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Effect of dexmedetomidine on postoperative nausea and vomiting in patients under general anaesthesia: an updated meta-analysis of randomised controlled trials

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ABSTRACT

Objectives To explore the effect of dexmedetomidine (DEX) on postoperative nausea and vomiting (PONV) in adult patients after general anaesthesia.

Design Systematic review and meta-analysis.

Eligibility criteria for selecting studies Randomised controlled trials (RCTs) comparing the efficacy of DEX with placebo or a single drug on PONV in adult patients after general anaesthesia.

Data sources We searched the PubMed, the Web of Science, the Cochrane Library and Embase (1 January 2000 to 30 June 2022) to select the relevant RCTs.

Data analysis All the relevant data were analysed by using RevMan V.5.4. Heterogeneity was tested for each outcome, and random-effect or fixed-effect models was selected according to the level of heterogeneity. The primary outcome was the incidence of PONV. The secondary outcomes were the incidence of bradycardia, perioperative opioid consumption, extubation time and the length of hospitalisation.

Results A total of 18 trials involving 2018 patients were included in this meta-analysis. Notably, 15 updated studies were not involved in the previous meta-analysis. The incidence of PONV in DEX group was lower than that in the control group (OR=0.49, 95% CI: 0.36 to 0.67) and the perioperative opioid consumption in DEX group was also decreased significantly (standard mean difference (SMD)=−1.04, 95% CI: −1.53 to −0.54). Moreover, the length of hospitalisation (SMD=−2.29, 95% CI: −4.31 to −0.28) and the extubation time (SMD=−0.75, 95% CI: −1.26 to −0.25) in DEX group were shorter. Whereas, more number of patients receiving DEX might increase the occurrence of bradycardia (OR=1.60, 95% CI: 1.13 to 2.27).

Conclusions DEX could decrease the occurrence of PONV in adult patients under general anaesthesia and promote the recovery after surgery. However, DEX might increase the occurrence of bradycardia.

PROSPERO registration number CRD 42022341548.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ An up-to-date assessment of the effectiveness of dexmedetomidine (DEX) on postoperative nausea and vomiting.
⇒ We excluded studies that DEX compared with opioids agents in our meta-analysis to eliminate the effect of opioids on postoperative nausea and vomiting.
⇒ The main limitation of this review was that varied quality and heterogeneity of included studies might affect the certainty of meta-analysis.

INTRODUCTION

Postoperative nausea and vomiting (PONV), as a familiar negative events after operation, is known as nausea, vomiting or retching within 1 day after operation, which may be due to the effect of anaesthetics on the emetic control centre in the medulla oblongata.[1] The incidence of PONV is about 30% and even rising to 60%–80% in high-risk populations. PONV, an extreme poor medical experience for patients undergoing general anaesthetic surgery, leads to many adverse influences including stomach discomfort, dehydration, water-electrolyte disorders, wound dehiscence, oesophageal injury, reflux and aspiration, which extend the time of hospitalisation and increase the medical costs.[2] Fortunately, prophylactic antiemetic agents could decrease the happening of PONV. However, these drugs produce some side effects including headache, restlessness, dry mouth, hypotension and cardiovascular complications, which limit their use in some cases.[3] Therefore, exploring suitable drugs and methods to prevent and treat PONV is necessary.

Dexmedetomidine (DEX), as a new adrenal α2 receptor agonist with high selectivity, has sedation, hypnosis and analgesia effects without respiratory depression, which is widely used in perioperative period. These

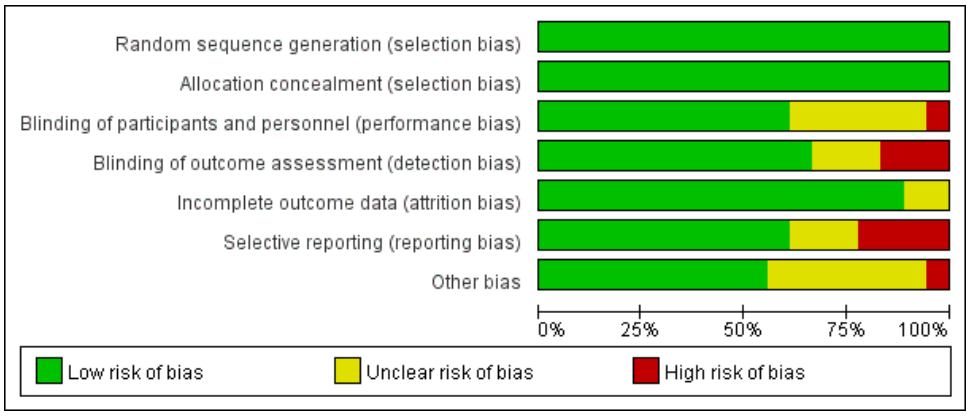

Figure 1 The risk-of-bias of included studies.

