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Efficacy of dezocine on preventing opioid-induced cough during general anaesthesia induction: a PRISMA-compliant systematic review and meta-analysis

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ABSTRACT

Objectives To systematically review the effects of dezocine (DZC) on the occurrence rate and severity of opioid-induced cough (OIC).

Design Systematic review and meta-analysis

Data sources PubMed, Embase, Cochrane Library, Ovid, Web of Science as well as Chinese BioMedical Literature & Retrieval System, China National Knowledge Infrastructure, Wanfang and VIP Data were searched from 1978 to 31 December 2020.

Inclusion criteria All randomised controlled trials (RCTs) comparing DZC with placebo on the occurrence rate and severity of OIC.

Data analysis All data were analysed by using RevMan V.5.3. Each outcome was tested for heterogeneity, and randomised-effects or fixed-effects model was used in the presence or absence of significant heterogeneity.

Results Our search yielded 33 RCTs including 4442 patients, and 2521 patients were allocated into the DZC group and 1921 into the control group. Fentanyl was administrated in 1880 patients and sufentanil in 2562 patients during the induction of general anaesthesia. The meta-analysis demonstrated that DZC significantly reduced the occurrence rate of OIC induced by either fentanyl (8.8% vs 49.7%, OR=0.07, 95% CI 0.04 to 0.12, p<0.00001) or sufentanil (5.0% vs 41.5%, OR=0.07, 95% CI 0.04 to 0.12, p<0.00001). The meta-analysis also indicated that the occurrence rate of mild, moderate and severe OIC in the DZC group was remarkably lower than that of the control group (mild: 3.6% vs 13.6%, OR=0.19, 95% CI 0.14 to 0.25, p<0.00001; moderate: 2.0% vs 13.6%, OR=0.12, 95% CI 0.09 to 0.18, p<0.00001; severe: 1.0% vs 13.9%, OR=0.08, 95% CI 0.05 to 0.12, p<0.00001). Additionally, the current meta-analysis indicated that DZC pretreatment was not associated with increased occurrence rate of adverse effects (7.0% vs 4.2%, OR=2.34, 95% CI 0.60 to 9.14, p=0.22) except for dizziness (11.8% vs 0%, OR=8.06, 95% CI 1.40 to 46.35, p=0.02).

Conclusion This meta-analysis demonstrated that DZC significantly inhibited OIC and may be used to manage OIC. More high-quality RCTs are needed to complement the safety of DZC.

PROSPERO registration number CRD42019141255.

Strengths and limitations of this study

- ► This is the first systematic review to investigate the occurrence rate of opioid-induced cough induced by either fentanyl or sufentanil.
- ► Subgroup analyses were performed on dose-effect of dezocine (DZC) and various kinds of opioids to investigate the optimal dosage of DZC.
- ► 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 occurrence rate 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] OIC is mostly transient, benign and self-limiting but could be associated with adverse effects such as hypertension, tachycardia, increased intracranial, ocular and abdominal pressures and airway obstruction.[1 2 15–17] OIC could be spasmodic, explosive[18] and life threatening at times.[19] OIC is especially undesirable during the induction of general anaesthesia. Numerous pharmacological interventions including lidocaine, atropine, magnesium sulfate ($MgSO_4$), dexamethasone, propofol, midazolam, muscular relaxant(rocurounium, vencuronium), ketamine, pentazocine, tramadol, α_2-agonists(clonidine, dexmeditomidine), ß2-agonists (terbutaline, ephedrine), sodium chromoglycate, beclomethasone, salbutamol, dextromethorphan, *etc*, and non-pharmacological interventions

