Review Article

Effect of dezocine administration in the prevention of fentanyl-induced cough during general anesthesia induction: a systematic review and meta-analysis of randomized controlled trials

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Abstract: Objectives: The aim of this study is to evaluate the efficacy and safety of dezocine administration in the prevention of fentanyl induced cough (FIC). Methods: Literature search based on Pubmed, EMBASE, ISI Web of Science, CENTRAL, CNKI was performed to identify potential randomized controlled trials (RCTs) assessing the effect of dezocine in FIC. Two reviewers selected each article independently according to predetermined inclusion criteria. Meta-analysis was conducted via RevMan 5.3. Results: A total of 15 RCTs involving 2074 patients that scheduled for elective surgeries were included, low dose dezocine administration, 0.1 mg/kg dezocine and high dose dezocine were effective in preventing FIC (low dose: RR 0.01 95% CI 0.00, 0.08; 0.1 mg/kg: RR 0.11 95% CI 0.06, 0.17; high dose: RR 0.15 95% CI 0.10, 0.23). The combined incidence of FIC in normal saline groups were around 51%. Subgroup-analysis and sensitivity analysis were performed. Discussion: The results of our study indicated a definite effect of dezocine administration, which is irrespective of the dosage of dezocine injection. Future studies with larger scale and strict design are recommended.

Keywords: Fentanyl induced cough, dezocine, anesthesia, meta-analysis, systematic review

Introduction

Fentanyl is a µ-opioid receptor agonist and has a clinical potency ratio of 50 to 100 times that of morphine, which was firstly synthesized in 1960. Fentanyl and its derivatives, such as sufentanil, alfentanil and remifentanil [1], are the most frequently used opioids in clinical anesthesia. These synthetic potent opioids derived from phenylpiperidine are frequently administered for their analgesic effect especially prior to induction of anesthesia. Fentanyl has the advantage of rapid onset, short duration of action, profound dose-dependent analgesia, and cardiovascular stability as well as less release of histamine mainly during laryngoscopy and endotracheal intubation [2, 3]. Like other opioids, several side effects of fentanyl were also reported, such as nausea, dry mouth, somnolence, hypoventilation, asthenia, constipation, and apnea. Another side effect under the spotlight is the fentanyl-induced cough (FIC).

Many reports have confirmed that fentanyl at induction of anesthesia can cause coughing with varying degrees and its derivatives trigger cough as well [4-6]. Some articles state that the incidence of fentanyl-induced cough varies between 2.7% and 65% [7, 8]. Although fentanyl-induced cough is transient, benign and self-limiting in most patients, its severity should not be ignored in the patients who are at the risk of an increase or increased intracranial pressure such as cerebral aneurysms, cerebral tumor, ruptured cerebral aneurysms, and the patients with acute glaucoma, penetrating eye injuries, or arterial aneurysm resection, and hypersensitive airway disease [9, 10].
With more and more attention focused on FIC, a growing number of intervention were introduced in reducing the incidence of FIC. Most reports demonstrated that pretreatment with some inhaled drugs, such as salbutamol, beclomethasone or cromolyn sodium, or with intravenous administration, ketamine, propofol or magnesium sulphate, can reduce the incidence of FIC before induction of anesthesia [11-13]. Uvelin and Rakic proposed some instructions on prevention of FIC, including (1) patients in condition of potentially raised intracranial pressure, acute glaucoma, serious airway responsiveness, raised intracranial pressure, penetrating eye injuries and younger non-smokers should be pre-treated against the occurrence of FIC even on a regular basis, because in most American Society of Anesthesiologists (ASA) I and II patients undergoing surgery, even if FIC occurs, it causes no serious effects; (2) intravenous lidocaine 0.5 mg/kg should be given at least 1 min before fentanyl administration and if we wish to prevent a hemodynamic response to laryngoscopy and intubation, the lidocaine dose can be higher (1-1.5 mg/kg i.v.) and ephedrine should be used in patients who are hypovolemic or hypotensive; (3) in the case of asthmatic patients who may benefit from avoiding FIC and already use salbutamol, beclomethasone or sodium chromoglycate aerosol, these agents should be used 15 min before fentanyl; (4) prolongation of fentanyl injection time to about 20 s helps prevent FIC [14]. Dezocine which is a mixed agonist-antagonist opioid, a full agonist of κ-receptor resulting in strong analgesic effect, sedation and mild respiratory depression and partial agonist of μ-receptor causing a weak effect or some effect against agonist, namely partial blocking effect, is a potent opioid drug [15, 16]. Dezocine, which has good analgesic effect and has less side effect than traditional opioid, was widely used in the clinical treatment of pain and auxiliary anesthesia. Several clinical studies have reported that dezocine had a significant effect in reducing incidence of FIC in general anesthesia cases. However, no published evidence based on randomized controlled trials (RCTs) could proved that applying dezocine was an effective approach to prevent the occurrence of FIC. Thus, our current study aims at evaluating the clinical effect and safety of dezocine on FIC in general anesthesia, compared with placebo control.