characteristics have enabled DEX to be a multifunctional drug in the presentments of numerous negative events during anaesthesia. For the last few years, the effect of DEX on PONV attracted increasing attention from anaesthesiologists. One clinical study reported that postoperative administration of DEX, as patient-controlled analgesia regimen, produced early antiemetic effects.[4] Another research indicated that intravenous DEX could prevent the occurrence of PONV in adult patients after laparoscopic hysterectomy.[5] While different results were observed in the similar articles,[6 7] it is still disputed whether intraoperative use of DEX can ameliorate the occurrence of PONV in patients after general anaesthesia.

As far as we know, no updated analysis of the data about the effect of DEX on PONV was performed during general anaesthesia. Therefore, in order to obtain the most recent proof, we thoroughly evaluated the effect of intraoperative use of DEX on PONV in adult patients

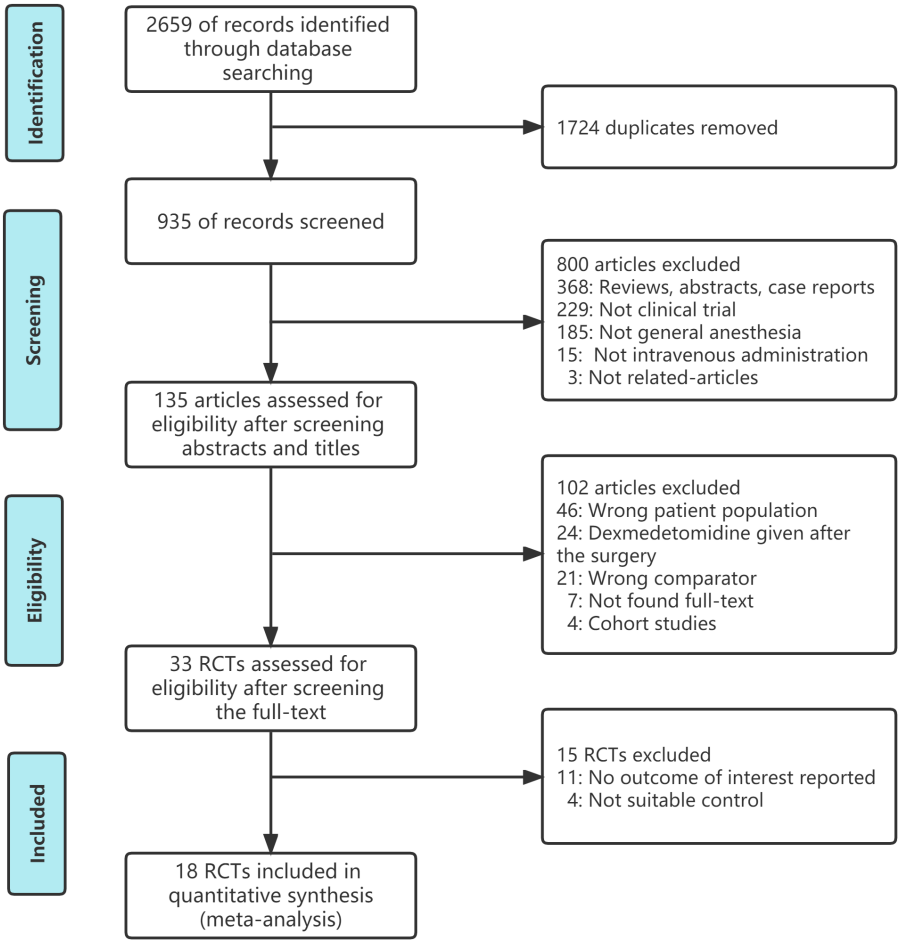

Figure 2 Flow diagram of the inclusion and exclusion process. RCTs, randomised controlled trials.

