Systematic Review and Meta-Analysis

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Efficacy and safety of dexmedetomidine combined with tramadol for patient-controlled intravenous analgesia in Chinese surgical patients

A systematic review and meta-analysis

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Abstract

Background: Patient-controlled intravenous analgesia (PCIA) has been suggested as an effective method of pain relief. There are several randomized controlled trials (RCTs) of dexmedetomidine (DEX) combined with tramadol for PCIA in Chinese surgical patients. The purpose of this study was to perform a systematic review and meta-analysis to evaluate the efficacy and safety of DEX combined with tramadol for PCIA in Chinese surgical patients from current data.

Methods: The RCTs of DEX combined with tramadol for PCIA were gathered from the PubMed, Excerpta Medica Database, Cochrane Library, Cochrane Library, China National Knowledge Infrastructure database, and VIP databases. After data extraction and quality assessment of the included RCTs, RevMan 5.3 software was employed for the meta-analysis of visual analog scale (VAS) scores, Ramsay sedation scores, effective pressure times for PCIA, tramadol consumption, and safety.

Results: Fourteen RCTs were included. Compared with tramadol alone, postoperative intravenous tramadol-DEX combination PCA led to lower VAS scores (weighted mean differences [WMD]$_{12h}$ = 0.14, 95% confidence interval [CI] v1.50 to 1.79; WMD$_{24h}$ = 0.78, 95% CI −0.92 to −0.62; WMD$_{48h}$ = 0.51, 95% CI −0.66 to −0.38; all $P < .05$), lower Ramsay sedation scores (WMD$_{24h}$ = 0.08, 95% CI −0.14 to −0.02; WMD$_{48h}$ = 0.09, 95% CI −0.11 to −0.07; all $P < .05$), and less postoperative tramadol consumption (WMD$_{0–24h}$ = −102.59 mg, 95% CI −149.68 to −55.49; WMD$_{0–48h}$ = −152.91 mg, 95% CI −259.93 to −45.89; all $P < .05$). With regard to safety, there was a significant difference between DEX-tramadol and tramadol for PCIA in terms of the incidence of postoperative nausea and vomiting, dizziness, chills, and restlessness (all $P < .05$).

Conclusion: According to the domestic evidence, this systematic review and meta-analysis suggests that DEX-tramadol PCIA is superior to tramadol in terms of analgesic efficacy and safety for Chinese surgical patients. However, because of some clear limitations (sample size and heterogeneity), these results should be interpreted with caution. Further large-scale and well-designed studies are needed to summarize and analyze the data to draw a more convincing conclusion.

Abbreviations: ADRs = adverse reactions, AEs = adverse events, DEX = dexmedetomidine, EBM = evidence-based medicine, PCIA = patient-controlled intravenous analgesia, PONV = postoperative nausea and vomiting, RCTs = randomized controlled trials, VAS = visual analog scale.

Keywords: dexmedetomidine, efficacy, meta-analysis, patient-controlled intravenous analgesia, safety, systematic review, tramadol

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PC and FC contributed equally to this work.

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1. Introduction

Opioids are the most commonly used medications to manage postoperative pain. However, it is difficult for surgical patients to take drugs orally to relieve pain. In contrast, the administration of intravenous analgesics is very appropriate.[1] Patient-controlled intravenous analgesia (PCIA), in which many drugs are mixed in a small container and delivered via a syringe, has been used in clinical practice for many years.[2] Tramadol hydrochloride is a centrally acting synthetic analgesic with opioid and nonopioid actions and has been commonly used the management of postoperative pain, visceral and cancer-related pain.[3] PCIA with tramadol is a convenient treatment regimen for postoperative pain and is widely used in clinical practice.[4] However, it is always associated with adverse reactions (ADRs), such as nausea and vomiting, which can affect the quality of life of patients and can lead to discomfort and mental consequences.

Dexmedetomidine (DEX) is an effective alpha-2 adrenalin receptor agonist that is mainly used for sedation, anti-anxiety, and analgesia in clinical patients. This drug can reduce opioid requirements and potentiate analgesia without any respiratory

depression during treatment and has been widely administered for the prevention and treatment of postoperative nausea and vomiting (PONV) during PCIA for several decades.[5] Due to the clinical benefits of DEX, the combination use of DEX-tramadol for PCIA is gaining popularity. Recently, several published studies have concentrated on this strategy and compared the analgesic efficacy and safety between DEX combined with tramadol and tramadol alone for PCIA, but the sample sizes were not sufficient, and the results were inconclusive.[6]

Thus, the evidence supporting its use remains controversial and a systematic evaluation of methodologic quality is lacking. This systematic review and meta-analysis was performed to compare the effects of postoperative intravenous DEX-tramadol and tramadol alone for PCIA on the efficacy and safety of analgesia in Chinese surgical patients.