Methods

The protocol of this systematic review is registered with PROSPERO (registration number: CRD42016037034). This systematic review was conducted in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [17].

Search strategy

A comprehensive literature search of PubMed, EMBASE, CENTRAL, ISI Web of Science and CNKI was conducted. All the above databases were searched from their inception dates up to the latest issue (June 2017), without language restriction. A combination of Medical Subheadings (MeSH) and free terms were used to retrieve all the potential articles. MeSH were manually modified based upon the specifications of each database. The following search strategy was used for the literature search in Pubmed, CENTRAL and ISI Web of Science: (“Cough” [Mesh] or cough or coughs) and (dezocine” [Supplementary Concept] or Wy 16225 or dezocine). For CNKI, search terms were “Dizuoxin” and “Ke”, which means dezocine and cough respectively. In addition, the bibliographies of relevant systematic reviews and clinical guidelines were manually searched. The reference section for each study was also searched.

Types of participants

To be included in our systematic review, the enrolled subjects had to be scheduled for elective surgery under general anesthesia and ASA physical status classification of I-II. Exclusive criteria included a history of chronic cough or smoking, known allergies, severe neurological, cardiovascular diseases, narcotic drug dependence and recent history of opioid application, pregnancy and delivery surgery.

Interventions

Patients in experimental groups were administered with dezocine solution prior to the anesthesia induction. No specific dosage of dezocine was imposed. Patients in the control groups received normal saline with an equal volume of dezocine solution in experimental group. Studies that compared dezocine with other pharmaceutical treatments were excluded.
Outcome measurements

The primary outcome measure was the incidence of FIC within 2 minutes after the administration of fentanyl, side-effects associated with dezocine administration were also documented.

Types of publication

The included studies were limited to be RCT aiming at assessing the efficacy and safety of dezocine in the prevention of FIC. Animal experiments, review articles, case reports and expert experience reports were excluded.

Data extraction

Two investigators (W. X. Jiang and J.M. Huang) screened each article independently and were blinded to the findings of the other reviewer. According to the predetermined inclusion criteria, two reviewers performed a strict screening to identify the qualification of articles independently, and they extracted data from these eligible articles using a standardized data collection form, which included first author, time of the publication, study of design, population characteristics of participants in different groups, interventions and control treatment, application of anesthesia, main outcome assessments.

Any disagreement between the two reviewers was resolved through discussion until a consensus was achieved. The third review author (J.M. Zhang) was consulted if a consensus could not be achieved.

Quality assessment

The Cochrane Collaboration’s tool was applied to evaluate the risk of bias among the selected RCTs, the evaluation was based on seven items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias [18]. Two reviewers (J.M. Huang and Z.T. Lv) assessed the risk of bias among studies independently, the results of risk of bias judgement were not revealed until both reviewers finished the evaluation of all included studies. The results were compared afterwards, disagreements regarding the risk of bias assessment were settled by discussion until a consensus was reached.