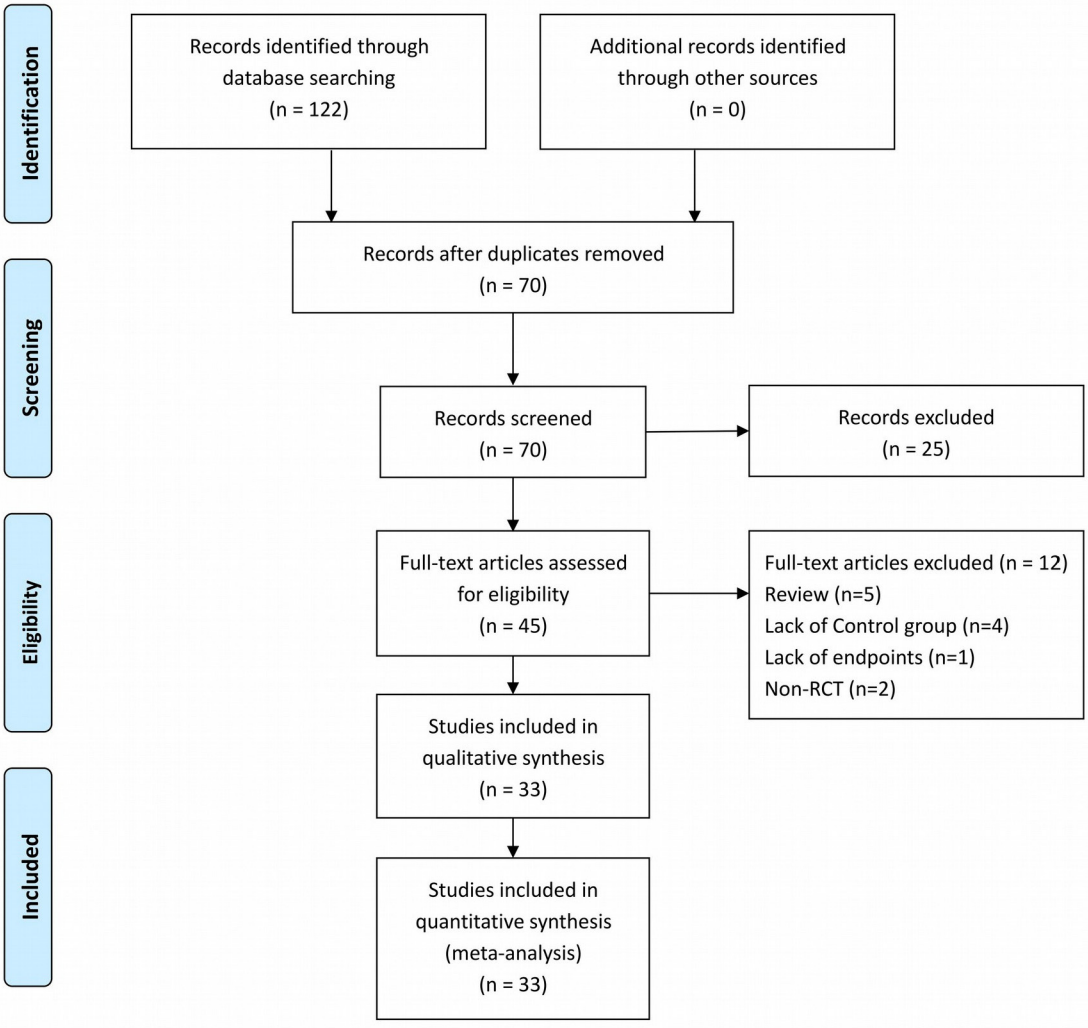

Figure 1 Flowchart.

such as priming, dilution and slow injection of opioids, have been used to manage OIC.[1 2 4–9 11–13 15 17 19–22] Unfortunately, the efficacy and safety of those antitussive interventions remain controversial.

Dezocine (DZC), a mixed opioid agonist/antagnost, was synthesised in 1970s and approved by the FDA of US for perioperative pain management but was discontinued with the closure of its parent company.[23–27] Although no longer used clinically in Western countries, DZC has gained popularity in China and been widely used as a perioperative analgesic for decades.[24 28–32] Recent studies suggested that pretreatment of intravenous DZC 0.1 mg/kg could completely suppress the cough induced by bolus injection of fentanyl or sufentanil during anaesthesia induction. For example, Sun and colleagues[4] evaluated the suppressive effect of DZC on fentanyl-induced cough (FIC). One hundred and twenty patients were randomised to receive DZC 0.1 mg/kg or placebo 10 min before fentanyl 5 µg/kg. They demonstrated that no DZC-pretreated patient had FIC, as compared with 70% (42/60) non-DZC-pretreated patients developing FIC. In another randomised controlled trials (RCT) involving 370 patients, Liu and colleagues[6] evaluated the antitussive effect of DZC 0.1 mg/kg on sufentanil-induced cough (SIC) during anaesthesia induction. They demonstrated the occurrence rate of SIC in the placebo group, which was 31% (59/185), while no SIC was observed in the DZC group. It is so encouraging that DZC might be more effective than those above-mentioned antitussive interventions, and that DZC could possibly eliminate OIC without causing OIC itself. Therefore, we performed this systemic review and meta-analysis to evaluate the efficacy of DZC on OIC during general anaesthesia induction and possible adverse effects.

METHODS

Patient and public involvement

No patient involved.

Table 1 Characteristics of the included RCTs and administration protocols of dezocine

		Patient characteristics		Opioids				Group dezocine		Group control		Outcomes reported				
Study	Language	Age (years)	Sex (M/F)	Type	Dose (μg/kg)	Duration (s)	Timing (min)	n	Dose (mg/kg)	n	Dose	CID	CIC	SCID	SCIC	Adverse effect
Qing-Ming *et al*[36]	Chinese	23–64	48/53	S	3.0	≤5 s	5	50	5 mg	50	Equal volume NS	2.00%	30.00%	0	6.00%	NR
Xiao-Ming and Guang-Hong[37]	Chinese	20–60	39/41	S	2.0	≤2 s	NR	40	5 mg	40	2 mL NS	5.00%	45.00%	0	25.00%	NR
Liang[38]	Chinese	20–60	66/58	F	5.0	≤3 s	10	62	0.1	62	Equal volume NS	9.68%	62.90%	NR	NR	NR
Ya-Ping *et al*[39]	Chinese	20–50	0/120	F	3.0 3.0 3.0	NR	10	40 40 40	0.05 0.1 0.15	14 13 13	5 mL NS	57.50% 17.50% 15.00%	64.29% 53.85% 53.85%	17.5% 2.5% 2.5%	20.00%	NR
Li Yan-Juan[40]	Chinese	23–72	134/106	S	0.3 0.3	≤10 s	10	80 80	0.05 0.1	40 40	Equal volume NS	2.50% 1.25%	32.50% 35.00%	0	7.50%	NR
Liu *et al*[6]	English	18–70	189/181	S	0.5	> 3 s	2	185	0.1	185	NS	0.00%	31.89%	0	13.51%	NR
Zhen-zhen *et al*[41]	Chinese	28–55	39/41	S	0.4	≤2 s	2	40	0.1	40	Equal volume NS	0.00%	72.50%	NR	NR	NR
Ming-fang *et al*[42]	Chinese	22–65	51/49	F	4.0	≤3 s	10	50	0.1	50	Equal volume NS	12.00%	68.00%	NR	NR	NR
Jian-Bin[43]	Chinese	20–65	119/81	S	0.5	NR	NR	100	5 mg	100	2 mL NS	5.00%	45.00%	0	39.00%	NR
Liang-Cheng *et al*[44]	Chinese	18–45	0/120	F	3.0	≤5 s	2	60	0.1	60	5 mL NS	1.67%	25.00%	0	3.33%	NR
Hui *et al*[45]	Chinese	18–65	40/80	F	4.0	≤5 s	2	60	0.05	60	Equal volume NS	0.00%	26.67%	0	11.67%	NR
Tian-yi *et al*[46]	Chinese	24–55	NR	S	0.4	NR	10	35	0.1	35	Equal volume NS	5.71%	57.14%	0	28.57%	NR
Jie *et al*[47]	Chinese	20–65	0/120	S	0.3	< 5 s	5	60	0.05	60	5 mL NS	8.33%	28.33%	3.33%	10.00%	NR
Da-Wei *et al*[48]	Chinese	19–70	44/52	S	0.3	≤10 s	8	48	0.1	48	5 mL NS	0.00%	64.58%	NR	NR	CH, RI, NE
Sun *et al*[4]	Chinese	20–60	68/52	F	5.0	≤2 s	10	60	0.1	60	NS	0.00%	70.00%	NR	NR	NR
Li *et al*[49]	Chinese	15–60	78/62	F	5.0	≤5 s	10	70	0.1	70	10 mL NS	1.43%	75.71%	NR	NR	NR
Jun-Liang and Rong[50]	Chinese	18–70	190/180	S	0.5	NR	Immediately	185	0.1	185	Equal volume NS	0.00%	31.89%	0	29.41%	TR, RI, NE
Zhi-Yong[51]	Chinese	22–61	67/53	S	NR	NR	NR	60	0.05	60	NS	16.67%	55.00%	0	6.67%	NR
Hui and En-Ming[52]	Chinese	25–65	42/58	S	0.3	< 5 s	10	50	0.1	50	2 mL NS	2.00%	32.00%	0	8.00%	NR
Li-Ping[53]	Chinese	60–85	59/41	S	0.3 0.3 0.3	≤5 s	5	25 25 25	0.04 0.08 0.12	9 8 8	5 mL NS	28.00% 12.00% 8.00%	44.44% 37.50% 37.50%	NR	NR	DI, DR