2. Methods

2.1. Data sources and search strategy

PubMed, Excerpta Medica Database, Cochrane Library, China National Knowledge Infrastructure database, Chinese Scientific Journals Full Text Database, Wanfang Data Knowledge Service Platform, and the Chinese Biomedical Literature Service System were searched from January 1997 to January 2019 using the keywords "dexmedetomidine," "tramadol," "patient-controlled analgesia," and "Chinese surgical patients" as well as "clinical trials." In addition, we also searched the abstracts that contained "dexmedetomidine combined with tramadol for patient-controlled intravenous analgesia in Chinese surgical patients" presented at the European Society for Medical Oncology and major meetings of the American Society of Clinical Oncology. The publication years were from 2004 to 2019. Finally, the references from the Web of Science database were also scanned to ensure that no additional studies were missed.

2.2. Study selection

We included studies meeting the following criteria:

(1) randomized clinical trials (RCTs);
(2) Chinese adult surgical patients receiving PCIA;
(3) trials comparing DEX and tramadol with tramadol for PCIA performed by medical staff;
(4) data available for the postoperative pain-related outcomes and adverse events (AEs).

The exclusion criteria were as follows:

(1) case series or single-arm trials;
(2) nonrandomized trials;
(3) DEX used in combination with tramadol for PCIA after surgery rather than for anesthesia intraoperatively;
(4) original studies that meet criterion
(5) (3) but lacked information such as visual analog scale (VAS) scores, Ramsay sedation scores, and AEs.

2.3. Data extraction and quality evaluation

We extracted from the included trials the following information: the first author, year of publication, number of patients enrolled in the study, treatment proposal, and types of surgical operation. The outcome variables included the following:

(1) VAS scores and Ramsay sedation scores at 6 time points (postoperative hours 4, 6, 8, 12, 24, and 48);
(2) tramadol consumption during postoperative hours 0 to 24 and 0 to 48;
(3) effective pressure times for PCIA; and
(4) the proportion of patients experiencing opioid-related AEs (PONV, dizzy, chills, drowsiness, and bradycardia).

We evaluated the methodological quality of the included studies, according to the following RCT quality evaluation standards of the Cochrane review manual 5.3.0:

(1) generation of the random allocation scheme;
(2) allocation concealment;
(3) blinding of participants and personnel;
(4) blinding of outcome assessment;
(5) incomplete outcome data; and
(6) selective reporting.

The risk of bias of each study was summarized as "high," "low" or "unclear." Any disagreement was settled by discussion or negotiation.

2.4. Statistical analysis

The statistical analysis was performed with Review Manager Version 5.3 software, which was provided by the Cochrane Collaboration, Oxford, UK. The effect size of categorical outcomes was determined by the pooled odds ratio (OR), along with 95% confidence intervals (CIs). The continuous results were calculated by weighted mean differences (WMD) with 95% CI. The between-study heterogeneity was assessed using the Chi-squared test. If I^2 was $< 50\%$ ($P > .1$), the fixed-effect model was used; if not ($I^2 > 50\%$, $P < .1$), the random effect model was employed, and we attempted to discover the cause of the heterogeneity. Egger test was used to evaluate the presence of publication bias. *P*-values less than .05 or .01 were considered significant. All analyses were based on previous published studies, and no ethics approval or patient consent was required.

3. Results

3.1. Search results

A total of 172 documents were obtained through the preliminary examination of the databases. Of those, 21 potential studies were considered eligible after reading the title and abstract. After analyzing the full-text articles, 7 studies that did not meet the inclusion criteria were excluded, and 14 studies[7–20] were found to be eligible for inclusion according to our criteria and were ultimately included in the meta-analysis. The selection procedure is described in Figure 1, which illustrates how the 14 studies were obtained.