Data synthesis and analysis

Risk ratio (RR) and the associated 95% confidence intervals (CIs) were calculated for incidence of FIC. Random-effect model was employed for meta-analysis in case of heterogeneity among our included studies; otherwise,
# Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study-design</th>
<th>Population</th>
<th>Intervention and Control</th>
<th>Application of anesthesia</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Cai et al., 2015</td>
<td>RCT</td>
<td>D: 40 patients; 48.2±11.6 years; C: 40 patients; 47.6±12.5 years</td>
<td>D: 0.1 mg/kg before the induction of anesthesia; C: 0.9% saline (10 ml) before the induction of anesthesia</td>
<td>Intravenous injection of dezocine/saline, fentanyl 3 μg/kg and etomidate 0.3 mg/kg; fentanyl and etomidate were injected in less than 5 s</td>
<td>Incidence of cough*</td>
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<tr>
<td>Gao et al., 2013</td>
<td>RCT</td>
<td>D1: 40 patients; 46.3±7.6 years; D2: 40 patients; 44.7±6.3 years; D3: 40 patients; 46.9±5.4 years; C: 40 patients; 43.1±8.7 years</td>
<td>D1: 0.05 mg/kg; D2: 0.1 mg/kg; D3: 0.15 mg/kg 10 min before the induction of anesthesia; C: 0.9% saline (5 ml) 10 min before the induction of anesthesia</td>
<td>Sequentially intravenously injection of fentanyl 3 μg/kg, midazolam 0.04 mg/kg, propofol 2 mg/kg, cisatracurium 0.15 mg/kg</td>
<td>Incidence of cough*</td>
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<tr>
<td>Fang, 2016 China</td>
<td>RCT</td>
<td>D: 62 patients; 20-60 years; S: 62 patients; 20-60 years</td>
<td>D: 0.1 mg/kg 10 min before the induction of anesthesia; C: 0.9% saline 10 min before the induction of anesthesia</td>
<td>Sequentially intravenously injection of fentanyl 3 μg/kg (within 5 s) and other anesthetics (not reported in detail)</td>
<td>Incidence of cough*</td>
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<tr>
<td>Huang et al., 2015</td>
<td>RCT</td>
<td>D: 50 patients; 44±11 years; C: 50 patients; 45±11 years</td>
<td>D: 0.1 mg/kg (10 ml) 5 min before the induction of anesthesia; C: 0.9% saline (10 ml) 5 min before the induction of anesthesia</td>
<td>Sequentially intravenously injection of fentanyl 3 μg/kg (within 5 s) and other anesthetics (not reported in detail)</td>
<td>Incidence of cough*</td>
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<tr>
<td>Liu et al., 2015</td>
<td>Double-blind, RCT</td>
<td>D: 185 patients; 52±13 years; C: 185 patients; 53±11 years</td>
<td>D: 0.1 mg/kg 3-5 s before the induction of anesthesia; C: 0.9% saline 3-5 s before the induction of anesthesia</td>
<td>Standardized anesthesia induction (details not reported); 2 min after anesthesia induction, all patients received 0.5 μg/kg sufentanil over 3 s</td>
<td>Incidence of cough*</td>
</tr>
<tr>
<td>Meng et al., 2013</td>
<td>RCT</td>
<td>D: 40 patients; 43.5±13.3 years; C: 40 patients; 43.4±13.6 years</td>
<td>D: 0.1 mg/kg 8 min before the induction of anesthesia; C: 0.9% saline 8 min before the induction of anesthesia</td>
<td>Midazolam 0.1 mg/kg, 2 min later intravenously injection of fentanyl 0.4 μg/kg (in 2 s), propofol 2 mg/kg and rocuronium bromide 1 mg/kg</td>
<td>Incidence of cough*</td>
</tr>
<tr>
<td>Pi et al., 2015</td>
<td>RCT</td>
<td>D: 50 patients; 46.2±8.6 years; C: 50 patients; 44.8±7.7 years</td>
<td>D: 0.1 mg/kg 10 min before the induction of anesthesia; C: 0.9% saline 10 min before the induction of anesthesia</td>
<td>Fentanyl 4 μg/kg intravenously injection in 3 s; propofol 2 mg/kg and rocuronium bromide 0.6 mg/kg</td>
<td>Incidence of cough*</td>
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<tr>
<td>Qiu et al., 2016</td>
<td>RCT</td>
<td>D: 60 patients; 33±10 years; N: 60 patients; 36±8 years</td>
<td>D: 0.1 mg/kg 2 min before the induction of anesthesia; C: 0.9% saline 2 min before the induction of anesthesia</td>
<td>Fentanyl 3 μg/kg intravenously injection in 3 s; 2 min later, propofol and cetatriptan were injected (not reported in detail)</td>
<td>Incidence of cough*</td>
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<tr>
<td>Sun et al., 2011</td>
<td>Double-blind, RCT</td>
<td>D: 60 patients; 46.6±10.3 years; C: 60 patients; 48.2±10.6 years</td>
<td>D: 0.1 mg/kg 10 min before the induction of anesthesia; C: 0.9% saline 10 min before the induction of anesthesia</td>
<td>Midazolam 0.1 mg/kg, fentanyl 5 μg/kg, propofol 1-1.5 mg/kg, and suxamethonium 1.5 mg/kg; the injection time of fentanyl was limited to under 2 s; propofol and suxamethonium were administered 2 min later, after the fentanyl bolus</td>
<td>Incidence of cough*</td>
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## Dezocine in fentanyl-induced cough

