyses will be done by examining the influence of statistical model on estimated treatment effects, and analyses which adopt the fixed-effects model will be repeated again by using randomised-effects model and *vice versa*. The influence of statistical model on estimated treatment effects will be showed in a table comparing the two models. In addition to that, sensitivity analyses will also be performed to evaluate the influence of individual study on the overall effects. The possible effects of opioid type and doses will be evaluated by subgroup analysis. Subgroup analysis will also be conducted to detect the potential effects of sex, age and heredity if possible. Publication bias will be

explored through visual inspection of funnel plots of the outcomes. All p values will be two-sided and statistical significance was defined as p<0.05.

ETHICS AND DISSEMINATION

This study is a protocol of meta-analysis of previously published literatures, ethical approval was not necessary according to the Ethical Committee of Fuwai Hospital. The study will be submitted to a peer-reviewed journal and disseminated *via* research presentations.

Contributors LH: substantial contributions to the conception and design of the work; the acquisition, analysis, interpretation of data for the work; drafting the work or revising it critically for important intellectual content and final approval of the version to be published. KS, YZ and JM: substantial contributions to the acquisition, analysis; revising the work critically; final approval of the version to be published. YY: substantial contributions to the conception and design of the work; revising the work critically for important intellectual content; final approval of the version to be published. All authors agree to be accountable for all aspects of the work.

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