The 14 selected studies, comprising a total of 848 Chinese surgical patients (DEX-tramadol combination group: 425 patients; tramadol monotherapy group: 423 patients), were all RCTs investigating the use of a DEX-tramadol combination compared with tramadol alone for postoperative PCIA. Of the 14 studies, 6 studies[7,9,13,14,17,18] combined DEX with tramadol for PCIA up to postoperative hour 24, and the other 8 trials[8,10–12,15,16,19,20] were up to hour 48. The dose of analgesics varied among trials, and the main characteristics of the included trials are listed in Table 1.

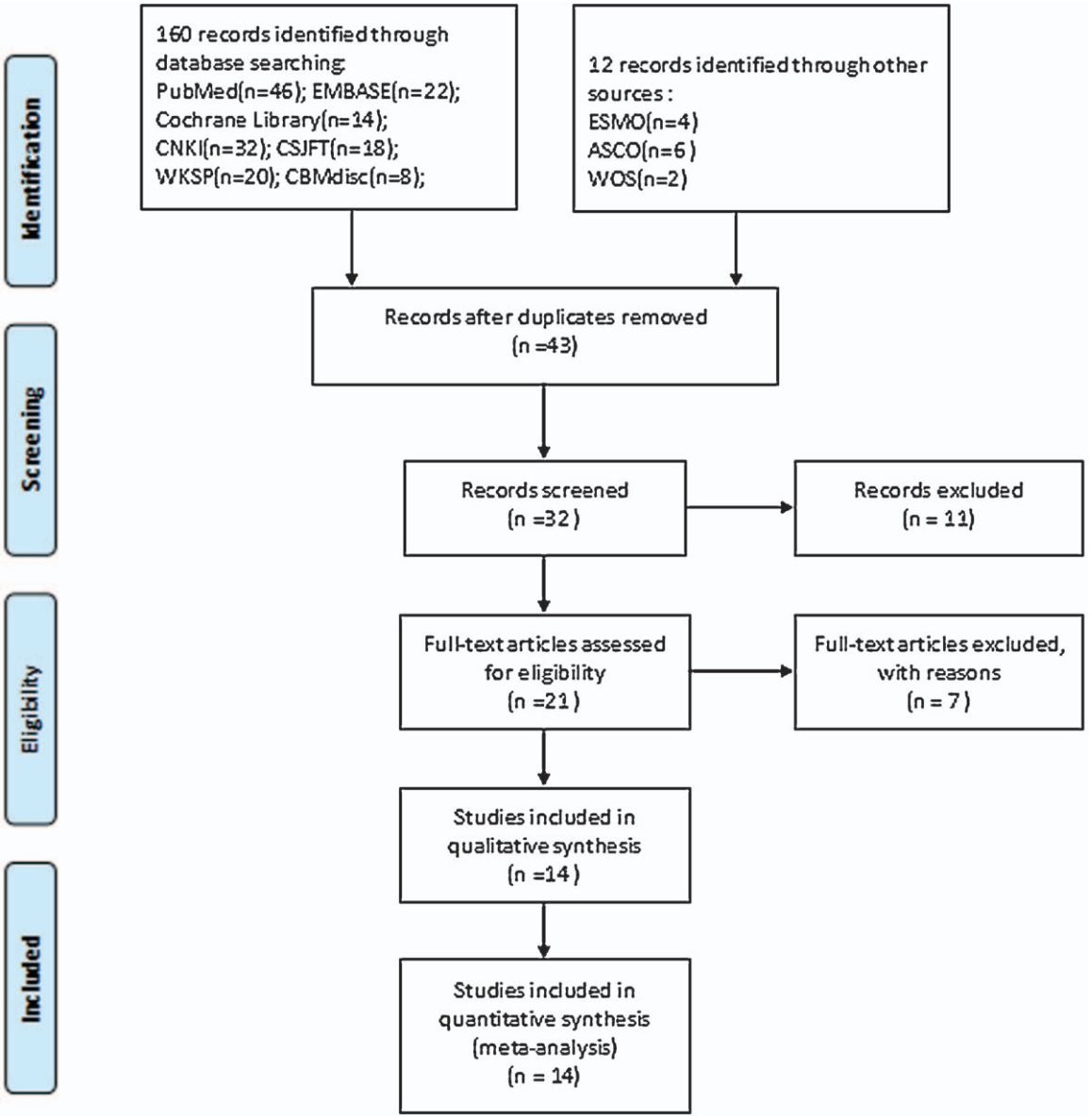

Figure 1. Chat for the search result and trials screen.