Table 1 Characteristics of the included trials

Author	Year	Age (years)		Gender male/female	Sample size	Type of surgery	Administration mode	Comparisons	Numbers of nausea and/or vomiting DEX/control	Scale used for assessing PONV
		DEX	Control							
Bakri *et al*[24]	2015	31.1±2.4	32.3±2.1	15/71	43/43	Laparoscopic cholecystectomy	1 µg/kg DEX intravenous	8 mg Dexa intravenous	9/12	A VAS of 0– 100 mm, 0 score meant no nausea, while 100 score meant the worst imaginable nausea
Peng *et al*[25]	2015	42.3±10.8	43.5±11.1	33/43	38/38	Craniotomy	Continuous infusion of DEX 0.5 µg/kg/hour intravenous	Equal volume of saline	16/28	0, absent; 1, nausea not requiring treatment; 2, nausea requiring treatment; and 3, vomiting.
Chen *et al*[26]	2016	56.67±2.705	60.17±1.644	29/31	30/30	Laparoscopic resection of colorectal cancer	Loading dose 1 µg /kg DEX, continuous infusion of 0.3 µg / kg/hour intravenous	Equal volume of saline	6/6	0, absent; 1, nausea not requiring treatment; 2, nausea requiring treatment; and 3, vomiting.
Bielka *et al*[27]	2018	55 (49–61)	53 (49–66)	July 53	30/30	Laparoscopic cholecystectomy	Continuous infusion of DEX 0.5 µg/kg/hour intravenous	Equal volume of saline	2/8	NR
Das *et al*[28]	2018	50.74±9.05	47.92±8.08	NR	50/50	Breast cancer surgery	Continuous infusion of DEX 0.6 µg/kg/hour intravenous	Equal volume of saline	2/8	NR
Wu *et al*[17]	2019	67	69	NR	NR	Laparoscopic radical prostatectomy	Loading dose 1 µg /kg DEX, continuous infusion of 0.5 µg / kg/hour intravenous	Equal volume of saline	2/10	NR
Bala *et al*[29]	2019	37.2±11.0	41±13.4	33/27	30/30	Transsphenoidal pituitary surgery	Loading dose 1 µg /kg DEX, continuous infusion of 0.5 µg / kg/hour intravenous	Equal volume of saline	2/6	NR
Wu *et al*[30]	2019	55.00±5.07	54.85±4.96	25/15	20/20	Cholangiojejunostomy or resection of tumour	Loading dose 0.5 µg /kg DEX, continuous infusion of 0.5 µg / kg/hour intravenous	Equal volume of saline	1/3	NR
Bakshi *et al*[31]	2020	51.8±12	47.2±13	14/26	19/21	Robotic-assisted laparoscopic oncosurgeries	Loading dose 1 µg /kg DEX, continuous infusion of 0.2 µg / kg/hour intravenous	Equal volume of saline	4/3	NR
Chen and Chen [32]	2020	42.68±7.59	43.35±6.82	41/36	39/38	Radical resection of gastric cancer	Loading dose 0.6 µg /kg DEX, continuous infusion of 0.4 µg / kg/hour intravenous	Equal volume of saline	1/3	NR
Asri *et al*[33]	2020	51±12	46±16	32/10	21/21	Thoracic surgery	Continuous infusion of DEX 0.3 µg/kg/hour intravenous	Equal volume of saline	0/5	NR
Pi and Yang [34]	2021	42.15±1.34	41.88±1.56	162/55	121/96	Thoracoscopic radical resection of lung cancer	Loading dose 0.4 µg /kg DEX, continuous infusion of 0.2 µg / kg/hour intravenous	Equal volume of saline	0/1	NR
Lu *et al*[35]	2021	70.1±5.8	70.4±6.5	445/230	344/331	Abdominal Surgery	Loading dose 0.5 µg /kg DEX, continuous infusion of 0.2 µg / kg/hour intravenous	Equal volume of saline	16/17	10-point rating scale 0: no PONV and 10: maximal PONV