Continued

Table 1 Continued

Study	Language	Patient characteristics		Opioids				Group dezocine		Group control		Outcomes reported				
		Age (years)	Sex (M/F)	Type	Dose (μg/kg)	Duration (s)	Timing (min)	n	Dose (mg/kg)	n	Dose	CID	CIC	SCID	SCIC	Adverse effect
Zhi and Feng[54]	Chinese	18–55	31–29	F	4	≤3 s	1	30	0.1	30	2 mL NS	13.33%	53.33%	0	23.33%	NR
Wen-Feng and Yong-Hua[55]	Chinese	18–55	33–27	F	4	≤3 s	1	30	0.1	30	2 mL NS	16.67%	50.00%	0	16.67%	NR
Wu 2014[56]	Chinese	18–60	105/55	F	3 3 3	< 3 s	10	40 40 40	0.1 0.2 0.3	14 13 13	Equal volume NS	7.50% 2.50% 0.00%	71.43% 61.54% 61.54%	0	15.00%	NR
Qing *et al*[57]	Chinese	20–65	102/98	S	0.5 0.5	< 3 s < 30 s	5 5	50 50	0.1 0.1	50 50	5 mL NS	6.00% 2.00%	80.00% 8.00%	0 0	7.50% 0	NR
Xu *et al*[35]	English	20–70	243/157	F	3 3 3	< 5 s	Immediately	100 100 100	0.025 0.05 0.1	34 33 33	NS	12.00% 4.00% 0.00%	41.18% 39.39% 39.39%	0	5.00%	NR
Ming-Feng and Yu[58]	Chinese	25–55	NR	F	3 3 3	NR	10	30 30 30	0.05 0.1 0.2	10 10 10	NS	56.67% 13.33% 6.67%	60.00% 60.00% 60.00%	26.67% 0 0	33.33%	DI, DR
Jian-Feng and Han-Zhong[59]	Chinese	25–56	41/39	F	3	< 3 s	12	40	0.1	40	2 mL NS	2.50%	45.00%	0	6.67%	NR
Ji-Hong[60]	Chinese	23–56	72/48	F	4	≤3 s	5	30	5 mg	30	10 mL NS	3.33%	46.67%	0	22.50%	NR
Lu-Hong[61]	Chinese	20–61	19/33	S	5	NR	5–8	26	0.1	26	NS	7.69%	65.38%	0	19.23%	NR
Qin-Shu[62]	Chinese	39±5	61/39	S	0.4 0.4 0.4	≤3 s	1 3 8	25 25 25	2 mg 2 mg 2 mg	9 8 8	Equal volume NS	28.00% 4.00% 4.00%	66.67% 50.00% 50.00%	0	8.00%	NR
Xiao-Zhen *et al*[63]	Chinese	18–56	92/108	S	0.4	≤6 s	3	50	5 mg	50	Equal volume NS	16.00%	44.00%	0	8.00%	NR
Tao-Yu *et al*[64]	Chinese	18–65	23/37	S	0.3	< 10 s	10	30	0.1	30	5 mL NS	0.00%	26.67%	0	3.33%	DI, DR
Fang[65]	Chinese	22–75	31/29	S	0.4	NR	2	30	0.1	30	Equal volume NS	3.33%	13.33%	NR	NR	NE

CH, chill; CIC, cough occurrence rate of control; CID, cough occurrence rate of dezocine; DI, dizziness; DR, drowsiness; NE, nausea and emesis; NR, not reported; RCT, randomised controlled trial; RI, respiratory inhibition; SCIC, severe cough occurrence rate of control; SCID, severe cough occurrence rate of dezocine; TR, truncal rigidity.

Registration

The protocol of current meta-analysis was published in PROSPERO on 11 November 2019.

Search strategy

We conducted a systemic review according to the Preferred Reporting Items for Systemic Reviews and Meta-Analyses Quality of Reporting of Meta-analysis (PRIMSA) Guidelines (online supplemental table 1).[33] Relevant trials were identified by computerised searches of PubMed, Embase, Cochrane Library, Ovid, Web of Science as well as Chinese BioMedical Literature & Retrieval System (SinoMed), China National Knowledge Infrastructure (CNKI), Wanfang Data and VIP Data till 31 December 2019, with an updated database search on 31 December 2020 prior to submission, 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*) (online supplemental table 2). No language restriction was used. Additionally, we used the bibliography of retrieved articles to further identify relevant studies.

Criteria for considering studies for this review

We included all RCTs comparing DZC with placebo or blank with respect to their effects on OIC. In studies that also included other comparator drugs, only data of DZC and placebo groups were abstracted. Primary outcomes of interest included the occurrence rate and severity of OIC. The severity of OIC was graded as mild (1–2 coughs), moderate (3–5 coughs) or severe (> 5 coughs).[6] Secondary outcomes of interest include possible adverse effects. Exclusion criteria included (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 (L-XH and KS) independently reviewed the titles and abstracts of all identified studies for eligibility, excluding obviously ineligible ones. The eligibility of those remaining studies for final inclusion was further determined by reading the full text.