3.2. Meta-analysis results of effectiveness between DEX-tramadol and tramadol for PCIA in Chinese surgical patients

3.2.1. Meta-analysis of VAS scores. In total, 10 trials[7,8,10–15,19,20] (n=426) were included in the meta-analysis for VAS scores at postoperative hours 4, 6, 8, 12 and 24. With regard to the pain intensity at 12 hours, 24 hours, and 48 hours, the results showed that pain scores in patients receiving PCIA with a DEX-tramadol combination were significantly lower than those in patients receiving tramadol alone. The WMD increased from 0.14 (95% CI: −1.50 to 1.79, $P=.0004$, $I^2=98\%$) at postoperative hour 12 to 0.78 (95% CI: −0.92 to −0.62), $P<.01$, $I^2=92\%$) at postoperative hour 24 and decreased to 0.51 (95% CI: −0.66 to −0.38), $P<.01$, $I^2=94\%$) at postoperative hour 48. The results for the VAS scores of the included trials are listed in Table 2.

3.2.2. Meta-analysis of Ramsay sedation scores. Data reporting the Ramsay sedation scores at postoperative hours 24 and 48 were described in 7 trials.[7,8,10,11,17–20] Significant differences in Ramsay sedation scores in patients receiving PCIA with a DEX-tramadol combination compared with patients receiving tramadol alone were found at all time points (WMD= 0.08, 95% CI: −0.14 to −0.02, $P=.03$, $I^2=53\%$; WMD=0.09, 95% CI: −0.11 to −0.07, $P<.01$, $I^2=40\%$, respectively, Table 2).

3.2.3. Meta-analysis of effective pressure times for PCIA. Data reporting effective pressure times for PCIA were described in 5 trials.[8,10,11,14,19] The effective pressure times for PCIA were significantly lower in patients receiving DEX-tramadol combination therapy than in patients receiving tramadol during postoperative hours 0 to 24 and 0 to 48 (WMD=−2.65, 95% CI: −4.52 to −0.79, $P<0.01$, $I^2=89\%$; WMD=−5.02, 95%CI: −6.52 to −3.50, $P<0.01$, $I^2=98\%$, Table 2).

Table 1

Characteristics of included studies.

Study	Sample, N			Surgery	Pain treatment after surgery (loading dose, PCA system)		Durations of treatment	Main outcomes
	D + T	D	T		D + T	T		
An et al 2016[7]	50	50	50	Cesarean section	T1 g + D200 μg/100 mL PCA	T1 g/100 mL PCA	24 h	①②④⑤
Jin et al 2016[8]	66	NA	66	Nephrectomy	T10 mg/kg + D2 μg/kg + A24 mg PCA	T10 mg/kg + A24 mg PCA	48 h	①②③④⑤
Li et al 2014[9]	46	NA	46	Gynecologic surgery	T1 mg/kg+D1 μg/kg PCA	T1 mg/kg PCA	24 h	①⑤
Li et al 2015[10]	100	100	100	Abdominal surgery	T0.7 mg/kg + D2 μg/kg PCA	F1 mg + T50 mg + A10 mg/100 mL PCA	48 h	①②③④⑤
Liu et al 2015[11]	30	30	30	Cesarean section	T15 mg/kg + D4 μg/kg + G3 mg PCA	T15 mg/kg + G3 mg PCA	48 h	①②③⑤
Wang et al 2016[12]	40	NA	40	Radical mastectomy	T1 g+D200 μg/100 mL PCA	T1 g/100 mL PCA	48 h	④⑤
Wang et al 2016[13]	20	20	20	Laparoscopic surgery	T1 mg/kg + D100 μg/100 mL PCA	T1 mg/kg PCA	24 h	①⑤
Wang et al 2016[14]	50	NA	50	Osteoarthroplasty	D2 μg/kg + T100 mg + A10 mg PCA	T100 mg + A10 mg/100 mL PCA	24 h	①③④⑤
Wang et al 2013[15]	30	NA	30	Nasal endoscopic surgery	D1 μg/kg + T1 mg/kg PCA	T1 mg/kg PCA	48h	①④⑤
Xu et al 2012[16]	40	NA	40	Radical mastectomy	T1 g + D200 μg/100 mL PCA	T1 g/100 mL PCA	48 h	④⑤
Yang et al 2013[17]	20	20	20	Fracture surgery	T400 mg + D100 μg/100 mL PCA	T500 mg + A5 mg/100 mL PCA	24 h	①②④⑤
Yuan et al 2016[18]	30	30	30	Fracture surgery	T400 mg + D100 μg/100 mL PCA	T500 mg/100 mL PCA	24 h	②④⑤
Zhao et al 2016[19]	60	NA	60	Hysterectomy	T600 mg + D100 μg + F100 mg/100 mL PCA	T600 mg + F100 mg/100 mL PCA	48 h	①②③④⑤
Zhou et al 2015[20]	20	NA	20	Cranial fossa surgery	T0.15 mg/kg + D1 μg/kg + A8 mg PCA	T0.15 mg/kg + A8 mg PCA	48 h	①②⑤

