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

Li-xian He 1, Ken Shao, Jie Ma, Yuan-yuan Zhao, Yun-tai Yao

ABSTRACT
Introduction Cough is often observed when administering 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 lac, 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.

INTRODUCTION
Cough is often observed when administering a bolus of opioids (eg, fentanyl1-4 sufentanil5-7 remifentanil8-13 alfentanil14), 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(MgSO4), dexamethasone, propofol, midazolam, muscular relaxant, ketamine, pentazocine, tramadol, α2-agonists, β2-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. 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.\textsuperscript{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.\textsuperscript{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 \textit{et al}\textsuperscript{5} demonstrated that no fentanyl-induced cough was observed in DZC group. In another randomised controlled trial (RCT), Liu and colleagues\textsuperscript{9} 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.\textsuperscript{34} The systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.\textsuperscript{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).\textsuperscript{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 systematic review according to the PRISMA guidelines.\textsuperscript{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.\textsuperscript{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 V5.3 (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

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<th>No.</th>
<th>Search strategy</th>
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<tr>
<td>#1</td>
<td>&quot;dezocine&quot;(Supplementary Concept) OR dezocine&gt;Title/Abstract)</td>
</tr>
<tr>
<td>#2</td>
<td>(((((((((((((Analgesics, Opioid)(MeSH Terms)) OR Opioid&gt;Title/Abstract)) OR Fentanyl(MeSH Terms)) OR Fentanyl&gt;Title/Abstract)) OR Phentanyl&gt;Title/Abstract)) OR Fentanyl Citrate&gt;Title/Abstract)) OR Sufentanyl(MeSH Terms)) OR Sufentanyl&gt;Title/Abstract)) OR Sufentanil(title/Abstract)) OR Remifentanil(title/Abstract)) OR Remifentanil Hydrochloride(title/Abstract)) OR Alfentanil(MeSH Terms)) OR Alfentanil&gt;Title/Abstract)) OR Alfentanil Hydrochloride(title/Abstract))</td>
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<td>#3</td>
<td>(Cough(MeSH Terms)) OR Cough&gt;Title/Abstract) OR Antitussive(title/Abstract)) OR Anti-tussive(title/Abstract))</td>
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<tr>
<td>#4</td>
<td>((((((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)</td>
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<tr>
<td>#5</td>
<td>#1 AND #2 AND #3 AND #4</td>
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Web of Science

| #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 (sufentanyl) explode all trees OR (sufentanyl); ti, ab, kw OR (remifentanil) explode all trees OR (remifentanil); ti, ab, kw OR (alfentanil) explode all trees OR (alfentanil); ti, ab, kw |
| #3  | (Cough) explode all trees OR (cough); ti, ab, kw OR (coughs) explode all trees OR (coughs); ti, ab, kw OR (antitussive) explode all trees OR (antitussive); ti, ab, kw |
| #4  | (Randomised Controlled Trial) explode all trees OR (Randomised 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) OR Randomised Controlled Trial) OR Controlled Clinical Trial(Publication Type)) OR Randomized OR Placebo) OR randomly) |
| #5  | #1 AND #2 AND #3 AND #4 |

SinoMed

| #1  | "地佐辛"(不加权:扩展) OR "地佐辛"(摘要:智能) |
| #2  | "阿片类(不加权:扩展)" OR "阿片类(中文标题:智能)" OR "镇痛"(不加权:扩展) OR "阿片类(中文标题:智能)" OR "阿片类(不加权:扩展)" |
| #3  | "咳嗽"(不加权:扩展) OR "咳嗽"(中文标题:智能) OR "咳嗽"(不加权:扩展) |
| #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

| #1  | "地佐辛" OR AB="地佐辛") AND (SU="阿片类镇痛药" OR "芬太尼" OR "舒芬太尼" OR "地佐辛") OR TI="阿片类镇痛药" OR "芬太尼" OR "舒芬太尼" OR "瑞芬太尼") AND (SU="咳嗽" OR "镇咳") OR TI="咳嗽" OR "镇咳") |

 Wanfang Data

| #1  | "地佐辛" OR AB="地佐辛") AND (SU="阿片类镇痛药" OR "芬太尼" OR "舒芬太尼" OR "瑞芬太尼") OR TI="阿片类镇痛药" OR "芬太尼" OR "舒芬太尼" OR "瑞芬太尼") AND (SU="咳嗽" OR "镇咳") OR TI="咳嗽" OR "镇咳") |

VIP Data

| #1  | "地佐辛" OR AB="地佐辛") AND (SU="阿片类镇痛药" OR "芬太尼" OR "舒芬太尼" OR "瑞芬太尼") OR TI="阿片类镇痛药" OR "芬太尼" OR "舒芬太尼" OR "瑞芬太尼") AND (SU="咳嗽" OR "镇咳") OR TI="咳嗽" OR "镇咳") |

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 Kuwait 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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REFERENCES