Study quality assessment

Two authors (JM and Y-YZ) independently assessed the risk of bias, using the tool described in the Cochrane Handbook for Systematic Reviews of Interventions[34] and GRADE scoring. Each potential source of bias was graded as low, uncertain or high risk of bias and showed as risk of bias summary and graph. The quality of each outcome was assigned a score of high quality, moderate quality, low quality and very low Quality.

Data abstraction

The following data were abstracted from the included studies to a data collection form by two authors (L-XH and KS) 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 were resolved by discussion among all authors during the process of data abstraction. The authors of the included RCTs were contacted if necessary.

Statistical analysis

All data were analysed by using RevMan V.5.3 (Cochrane Collaboration, Oxford, UK). Pooled OR and 95% CI were estimated for dichotomous data, and weighted mean difference and 95% CI for continuous data, respectively. Each outcome was tested for heterogeneity, and randomised-effects or fixed-effects model was used in the presence or absence of significant heterogeneity (Q-statistical test p<0.05). Sensitivity analyses were done by examining the influence of statistical model on estimated treatment effects, and analyses which adopted the fixed-effects model were repeated again by using randomised-effects model and *vice versa*. In addition to that, sensitivity analysis was also performed to evaluate the influence of individual study on the overall effects. The possible effects of opioid type and doses were evaluated by subgroup analysis. Publication bias was explored through visual inspection of funnel plots of the outcomes. All p values were two sided and statistical significance was defined as p<0.05.

RESULTS

Characteristics of the included trials

As shown in figure 1, initial literature search generated 70 results. Finally, 33 RCTs[4 6 35–65] involving 4442 patients were included in the meta-analysis. Of the 33 RCTs, 30[36–65] were written in Chinese, and the other 3[4 6 35] in English (table 1). The 33 RCTs were performed, respectively, in 2 provincial hospitals,[36 44] 13 affiliated hospitals,[4 6 35 38 41 46 48 49 52 54–56 63] 16 urban hospitals[37 39 40 42 43 45 47 50 51 53 57 59 61 62 64 65] and 2 county hospitals[58 60] from 15 provinces and municipalities in China. All enrolled patients were of American society of Anesthesiologists physical status classification I–II, whose ages ranged from 18 to 85 year (table 1). No included RCT reported the OIC induced by remifentanil or alfentanil. As shown in table 1, fentanyl was administrated in 1880 patients during the induction of general anaesthesia with dosages of 2.0 µg/kg to 5.0 µg/kg and sufentanil in 2562 patients with dosages of 0.3 µg/kg to 5.0 µg/kg. The injection duration of fentanyl and sufentanil varied from 2 s to 30 s. Out of the 4442 patients, 2521 were allocated into the DZC group and 1921 into the control (placebo) group. DZC administration protocols differed among the 33 included trials. DZC was administered intravenously with dosages of 0.025 mg/kg to 0.3 mg/kg (or 2 mg to 5 mg), 1 to 10 min prior to fentanyl or sufentanil injection (table 1).

Methodological quality

The risk of bias analysis is shown in figures 2 and 3. There were no patient withdrawal or dropout, neither selectiveness nor bias in all 33 RCTs.

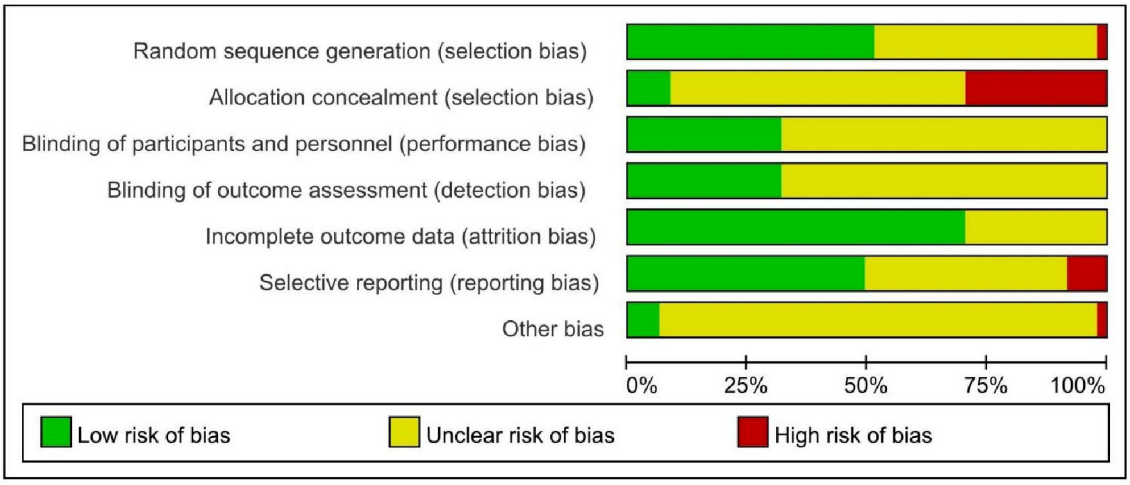

Figure 2 Risk of bias graph.

Quality of evidence

For primary outcome, GRADE scoring shows high quality of evidence on DZC preventing OIC(table 2). While for secondary outcomes, high quality of evidence appeared in drowsiness, moderate quality of evidence in dizziness and nausea, very low quality of evidence in truncal rigidity, chill and respiratory inhibition (table 3).