① Visual analog scale (VAS) scores; ② Ramsay scores; ③ Effective pressure times for PCA; ④ Tramadol consumption; ⑤ Adverse reaction rate.
A = ondansetron, D = dexmetomidine, F = flurbiprofenaxetil, G = granisetron, PCA = patient-controlled analgesia, T = tramadol.

3.2.4. Meta-analysis of tramadol consumption. The analysis of the postoperative opioid requirements included 8 trials.[7,8,10,14,16–19] A significant decrease in tramadol consumption was observed in patients receiving the combination of DEX-tramadol for PCIA during postoperative hours 0 to 24 (WMD_{0-24h} =, −102.59 mg, 95% CI: −149.68 to −55.49, $P < .01$, $I^2 = 99\%$) and postoperative hours 0 to 48 (WMD_{0-48h} = −152.91 mg, 95% CI: −259.93 to −45.8–9, $P = .005$, $I^2 = 96\%$, Table 2) when compared to the patients receiving tramadol alone.

Table 2

Meta-analysis results of effectiveness between DEX-tramadol and tramadol for PCIA in Chinese surgical patients.

Outcomes	Trails (n)	Participants (n)		I^2 test		Statistical method	Results of meta-analysis	
		D + T	T	I^2%	*P*-value		Estimated benefit (95% CI)	*P*-value
VAS scores								
At 4 h	6[7,10–12,14,19]	286	286	97%	<.01	Random	WMD = 0.14 [−1.50, 1.79]	.09
At 6 h	3[13,14,20]	80	80	96%	<.01	Random	WMD = 0.52 [−0.09, 1.14]	.12
At 8 h	6[7,10–12,14,19]	286	286	95%	<.01	Random	WMD = −0.74 [−1.06, −0.42]	.07
At 12 h	7[7,10–12,14,15,19]	256	256	98%	<.01	Random	WMD = −0.76 [−1.22, −0.36]	.0004
At 24 h	10[7,8,10–15,19,20]	426	426	92%	<.01	Random	WMD = −0.78 [−0.92, −0.62]	<.01
At 48 h	5[8,10,11,19,20]	216	216	94%	<.01	Random	WMD = −0.51 [−0.66, −0.38]	<.01
Ramsay scores								
At 4 h	4[7,10,11,19]	186	186	95%	<.01	Random	WMD = 0.04 [−0.50, 0.60]	.82
At 6 h	2[13,22]	60	60	94%	<.01	Random	WMD = −0.72 [−2.06, 0.69]	.28
At 8 h	4[7,10,11,19]	200	200	97%	<.01	Random	WMD = 0.10 [−0.45, 0.62]	.74
At 12 h	3[10,11,20]	110	110	92%	<.01	Random	WMD = −0.32 [−0.80, 0.11]	.17
At 24 h	7[7,8,10,11,17–20]	316	316	53%	.06	Random	WMD = −0.08 [−0.14, −0.02]	.03
At 48 h	5[8,10,11,19,20]	216	216	40%	.15	Fixed	WMD = −0.09 [−0.11, −0.07]	<.01
Effective pressure times for PCIA								
At 24 h	3[8,10,14]	156	156	89%	.008	Random	WMD = −2.65 [−4.52, −0.79]	<.01
At 48 h	4[8,10,11,19]	196	196	98%	<.01	Random	WMD = −5.02 [−6.52, −3.50]	<.01
Tramadol consumption								
0–24 h	7[7,8,14,16–19]	310	310	99%	<.01	Random	WMD = −102.59 [−149.68, −55.49]	<.01
0–48 h	4[8,10,16,19]	206	206	96%	<.01	Random	WMD = −152.91 [−259.93, −45.89]	.005

CI = confidence interval, D = dexmetomidine, PCIA = patient-controlled intravenous analgesia, T = tramadol, VAS = visual analog scale, WMD = weighted mean differences.