Continued

Table 1 Continued

Author	Year	Age (years)		Gender male/female	Number	Type of surgery	Administration mode	Comparisons	Numbers of nausea and/or vomiting DEX/control	Scale used for assessing PONV
		DEX	Control							
Bafna *et al*[36]	2021	27.23+7.75	27.49+8.68	38/32	35/35	Endoscopic sinus surgery	Loading dose 1 µg /kg DEX, continuous infusion of 1 µg /kg/hour intravenous	Loading dose 2 µg /kg clonidine, continuous infusion of 1 µg /kg/hour intravenous	4/1	NR
Prashantha[37]	2021	37.73±7.24	35.63±12.61	19/61	40/40	Laparoscopic cholecystectomy	DEX IV	Saline intravenous	5/14	NR
Chen *et al*[38]	2021	55.93±11.14	55.64±10.81	41/35	38/38	Thoracoscopic pulmonary segmentectomy	0.6 µg/kg DEX infusion from 10 min before induction	Equal volume of saline	1/1	NR
Yan and Ti-jun[7]	2021	73.2±5.8	72.7±4.3	42/58	50/50	Total hip arthroplasty	Continuous infusion of DEX 0.3 µg/kg/hour intravenous	Equal volume of saline	5/4	NR
Chen *et al*[16]	2021	50.76±8.32	51.07±9.43	44/36	40/40	Intestinal surgery	Loading dose 1 µg /kg DEX, continuous infusion of 0.4 µg / kg/hour intravenous	Equal volume of saline	1/6	NR

DEX, dexmedetomidine; Dexa, dexamethasone; NR, not reported; PONV, postoperative nausea and vomiting; VAS, Visual Analogue Scale.

experiencing general anaesthesia according to the results from the 18 randomised controlled trials (RCTs) in our meta-analysis.

METHODS

Patient and public involvement

No patient involved.

Registration

This meta-analysis was prepared by following the criteria as outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysesguidelines[8] (online supplemental document 1). The meta-analysis was registered on PROSPERO (registry number: CRD 42022341548).

Search strategy

Two investigators independently searched for articles published in PubMed, the Web of Science, Embase and the Cochrane Library. The complete search strategy protocol is shown in online supplemental document 2. In order to ensure the contemporary practice, the literature was searched from 1 January 2000 to 30 June 2022.

Inclusion and exclusion criteria

The inclusion criteria were in accordance with patient–intervention–comparison–outcome:

1. Patients: adult participants undergoing general anaesthetic surgery.
2. Intervention: received a single or continuously administered intravenous dose of intraoperative DEX.
3. Comparison: received a single or continuously administered intravenous injection of placebo or comparator.
4. Outcomes: the incidence of PONV and bradycardia, the perioperative opioid consumption, the extubation time and the length of hospitalisation.

The reviews, abstracts, case reports or duplicates were excluded. Additionally, some RCTs meeting the following criteria were also excluded: (1) drug/drugs (including DEX) versus combinational drugs; (2) DEX compared with opioids agents; (3) adult patients undergoing surgery under local or spinal–epidural anaesthesia; and (4) full text not available.

Data extraction and analysis

All information of the articles was collected independently by two researchers using standardised forms. Any problems were decided by a third author in order to discuss and reach an agreement. The corresponding data were collected: first author, type of surgery, publication year, number of patients, administrations for patients, the incidence of PONV and bradycardia, the perioperative opioid consumption, the extubation time and the length of hospitalisation. A standardised Excel file was used to save the extracted data. And all the data were pooled together. Studies were excluded when the primary outcome was not clearly reported with quantifiable data or it was