Effects of interventions

Occurrence rate of OIC

All the 33 included studies reported the occurrence rate of OIC. As shown in figure 4, meta-analysis demonstrated that the occurrence rate of OIC in the DZC group was statistically lower than that of the control group (6.7% vs 44.5%, OR=0.07, 95% CI 0.05 to 0.11, p<0.00001, I^2=56%). To analyse the type effects of opioids (fentanyl and sufentanil), subgroup analysis was performed, which indicated that DZC significantly reduced the occurrence rate of FIC (8.8% vs 49.7%, OR=0.07, 95% CI 0.04 to 0.12, p<0.00001, I^2=61%) and SIC (5.0% vs 41.5%, OR=0.07, 95% CI 0.04 to 0.12, p<0.00001, I^2=53%). As shown in online supplemental figure 1, subgroup analysis demonstrated that the FIC occurrence rate increased from 45.0%, 43.1%, 47.5% to 73.1% in the control group when fentanyl dosage increased from 2, 3, 4 to 5 µg/kg, respectively. Dose effect of sufentanil dosage on the occurrence rate of SIC is shown in online supplemental figure 2.

Twenty-two RCTs[6 35–37 39 40 43 45–47 50–52 56–64] reported the occurrence rate of mild and moderate OIC. As shown in online supplemental figures 3; 4, meta-analysis demonstrated that DZC group showed significantly lower occurrence rate of OIC than control group both on mild and moderate grades (mild OIC: 3.6% vs 13.6%, OR=0.19, 95% CI 0.14 to 0.25, p<0.00001, I^2=22; moderate OIC: 2.0% vs 13.6%, OR=0.12, 95% CI 0.09 to 0.18, p<0.00001, I^2=0). Subgroup analysis demonstrated that DZC significantly reduced the occurrence of either FIC (mild FIC: 5.2% vs 15.3%, OR=0.25, 95% CI 0.16 to 0.38, p<0.00001, I^2=28; moderate FIC: 3.1% vs 14.2%, OR=0.17, 95% CI 0.10 to 0.28, p<0.00001, I^2=0) or SIC (mild SIC: 2.4% vs 12.9%, OR=0.14, 95% CI 0.09 to 0.22, p<0.00001, I^2=11; moderate SIC: 1.1% vs 13.4%, OR=0.10, 95% CI 0.06 to 0.17, p<0.00001, I^2=0) when compared with placebo.

Twenty-five enrolled RCTs[6 35–37 39 40 43–47 50–52 54–64] reported the occurrence rate of severe OIC. As shown in online supplemental figure 5, meta-analysis demonstrated that the occurrence rate of severe OIC in the DZC group was remarkably lower than that of the control group (0.9% vs 13.7%, OR=0.08, 95% CI 0.05 to 0.12, p<0.00001, I^2=0). Subgroup analysis demonstrated that DZC significantly reduced the occurrence of either severe FIC (1.8% vs 13.5%, OR=0.12, 95% CI 0.07 to 0.20, p<0.00001, I^2=0) or severe SIC (0.3% vs 13.9%, OR=0.05, 95% CI 0.03 to 0.10, p<0.00001, I^2=0) when compared with placebo.

Subgroup analyses were also performed to investigate the dose effects of DZC on FIC and SIC occurrence rates. As shown in online supplemental figures 6; 7, DZC could effectively suppress OIC by fentanyl or sufentanil when administered at dosages ranging from less than 0.1 mg/kg to 0.3 mg/kg (or 5 mg). The dose of 0.1 mg/kg is mostly investigated and suggested as the optimal dose. Whether the prophylactic effect of DZC on OIC is dose dependent remains further verification.

Adverse effects

Six RCTs[48 50 53 58 64 65] reported possible side effects of DZC administration. As shown in figure 5, meta-analysis suggested that the occurrence rates of drowsiness, truncal rigidity, chill, respiratory inhibition, nausea and emesis of the DZC group were all comparable to those of the control group, with exception that the DZC-treated patients had higher occurrence rate of dizziness as compared with placebo (11.8% vs 0%, OR=8.06, 95% CI 1.40 to 46.35, p=0.02, I^2=0%).

Sensitivity analyses and publication bias

Sensitivity analysis showed that treatment effects on all the outcomes were not affected by the choice of statistical model (table 4). Sensitivity tests were also performed by exclusion of some studies to analyse the influence of the

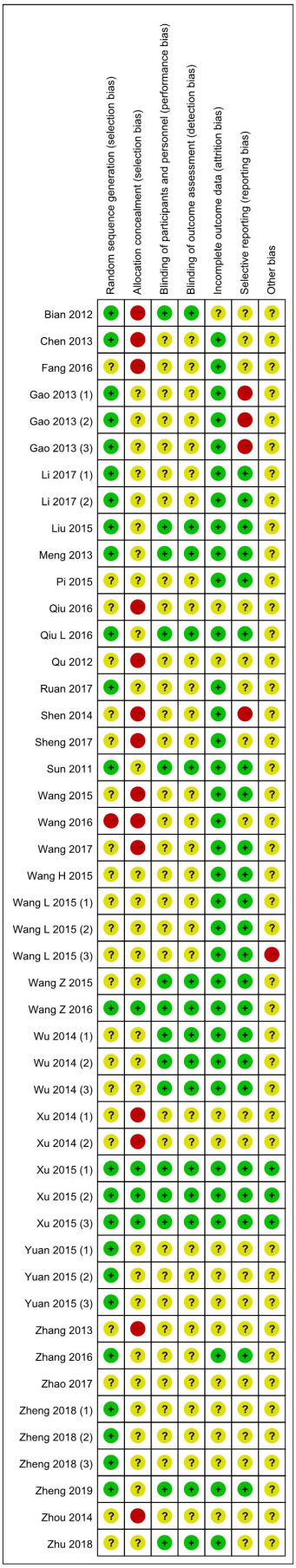

Figure 3 Risk of bias summary.

overall treatment effect on high heterogeneity outcomes (table 4), and no contradictory results were found in pooled OR and 95% CI. For occurrence rate of OIC, heterogeneity changed from 61% to 35% for FIC by exclusion of three studies conducted from Ya-Ping *et al* (female patients only),[39] Li *et al*[49] and Ming-Feng and Yu[58] (preoperative medication with phenobarbital) and 53% to 36% for SIC by exclusion of four studies conducted from Jie *et al* (female patients only),[47] Qing *et al* (duration of sufentanil injection more than 10 s),[57] Li-Ping[53] and Xiao-Zhen *et al*[63] (preoperative medication with phenobarbital). For occurrence rate of adverse effects, heterogeneity changed from 73% to 0% by exclusion of one study from Sheng *et al* (preoperative medication with phenobarbital).[48] No significant publication bias was detected by funnels plot examination for the occurrence rate of OIC (online supplemental figure 8A) and the occurrence rate of mild, moderate and severe OIC (online supplemental figure 8B, online supplemental figure 8C and online supplemental figure 8D).