Table 3

Meta-analysis results of safety between DEX-tramadol and tramadol for PCIA in Chinese surgical patients.

Outcomes	Trails (n)	Participants (n)		I^2 test		Statistical method	Results of meta-analysis	
		D + T	T	I^2%	*P*-value		Estimated benefit (95% CI)	*P*-value
D + T versus T								
PONV	10[7,8,10–12,14,15,17,19,20]	446	446	0%	.97	Fixed	OR = 0.26 [0.16, 0.42]	<.01
Dizzy	7[8,14–16,10,11,19]	380	380	0%	.46	Fixed	OR = 0.29 [0.14, 0.61]	<.01
Chills	5[9,10,13,14,20]	216	216	0%	.94	Fixed	OR = 0.18 [0.06, 0.52]	.0002
Drowsiness	3[13,14,19]	140	140	0%	.82	Fixed	OR = 0.43 [0.16, 1.18]	.10
Bradycardia	2[10,11]	130	130	31%	.23	Fixed	OR = 0.46 [0.21, 1.02]	.06
Restlessness	2[10,13]	130	130	10%	.29	Fixed	OR = 0.03 [0.02, 0.08]	<.01
Total adverse reaction rate	14[7–20]	1442	1442	35%	.03	Fixed	OR = 021 [0.15, 0.27]	<.01

CI = confidence interval, D = dexmetomidine, OR = odds ratio, T = tramadol.

3.3. Meta-analysis results of safety between DEX-tramadol and tramadol for PCIA in Chinese surgical patients

For the safety analysis, we selected several of the most frequent AEs. All the meta-analysis results regarding AEs are listed in Table 3. Data reporting AEs were described in 14 trials.[7–20] There were lower incidences of PONV (OR = 0.26, 95% CI: 0.16–0.42, $P < .01$, $I^2 = 97\%$), dizziness (OR = 0.29, 95% CI: 0.14–0.61, $P < .01$, $I^2 = 46\%$), chills (OR = 0.18, 95% CI: 0.06–0.52, $P = .0002$, $I^2 = 94\%$), and restlessness (OR = 0.03, 95% CI: 0.02–0.08, $P < .01$, $I^2 = 10\%$) in patients receiving PCIA with DEX-tramadol combination than in patients receiving tramadol alone. The total ADR rate in patients treated with DEX-tramadol was significantly lower than that in patients treated with tramadol alone (OR = 0.21, 95% CI: 0.15–0.27, $P < .01$, $I^2 = 35\%$). There was no report of other AEs, including rash, bradycardia, diarrhea, or respiratory depression, in either group.

3.4. Risk of bias in included studies

The risk of bias assessment of the included studies is shown in Table 4. Six trials[7,11,13,14,16,19] detailed the methods of randomization, 10 trials[7–9,11–14,16,18,20] detailed the methods of double-blinding, and 11 trials[7,8,10–14,16–19] clearly reported allocation concealment. The funnel plot shows a certain asymmetry (Fig. 2), indicating that there is some degree of publication bias. However, the number of studies included was only ten, and the funnel plots may not be very reliable. Egger test revealed that there was no significant difference in the ORs of AEs in our study ($P = .32$).

4. Discussion

Critically ill hospitalized patients are often in need of many drugs for postoperative pain management.[21] Over the years, opioid drugs such as fentanyl, tramadol, and morphine have been the preferred drugs for postoperative pain, occupying an important position in postoperative pain management.[22] The opioid analgesic effect is considerable, but opioids cause several ADRs, such as nausea, vomiting, dizziness, and drowsiness, which are very detrimental to treatment and recovery during postoperative analgesia.[4,5] Postoperative multimodal analgesia (MA) pain management with different types of postoperative analgesics may provide powerful pain relief with reduced side effects for patients who have undergone operations.[6,23] Recent studies have revealed that the analgesic effect of α-2 adrenoceptor agonist DEX, which has a higher affinity for the α-2 adrenergic receptor than the α-1 adrenergic receptor at a ratio of 1620:1, maybe a new treatment approach for MA treatment.[24]

To the best of our knowledge, this is the first meta-analysis evaluating the efficacy and safety of DEX combined with tramadol for PCIA in Chinese surgical patients.[25] In the current meta-analysis including data from 848 patients, we found that the DEX-tramadol combination PCIA strategy led to lower

Table 4

Risk of bias of included trials.