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Details</th>
<th>Treatment</th>
<th>Incidence of cough</th>
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<tr>
<td>Wang et al., 2016 China</td>
<td>RCT</td>
<td>Scheduled for elective surgery; ASA I-II;</td>
<td>D: 0.1 mg/kg 1 min before the induction of anesthesia; C: 0.9% saline (2 ml) 1 min before the induction of anesthesia</td>
<td>Incidence of coughb</td>
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<td>D: 30 patients; 41±13 years; C: 30 patients; 39±13 years</td>
<td>Fentanyl 4 ug/kg intravenously injection in 3 s; 1 min later, midazolam 0.1 mg/kg, propofol 2 mg/kg, cisatricurium 0.2 mg/kg</td>
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<tr>
<td>Wang and Liu, 2015 China</td>
<td>RCT</td>
<td>Scheduled for elective surgery; ASA I-II;</td>
<td>D: 0.1 mg/kg 1 min before the induction of anesthesia; C: 0.9% saline 1 min before the induction of anesthesia</td>
<td>Incidence of coughb</td>
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<tr>
<td></td>
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<td>D: 30 patients; 45±12 years; C: 30 patients; 40±11 years</td>
<td>Fentanyl 4 ug/kg intravenously injection in 3 s; 15 s later, intravenously injection of midazolam 0.1 mg/kg, propofol 2 mg/kg and cisatracurium 0.2 mg/kg</td>
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<tr>
<td>Wang, 2015 China</td>
<td>RCT</td>
<td>Scheduled for elective surgery; ASA I-II;</td>
<td>D1: 0.04 mg/kg; D2: 0.08 mg/kg; D3: 0.12 mg/kg 5 min before the induction of anesthesia; C: 0.9% saline (5 ml) 5 min before the induction of anesthesia</td>
<td>Incidence of coughb</td>
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<td>D1: 25 patients; 72.0±2.8 years; D2: 25 patients; 69.6±3.1 years; D3: 25 patients; 70.7±2.7 years; C: 25 patients; 71.1±3.3 years</td>
<td>Fentanyl 0.3 ug/kg intravenously injection in 5 s</td>
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<tr>
<td>Xu et al., 2015 China</td>
<td>Double-blind, RCT</td>
<td>Scheduled for elective surgery; ASA I-II;</td>
<td>D1: 0.025 mg/kg; D2: 0.05 mg/kg; D3: 0.1 mg/kg just before the induction of anesthesia; C: 0.9% saline just before the induction of anesthesia</td>
<td>Incidence of coughb</td>
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<td></td>
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<td>D1: 100 patients; 46±13 years; D2: 100 patients; 43±14 years; D3: 100 patients; 44±14 years; C: 100 patients; 45±12 years</td>
<td>Fentanyl 3 ug/kg intravenously injection in 5 s</td>
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<tr>
<td>Yuan and Chen, 2015 China</td>
<td>RCT</td>
<td>Scheduled for elective surgery; ASA I-II;</td>
<td>D1: 0.05 mg/kg; D2: 0.1 mg/kg; D3: 0.2 mg/kg 10 min before the induction of anesthesia; C: 0.9% saline 10 min before the induction of anesthesia</td>
<td>Incidence of coughb</td>
</tr>
<tr>
<td></td>
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<td>D1: 30 patients; 22-55 years; D2: 30 patients; 22-55 years; D3: 30 patients; 22-55 years; C: 30 patients; 22-55 years</td>
<td>Intravenously injection of fentanyl 3 ug/kg; 2 min later, midazolam 0.05 mg/kg, etomidate 0.3 mg/kg, cisatracurium 0.2 mg/kg</td>
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<tr>
<td>Zhang and Cao, 2013 China</td>
<td>RCT</td>
<td>Scheduled for elective surgery; ASA I-II;</td>
<td>D: 0.1 mg/kg 10 min before the induction of anesthesia; C: 0.9% saline (2 ml) 10 min before the induction of anesthesia</td>
<td>Incidence of coughb</td>
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<td></td>
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<td>D: 40 patients; 46±5.9 years; C: 40 patients; 47±4.8 years</td>
<td>Midazolam 0.1 mg/kg; 2 min later, intravenously injection of fentanyl 3 ug/kg in 3 s, propofol 1.5-2 mg/kg and rocuronium bromide 1 mg/kg</td>
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RCT: randomized controlled trial; D: dezocine group; C: control group; incidence of cougha: incidence of cough in 2 minutes after fentanyl injection; incidence of coughb: incidence of cough in 1 minute after fentanyl injection; incidence of coughc: incidence of cough in 15 seconds after fentanyl injection.
Dezocine in fentanyl-induced cough