DISCUSSION

Cough suppression is one useful side effect of opioids, which is the basis of their use in cough suppressants. Opioids depress the cough reflex by directly acting on the medullary cough centre.[16] Fentanyl and its derivatives sufentanil are commonly used opioid analgesics in the induction and maintenance of general anaesthesia. Intravenous bolus injection of fentanyl or sufentanil often cause cough. The present meta-analysis demonstrated that the occurrence rates of FIC and SIC were 49.7% and 41.5%, respectively, the occurrence rates of severe FIC and severe SIC were 13.5% and 13.9%, respectively, which is consistent with previous reports.[2 4 6 7 15] However, significant heterogeneity was found in the results, which may have affected the rigour of those findings. The heterogeneity may be explained by study design. For example, sex of the patients in excluded study in sensitivity analysis was obviously different from others. It was reported by Solanki *et al*[66] that occurrence rate of FIC was low when studied in female cancer patients (12.7%). However, contradictory results of 57.5% and 28.3% were observed in the two excluded study enrolling women only.[39 47] This may suggest that sex to some extent contributes to heterogeneity. In addition to that, study from Qing *et al*[57] with significant low SIC occurrence rate (3% in DZC group and 8% in Control group) was excluded owing to prolonged injection time (>30 s) in sensitivity analysis, which though made no influence on pooled effect, may improve the credibility of current meta-analysis.

Till now, the mechanism of OIC remains poorly understood. Various hypotheses have been proposed, which may involve opioid receptors, C-fibre receptors, rapid adapting pulmonary stretch receptors, histamine release and citrate in fentanyl and sufentanil injection.[1–3 15–17] Additionally, many factors can contribute to the occurrence of OIC, which can be divided into two categories.

Table 2 Quality assessment for primary outcomes

Quality assessment							Number of patients		Effect			Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DZC	Control	Relative (95% CI)	Absolute	Quality	
Effect of DZC on OIC occurrence rate												
47	Randomised trials	Serious	Serious	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1 dose response gradient	169/2521 (6.7%)	857/1921 (44.6%)	OR 0.07 (0.05 to 0.1)	393 fewer per 1000 (from 372 fewer to 407 fewer)	ÅÅÅÅ HIGH	CRITICAL
								50%		435 fewer per 1000 (from 409 fewer to 452 fewer)		
Effect of DZC on FIC occurrence rate												
23	Randomised trials	Serious	Serious	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1 dose response gradient	101/1150 (8.8%)	363/730 (49.7%)	OR 0.07 (0.04 to 0.12)	433 fewer per 1000 (from 391 fewer to 459 fewer)	ÅÅÅÅ HIGH	CRITICAL
								53.9%		463 fewer per 1000 (from 416 fewer to 494 fewer)		
Effect of DZC on SIC occurrence rate												
24	Randomised trials	Serious	Serious	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1 dose response gradient	68/1371 (5%)	494/1191 (41.5%)	OR 0.07 (0.04 to 0.12)	368 fewer per 1000 (from 336 fewer to 387 fewer)	ÅÅÅÅ HIGH	CRITICAL
								44.2%		389 fewer per 1000 (from 355 fewer to 411 fewer)		

DZC, dezocine; FIC, fentanyl-induced cough; OIC, opioid-induced cough; SIC, sufentanil-induced cough.

Table 3 Quality assessment for secondary outcomes

Quality assessment							Number of patients		Effect			
Numbero of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DZC	Control	Relative (95% CI)	Absolute	Quality	Importance
Dizziness												
3	Randomised trials	Serious	Serious	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1	10/85 (11.8%)	0/85 (0%) 0%	OR 8.06 (1.40 to 46.35)	– –	ÅÅÅO MODERATE	IMPORTANT
Drowsiness												
3	Randomised trials	Serious	No serious inconsistency	No serious indirectness	Serious	Strong association reduced effect for RR>>1 or RR<<1	6/85 (7.1%)	0/85 (0%) 0%	OR 4.91 (0.80 to 30.19)	– –	ÅÅÅÅ HIGH	IMPORTANT
Truncal rigidity												
1	Randomised trials	Very serious	No serious inconsistency	No serious indirectness	Serious	None	4/185 (2.2%)	0/185 (0%) 0%	OR 9.2 (0.49 to 172.07)	– –	ÅOOO VERY LOW	CRITICAL
Chill												
1	Randomised trials	Serious	Serious	No serious indirectness	Very serious	None	2/48 (4.2%)	11/48 (22.9%) 22.9%	not pooled	not pooled not pooled	ÅOOO VERY LOW	IMPORTANT
Respiratory inhibition												
2	Randomised trials	Serious	Very serious	No serious indirectness	Serious	None	17/233 (7.3%)	9/233 (3.9%) 9.4%	OR 1.7 (0.00 to 766.69)	25 more per 1000 (from 39 fewer to 930 more) 56 more per 1000 (from 94 fewer to 894 more)	ÅOOO VERY LOW	CRITICAL
Nausea and emesis												
3	Randomised trials	Serious	Serious	No serious indirectness	No serious imprecision	Reduced effect for RR>>1 or RR<<1	24/263 (9.1%)	18/263 (6.8%) 6.7%	OR 1.32 (0.03 to 53.18)	20 more per 1000 (from 66 fewer to 728 more) 20 more per 1000 (from 65 fewer to 725 more)	ÅÅÅO MODERATE	IMPORTANT

DZC, dezocine.