References	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
An et al 2016[7]	Low	Low	Low	Low	Low	Low
Jin et al 2016[8]	Unclear	Low	Low	Unclear	Unclear	Low
Li et al 2014[9]	Unclear	Unclear	Low	Low	Low	Low
Li et al 2015[10]	Unclear	Low	Unclear	Unclear	Low	Low
Liu et al 2015[11]	Low	Low	Low	Unclear	Low	Low
Wang et al 2016[12]	Unclear	Low	Low	Unclear	Low	Low
Wang et al 2016[13]	Low	Low	Low	Low	Low	Low
Wang et al 2016[14]	Low	Low	Low	Low	Low	Low
Wang et al 2013[15]	Unclear	High	Unclear	Unclear	Low	Low
Xu et al 2012[16]	Low	Low	Low	Unclear	Low	Low
Yang et al 2013[17]	Unclear	Low	Unclear	Low	Low	Low
Yuan et al 2016[18]	Unclear	Low	Low	Unclear	Low	Low
Zhao et al 2016[19]	Low	Low	Unclear	Unclear	Low	Low
Zhou et al 2015[20]	Unclear	Unclear	Low	Low	Low	Low

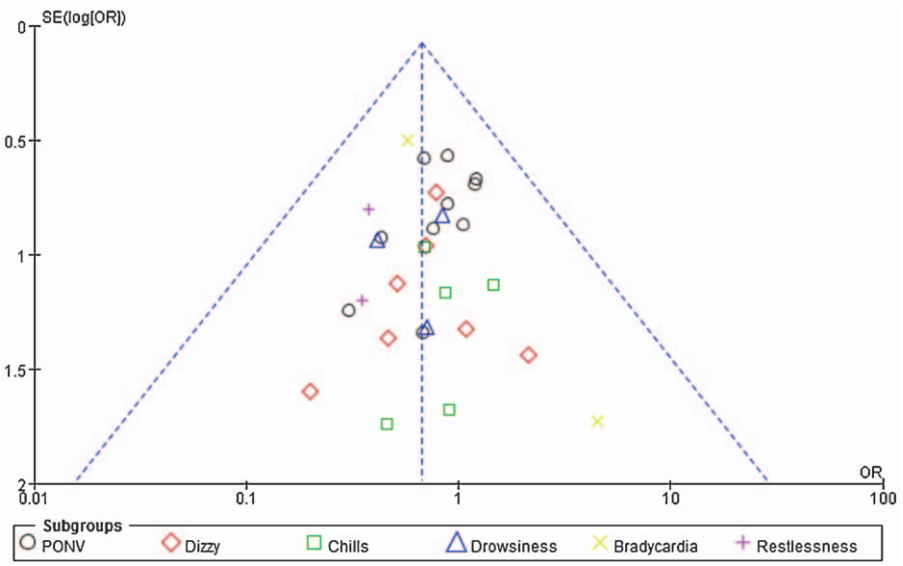

Figure 2. Funnel plot analysis for publication bias assessment.

postoperative pain intensity, lower postoperative opioid consumption, and lower incidences of PONV and dizziness compared to tramadol alone. These findings of this meta-analysis suggest that the combined use of DEX-tramadol for PCIA provided superior pain relief than tramadol alone.

Previous studies have concentrated on the use of DEX for preoperative or intraoperative analgesia.[3,24] The current meta-analysis revealed that the postoperative administration of the combination of DEX and tramadol induced analgesic and tramadol-sparing effects. In addition, published meta-analyses have shown that the use of the DEX-tramadol combination for PCIA in patients resulted in significantly greater pain relief compared with opioids alone. In this meta-analysis, patient-reported pain intensity was found to be less in the DEX-tramadol group at 24 and 48 hours compared to the tramadol group. Because of the negative WMD in VAS scores and Ramsay sedation scores between the DEX-tramadol and tramadol groups, it can be deduced that DEX combined with tramadol for PCIA is likely to be more effective at treating pain compared with conventional analgesia.[26] These improved analgesic effects provided by DEX may result from modulation of the release of catecholamines, synergistic analgesic interactions with the opioid tramadol, and attenuation of the stress response to surgery and anesthesia.[27]