Results

Literature search results

An initial literature search yielded a total of 172 potential eligible studies including 6 from Pubmed, 37 from EMBASE, 5 from CENTRAL, 17 from ISI Web of Science and 107 from CNKI. 24 duplicates for retrieving were deleted and 148 potential relevant studies were screened for titles and abstracts. Finally, 18 studies were downloaded for a full-text screen, 1 study was duplicate for publication, 1 was not relevant and 1 used unsuitable intervention. The remaining 15 articles [19-33] were deemed eligible to be included in this review (Figure 1).

Characteristics of included studies

Twelve studies were included in our systematic review, all of them were conducted in China and published from 2011 to 2015. Each study was performed in a single center, 3 of them [22, 25, 28] were written in English while the remaining 9 studies [19-21, 23, 24, 26, 27, 29, 30] were written in Chinese and published in Chinese academic journals. A total of 1080 subjects scheduled for elective surgeries were assigned into dezocine groups and 690 homogeneous participants were allocated into control groups. All the enrolled subjects were administered
Dezocine in fentanyl-induced cough

with dezocine solution or normal saline with the same volume prior to anesthesia induction. Four studies [20, 26, 28, 29] employed a four-arm parallel design to compare clinical effect of different doses of dezocine administration with placebo control, the other eight studies used a two-arm parallel design. The doses of dezocine administration varied from 0.05 mg/kg to 0.20 mg/kg, occurrence of FIC within two minutes after fentanyl injection was observed in all the studies (Table 1).

Risk of bias assessment

The risk of bias among studies were assessed using the Cochrane Collaboration’s Tool. All the included studies claimed that they have assigned patients randomly into dezocine and control groups, but only half of the studies reported method of random sequence generation. Two studies [22, 28] provided detailed information about allocation concealment and double-blind. Study conducted by Sun and co-workers [25] employed double-blind, but they failed to report procedure of allocation concealment. In addition, two studies [27, 30] assessed outcomes by a postoperative observer who was blind to the patients’ assigned groups. Good compliance seemed to be achieved by all studies, all the recruited subjects finished their trial (Figure 2 and Figure 3).
Meta-analyses