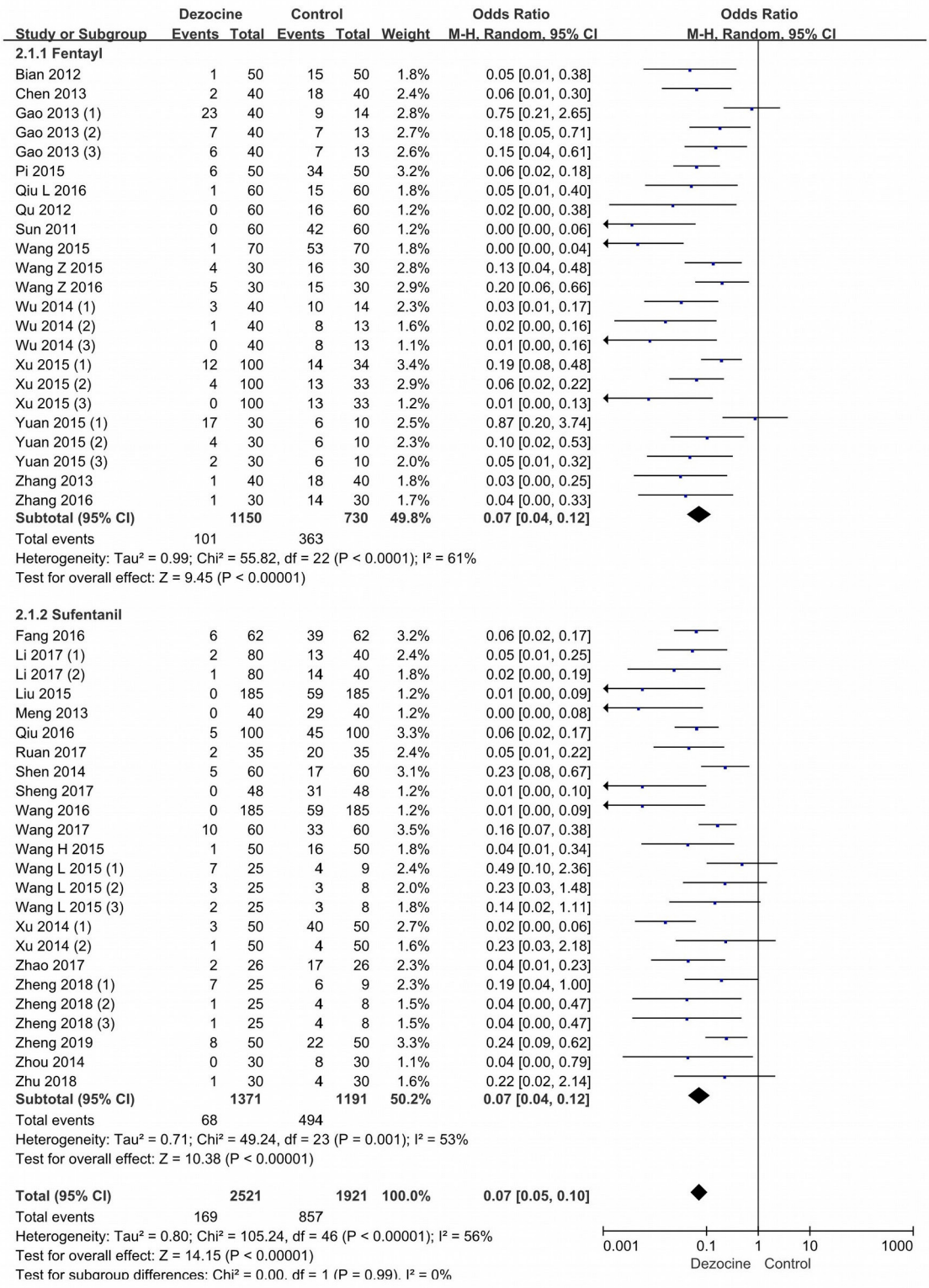

Figure 4 Forest plot of OIC occurrence rate. OIC, opioid-induced cough.

One is patients' individual physical conditions (age, sex, smoking status, disease history, etc). Another is usage of opioids (drug category, dosage, concentration, injection site, injection concentration, injection rate, etc).[15] Subgroup analysis suggested possible dose–effects of fentanyl and sufentanil on the occurrence rates of OIC.

OIC is associated with adverse effects and should be avoided. The antitussive efficacy of numerous