DEX is a potent and highly selective agonist and is approved by the US Food and Drug Administration for the postoperative sedation of patients requiring mechanical ventilation for less than 24 hours. Unlike the usual tranquilizers, DEX acts mainly on the central nervous system in the locus coeruleus to exert the same calming effect as natural sleep. However, no evidence has been found in our meta-analysis to show this DEX-induced excessive sedation during postoperative PCA. There may be a number of reasons for this:

(1) PCA permits patients to titrate intravenous opioids, which may play an important role in the prevention of additional sedative effects;
(2) if higher doses of PCA are needed to provide more effective pain relief during the analgesic period, the pain could counteract the excessive sedation; and
(3) the sedation levels may decrease along with the reduction in the cumulative dose of opioids for PCA.

The results of our meta-analysis also showed that there were significantly lower postoperative opioid consumption levels at 24 hours (WMD of 102.59 mg, tramadol consumption) and 48 hours (WMD of 152.91 mg, tramadol consumption) in patients administered the tramadol-DEX combination, and they needed less postoperative rescue analgesia. In addition, our meta-analysis demonstrated that the addition of DEX to tramadol for PCIA might significantly decrease the incidences of PONV, dizziness, chills, and restlessness. There are 2 possible explanations:

(1) the low dose of tramadol in the DEX-tramadol combination reduced the risk of side effects associated with opioid drugs and
(2) the antiemetic characteristics of DEX, due to the decrease in norepinephrine activity and sedative effect, may explain the lower incidence of PONV.[28,29]

However, there are no reports to date about the details of perioperative antiemetic prophylaxis.

There are several limitations in our analysis. First, because only 14 RCTs were included, the number of studies is small, and the sample size of patients in our study was also insufficient, potentially making the conclusions less convincing. Second, the difference in PCA dose regimens increased the bias in the calculations of tramadol consumption. Third, pain perception is individual and is impacted by participants' tolerance, the progression of labor, human influences (eg, psychological influence from doctors or nurses), analgesic doses, and other factors. Thus, the pain score by itself may not reflect pain relief efficacy.[30] Fourth, it is difficult for us to correlate our data with the dose delays/interruptions or discontinuations secondary to AEs in the analysis. Fifth, we observed significant heterogeneities in analytical indicators such as VAS scores, Ramsay scores, effective pressure times for PCIA and tramadol consumption; therefore, these findings must be assessed with caution. Sixth, because the studies included in this analysis were from China, the

results need confirmation in a wider range of ethnicities. Furthermore, there may have been publication bias; it could not be completely excluded based on the funnel plot. Finally, there is a lack of data on the long-term outcomes of the effect of DEX combined with tramadol for PCIA in the treatment of chronic pain. Therefore, it is necessary to carry out more large-scale and high-quality RCTs to summarize and analyze the data to confirm this conclusion.

Furthermore, a frequent problem is that mixing 2 or more injections together in infusion solutions induces physical changes, and the chemical degradation of ingredients could cause precipitation/crystallization and therefore reduce the analgesic efficacy.[31] Many clinical studies have evaluated the efficacy of DEX as an adjunct to tramadol PCIA for pain relief, but little or no information is available about the physical or chemical changes in the analgesic mixtures.[32] Therefore, clinicians should evaluate the compatibility and stability of binary admixtures of DEX and tramadol in the future to improve the safety and efficacy of these drugs.

5. Conclusion

In summary, our systemic review and meta-analysis initially demonstrated that the analgesic effects of DEX-tramadol for PCIA in Chinese surgical patients; we found that compared with tramadol alone, the DEX-tramadol combination resulted in superior analgesia effect, significant opioid sparing effects, and fewer AEs. Postoperative DEX administration may play an important role in multimodal treatment regimens for postoperative pain. Opioid-DEX combination is a safe and effective strategy for postoperative intravenous PCA. However, all the clinical trials involved had small sample sizes and no blinding, and their results may be unreliable. We urgently hope that large-scale, high-quality, double-blinded, and multicenter RCTs will be performed in the future to further confirm the efficacy and safety of PCIA with the DEX-tramadol combination.

Author contributions

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