Before the meta-analysis was conducted, we divided different comparisons into three groups according to the doses of dezocine administration: low-dose (<0.1 mg/kg), 0.1 mg/kg and high-dose (>0.1 mg/kg). Four studies [20, 26, 28, 29] compared low-dose dezocine with normal saline injection. No obvious heterogeneity was present (P=0.76, I²=0%), so the fixed-effect model was employed for statistical analysis. The pooled data indicated that low-dose dezocine administration could significantly reduce the incidence of FIC when compared with placebo control (RR 0.20, 95% CI 0.13, 0.30; P<0.00001) (Figure 4). Fourteen studies [19-25, 27-30] administered dezocine with a dosage of 0.1 mg/kg. As the heterogeneity across studies was obvious, random-effect model was used (P<0.0002, I²=67%). The combination of data showed that 0.1 mg/kg of dezocine administration could significantly reduce the incidence of FIC (RR 0.10, 95% CI 0.08, 0.14; P<0.00001) (Figure 5 and Figure 6). Three studies [20, 26, 29] compared high-dose dezocine with normal saline control, we used fixed-effect model because no obvious heterogeneity was present (P=0.56, I²=0%). The result of meta-analysis indicated a significant lower incidence of FIC in dezocine groups than it in control groups (RR 0.20, 95% CI 0.11, 0.36; P<0.00001) (Figure 7).

Subgroup-analysis

Subgroup-analysis in the comparison of 0.1 mg/kg dezocine versus control was conducted according to pre-determined criteria, three studies [22, 25, 28] with double-blinding and the remaining eight studies without double-
Dezocine in fentanyl-induced cough

blinding were assigned into two subgroups. The heterogeneity within two subgroups were then accepted and the results of two groups were consistent (double-blind RCT: RR 0.01, 95% CI 0.00, 0.05; P<0.00001; I²=0%; RCT without double-blinding: RR 0.19, 95% CI 0.12, 0.28; P<0.00001; I²=46%) (Figure 5). Stratified analysis by dose of fentanyl injection indicated that 0.1 mg/kg dezocine was effective in attenuating FIC when patients were injected with different doses of fentanyl (<3 ug/kg group: RR 0.01, 95% CI 0.00, 0.08; 3 ug/kg group: RR 0.11, 95% CI 0.06, 0.17; >3 ug/kg group: RR 0.15, 95% CI 0.10, 0.23) (Figure 6). Sensitivity-analysis also revealed that the effect of 0.1 mg/kg dezocine administration was firm when we removed each of the related studies one at a time (detailed data not shown).

Adverse events

Wang et al. [27] reported that six patients in dezocine groups were with dizziness and 4 patients were with somnolence, Yuan and co-workers [29] documented that two patients who were administered with dezocine were with dizziness and one patient was with somnolence. Four studies [22, 25, 27, 28] reported that there were no adverse events associated with dezocine administration.

Discussion

To the best of our knowledge, there is no published systematic review that summarizes all the potential RCTs to assess the clinical effect of dezocine in the prevention of FIC. Our current work highlights the definite efficacy of dezocine administration, the curative effect of dezocine injection was consistent when administered with different doses. However, the conclusion is hampered by methodological deficiencies of several studies, and the evidence supporting the safety of dezocine was insufficient.

Fentanyl was widely used in many areas among the world, especially in those developing countries. Although various mechanisms responsible for FIC have been proposed, the exact mechanism remains unclear. Several hypotheses have been proposed, including (1) some kind of opioid receptors, perhaps μ-receptor, exist the respiratory tract, which participated in cough and played an important mediating role [34]; (2) fentanyl could inhibit central sympathetic outflow, thereafter activating the vagus nerve [35]; (3) histamine and neuropeptides released after intravenous fentanyl administration involve in FIC [34, 36]; (4) a pulmonary chemoreflex mediated by either irritant receptors (rapidly adapting receptors) or vagal C-fiber receptors near the pulmonary vessels might play a role in FIC [37]; and (5) stimulation of the irritant receptors in the upper pulmonary mucosa secondary to fentanyl-induced tracheal smooth muscle constriction [38].

Animal experiments have demonstrated that the use of a low-efficacy opioid in association with a high efficacy opioid will not only enhance the analgesic effect but also antagonize some of undesirable side effects of the higher efficacy opioid, such as pruritus and nausea. The double benefit effect may due to the opioid receptors agonized and antagonized [25]. A potential explanation for the clinical effect of dezocine is that dezocine suppresses FIC by κ-receptor antagonism or inhibits norepinephrine and serotonin reuptake. In addition, the documented adverse events associated with dezocine administration seemed scarce, but the existing evidence to support the safety of dezocine is not sufficient, only six studies reported slight side effects in dezocine groups.