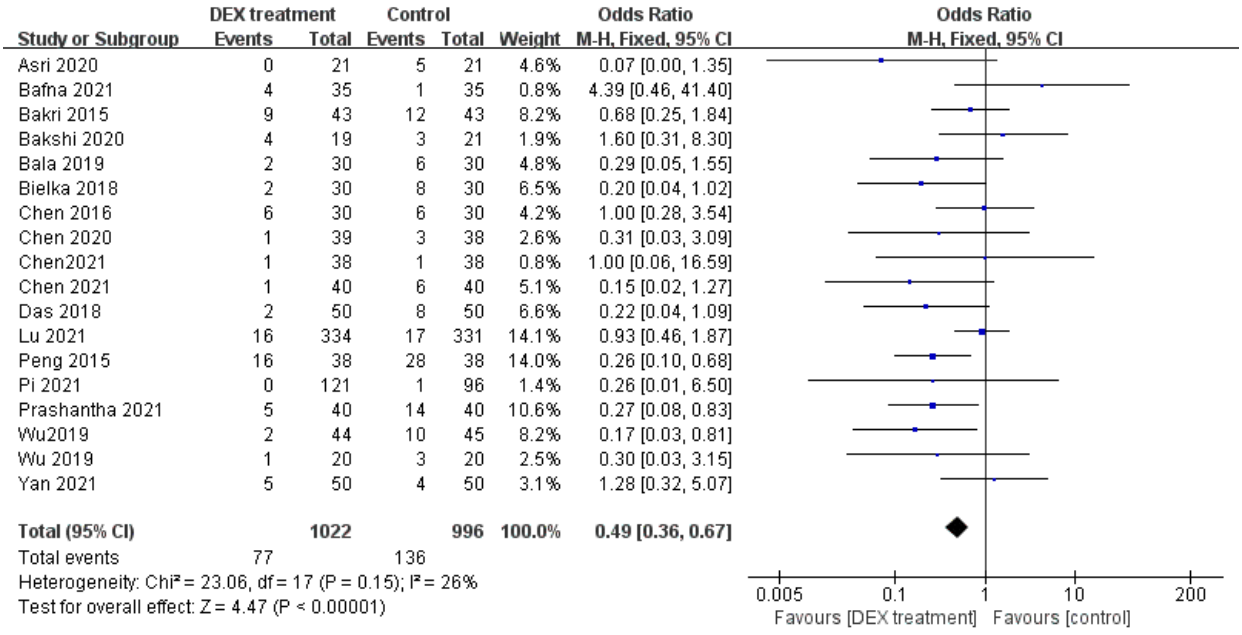

Figure 3 The total effect of DEX on postoperative nausea and vomiting. DEX, dexmedetomidine.

not possible to extract and calculate the appropriate data from the published results.

Risk-of-bias assessment

In accordance with the Cochrane risk-of-bias tool,[9] the risk-of-bias in the included articles were evaluated by two authors independently (figure 1). According to the following criteria: bias from selection, performance, detection, attrition, reporting and other, we reviewed and scored each study as 'high', 'unclear' and 'low'.

Statistical analysis

We used the Review Manager V.5.4 software to perform statistical analysis. For dichotomous data, we calculated ORs with 95% CIs. And when the outcome was expressed using varied approaches, we used standard mean difference (SMD) and 95% CIs to analyse the continuous data. We used the *I*-square (I^2) test to evaluate the heterogeneity of included studies. A random-effects model was chosen when $I^2 \geq 50\%$, otherwise a fixed-effect model was selected. Funnel plots were used for quality assessment of bias. And the sensitivity analysis was performed by removing these studies and observing the consistency for this meta-analysis involving at least 10 trials.

RESULTS

Study selection

The procedure of article screening, selection of articles and the causes for exclusion are displayed in the flow diagram (figure 2). The initial search included 2659 documents, and after taking out the duplicates and checking the abstracts and titles, 33 trials were considered potentially eligible. After carefully reading the full-text studies, 18 studies were eventually included, of which 15 studies were new articles appearing after the previously published meta-analyses.

Study characteristics

The main characteristics of the 18 articles are summed up in table 1. Sixteen articles in the included studies investigated the efficacy of DEX compared with saline, two trials examined the efficacy of DEX compared with clonidine and dexamethasone, respectively. The 18 articles

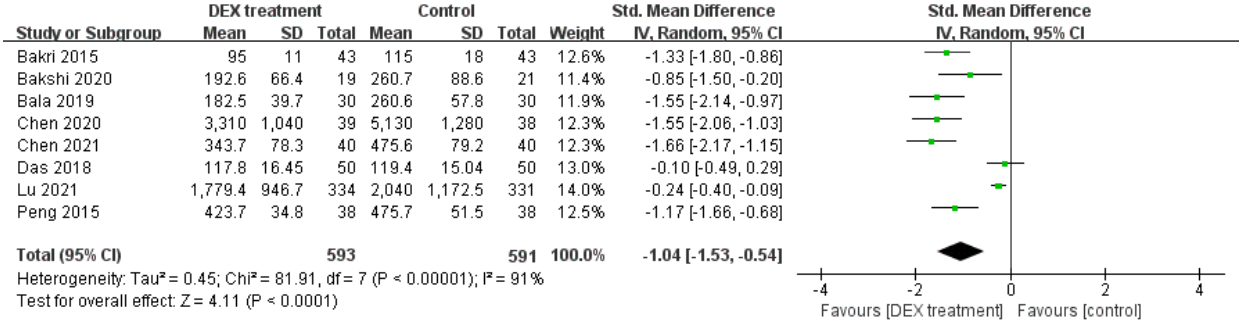

Figure 4 Perioperative opioid consumption in DEX and control group. DEX, dexmedetomidine.