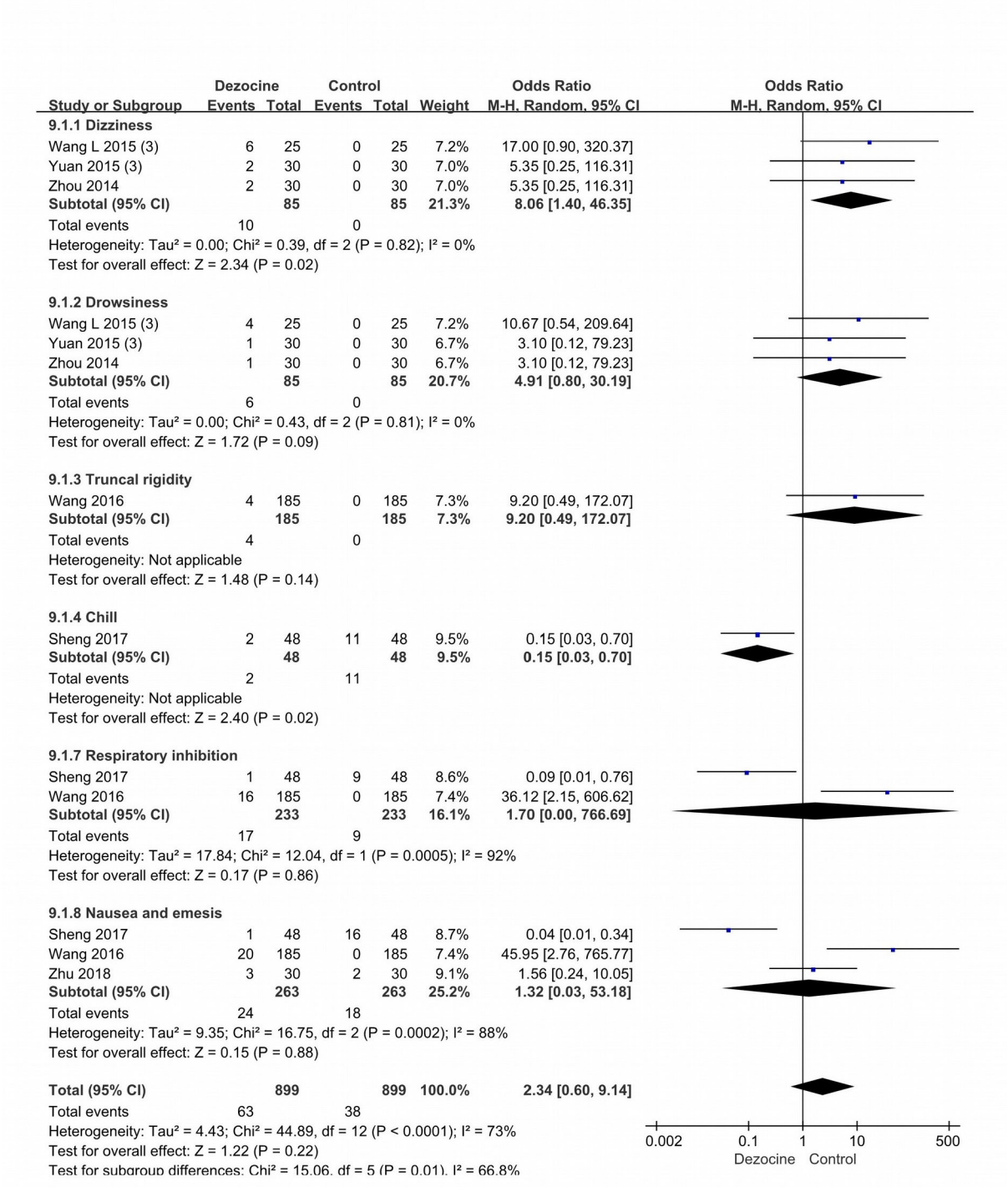

Figure 5 Possible adverse effects.

pharmaceutical and non-pharmaceutical interventions has been tested, some proved to be effective, some ineffective and some have side effects.[15] DZC, a mixed κ and μ opioid receptor agonist-antagonist, is not a well-known drug in Western countries.[24–27] However, DZC is widely applied as perioperative pain analgesic agent in China for decades.[24–26 28–32] The present meta-analysis demonstrated that DZC could significantly suppress both FIC and SIC, with several trials[4 6 35 41 45 48 50 56 64] reporting that DZC could completely prevent OIC. Furthermore, the subgroup analysis of the present meta-analysis suggested that the antitussive effect of DZC on FIC and SIC may be dose dependent. The mechanism responsible for the antitussive effect of DZC remains unknown. Possible explanation for this phenomenon is that DZC suppresses OIC by μ-receptor antagonism or norepinephrine/serotonine reuptake inhibition and reduce cough.[15] Whether a central gating mechanisms via

Table 4 Reliability of results

Influence of statistical model on estimated treatment effects of primary outcomes			
Statistical model	Cough occurrence rate OR (95% CI)	Severe cough occurrence rate OR (95% CI)	Adverse effects occurrence rate OR (95% CI)
Fixed effects	0.07 (0.05 to 0.08)	0.08 (0.05 to 0.12)	1.61 (1.09 to 2.39)
Random effects	0.07 (0.05 to 0.10)	0.11 (0.07 to 0.18)	2.34 (0.60 to 9.14)

Sensitivity analyses of high heterogeneity outcome									
Heterogeneity outcome	Excluded trials	Group DZC (n)	Group C (n)	Heterogeneity I^2 (%)	Heterogeneity *P*	Analysis model	OR	95% CI	Overall effect *P*
FIC (%)	39, 49, 58	280	140	35	0.08	M-H, fixed	0.06	(0.04 to 0.08)	<0.00001
SIC (%)	47, 53, 57, 63	285	235	36	0.07	M-H, fixed	0.04	(0.03 to 0.06)	<0.00001
Adverse effects (%)	48	48	48	0	0.59	M-H, fixed	10.75	(4.75 to 24.33)	<0.00001

DZC, dezocine; FIC, fentanyl-induced cough; SIC, sufentanil-induced cough.

C-fibre receptors or inhibition of histamine release play a role in the cough suppression elicited by DZC needs to be investigated.[4]

Because of its partial μ agonism, DZC exhibits a ceiling effect for common opioids-related adverse effects such as respiratory depression.[24–26] The meta-analysis suggested that DZC did not increase the occurrence rates of drowsiness, truncal rigidity, chill, respiratory inhibition, nausea and emesis but was associated with higher occurrence rate of dizziness. Whether DZC pretreatment interferes with opioid analgesia remains to be verified. Initial evidence indicated that DZC can enhance the analgesic effect of opioids and reduced OIC and opioid-related side effects.[67 68]

This study has some limitations. First, meta-analysis can increase the power of analysis by pooling many small low-quality studies, but different clinical practices, varied quality and heterogeneity of included studies may limit the certainty of the findings of meta-analysis. For example, there were no differences in DZC and control group on OIC occurrence rate when using preoperative medication of phenobarbital 30 min before anaesthesia induction.[53 58] One possible explanation is that sedatives exhibit similar effect on suppressing OIC as well according to previous study.[2] Second, all the 33 included RCTs were performed in China. The antitussive effectiveness of DZC may not be generalised to the whole world and remains to be investigated in other ethnicities. Third, the doses, injection rates or injection order of fentanyl or sufentanil varied among these included trials. For example, Sun and colleagues[4] reported DZC administered 10 min before anaesthesia induction could prevent FIC, which may be not a convenient practice in clinical settings. To determine the proper administration protocol of DZC for OIC prevention, a prospective randomised, placebo-controlled, triple-blinded trial is ongoing in our centre.

CONCLUSIONS

This meta-analysis has demonstrated that, DZC significantly inhibited OIC and may be used to manage OIC induced by fentanyl or sufentanil. More high-quality RCTs are needed to complement the safety of DZC.

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