The pooled data in our analysis revealed a 51% incidence of FIC in normal saline injection groups. There were several factors report-
Dezocine in fentanyl-induced cough

ed involving discrepancies on incidence of FIC, including: (1) age, incidence of fentanyl-induced cough is high in infants and children, even in small doses (1 µg/kg) [39]; (2) smoking, a controversy conclude on the implication of smoking, even considered a protective factor against fentanyl-induced cough [40]; (3) ethnicity, the incidence of FIC in Asian population is more obvious than it in European one [41]; (4) dose of fentanyl injection, incidence of FIC increases proportionally with the doses [42]; (5) speed of injection, a longer injection time can reduce the incidence of FIC [40]; (6) route of administration, peripheral intravenous injection could reduce incidence of FIC than injection by a central line [7].

All of our included studies achieved a baseline similarity, and the ethnicity of enrolled subjects were all Han nationality, fentanyl was injected intravenously. However, the dose and speed of fentanyl injection were inconsistent across studies. We firstly stratified all included studies based upon the doses of dezocine injection, each comparison revealed a significant efficacy of dezocine in the prevention of FIC. As the heterogeneity within 0.1 mg/kg group was present, we subsequently divided these studies according to whether double-blinding was performed in their studies, both subgroups indicated that dezocine was more effective than saline. Considering that the lack of blinding might lead to exaggeration of conclusions, the results of subgroup-analysis was in contrary to our expectation, RCTs with double-blinding yielded a significantly better effect of dezocine than RCTs without blinding, no FIC occurred in the studies with double-blinding. With regard to this discrepancy, future studies with rigorous study design and sufficient sample-size are urgently needed. Subgroup-analysis was also conducted according to the dose of fentanyl injection, dezocine administration was effective in attenuating FIC regardless of dose of fentanyl injection. However, the heterogeneity in high dose fentanyl group (>3 µg/kg) was still obvious, suggesting that some other confounding factors such as speed of fentanyl injection, insufficient sample sizes should be questioned.

There are several limitations of our study. Firstly, the majority of included studies had several methodological deficiencies, which could limit the value of conclusions regarding the clinical effect of dezocine administration in general anesthesia; the majority of studies failed to provide detailed information about method for random sequence generation and procedure of allocation concealment. Secondly, the now-existing evidence in terms of the safety of dezocine was insufficient to guarantee that dezocine is a routine medication in general anesthesia, the majority of our included studies did not document adverse events associated with dezocine administration. Thirdly, our included studies were all conducted in China, only three trials were published in English, the remaining were written in Chinese, making it difficult for foreign researchers to get access and understand the content. This might be a result of different countries’ drugs admittance system, dezocine may not be accessible in every country nor available for clinical application in all hospitals. Thus, future larger-scale RCTs within western context are recommended. Lastly, as the baseline incidence of FIC was reported to be around 40%, assuming a 50% decrease of incidence of FIC after dezocine administration, 81 patients were required in each group to achieve 80% power at a two-sided 5% significance level based on our calculation (PASS software, version 12.0, available on www.ncss.com). However, only two of our selected studies reached this standard.

In conclusion, the findings of this meta-analysis suggest that dezocine administration could effectively suppress the occurrence of fentanyl-induced cough during general anesthesia, irrespective of dosage. Conclusion regarding the safety of dezocine administration could not be drawn due to the paucity of evidence provided by our included studies. Additional studies with larger-scale and rigorous study-design are still needed.

Conclusion

The findings of our current work suggested a definite effect of dezocine administration in the prevention of FIC in general anesthesia induction, conclusions regarding the safety of dezocine could not be drawn due to the paucity of existing evidence. Additional RCTs with larger scale and rigorous design are still needed.

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Dezocine in fentanyl-induced cough

Disclosure of conflict of interest

None.

Abbreviations

FIC, Fentanyl induced cough; RCTs, Randomized controlled trials; ASA, American Society of Anesthesiologists; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MeSH, Medical Subheadings; RR, Risk ratio; CIs, confidence intervals.

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Dezocine in fentanyl-induced cough