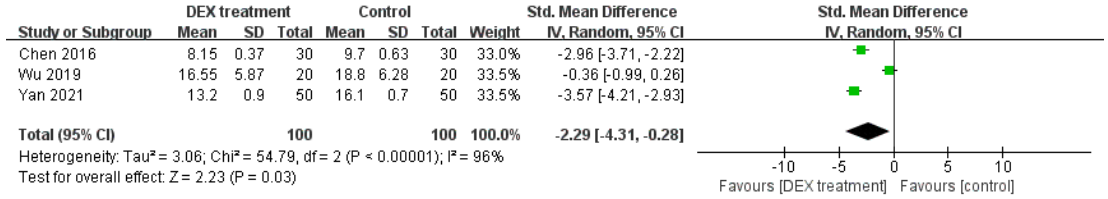

Figure 5 The effect of dexmedetomidine on the length of hospitalisation.

including a total of 2018 patients in this meta-analysis were published from 2015 to 2021 with sample sizes varying from 19 to 334 participants.

The association between DEX and PONV

All 18 trials involved the effect of DEX on the incidence of PONV. There was no heterogeneity between the articles (p<0.00001, I^2=26%, figure 3), so a fixed-effects model was chosen. The consequences revealed that the occurrence of PONV in DEX group was lower than that in the control group (OR=0.49, 95% CI: 0.36 to 0.67, figure 3), which indicated that DEX notably prevent the happening of PONV in adult patients after general anaesthetic surgery.

The association between DEX and perioperative opioid consumption

Eight studies assessed the effect of DEX on perioperative opioid consumption. Because of a high heterogeneity (p<0.00001, I^2=91%, figure 4), a random-effect model was selected. The consequences of this meta-analysis indicated that the perioperative opioid consumption was lower in DEX group (SMD= −1.04, 95% CI: −1.53 to −0.54, figure 4). Our results suggested that DEX decreased the perioperative opioid consumption significantly.

Other recovery outcomes

Four literatures including 200 patients involved the length of hospitalisation. The study heterogeneity was high (p<0.00001, I^2=96%, figure 5), so a random-effect model was selected. The consequence found that the length of hospitalisation in DEX group was shorter (SMD= −2.29, 95% CI: −4.31 to −0.28, figure 5). Four trials including 292 subjects referred to the extubation time. A random-effect model was chosen due to high heterogeneity (p=0.004, I^2=77%, figure 6). There was a shorter time to extubation in DEX group (SMD= −0.75, 95% CI: −1.26 to −0.25, figure 6). Therefore, meta-analysis of the eight literatures indicated that DEX could accelerate the recovery of patients after anaesthesia.

Side effects

Eight trials described the incidence of bradycardia. A fixed-effect model was selected considering the little heterogeneity (p=0.32, I^2=14%, figure 7). Compared with the control group, the number of participants who developed bradycardia in the DEX group was higher (OR=1.60, 95% CI: 1.13 to 2.27, figure 7). The consequences from this meta-analysis revealed that DEX might increase the occurrence of bradycardia.

Risk of bias

Publication bias of literatures including the incidence of PONV in our meta-analysis was assessed by funnel plots, and no publication bias was found (figure 8). We removed each study one by one for sensitivity analysis and found that the results did not change (online supplemental document 3).

DISCUSSION

This present meta-analysis showed that DEX is a potential effective agent for decreasing the incidence of PONV and promoting the recovery of adult patients undergoing general anaesthetic surgery, but it might increase the incidence of bradycardia.

PONV is an unsatisfactory experience and painful adverse event for patients, especially in the first day after surgery. Its incidence is approximately 30% and up to 80% without prevention.[1 10] Moreover, some surgical types were associated with the high occurrence of PONV, especially in gynaecological surgery, otolaryngology surgery and neurosurgery.[3] There are many risk factors that can increase the incidence of PONV by 20%, respectively, in patients, including anaesthetic factors, surgical factors, female, non-smokers and the medical history of motion sickness and/or PONV.[11] These risk factors might also vary with the premedication, anaesthetic technique and postoperative management.[12] Among the factors of anaesthesia, general anaesthesia is more likely to cause PONV

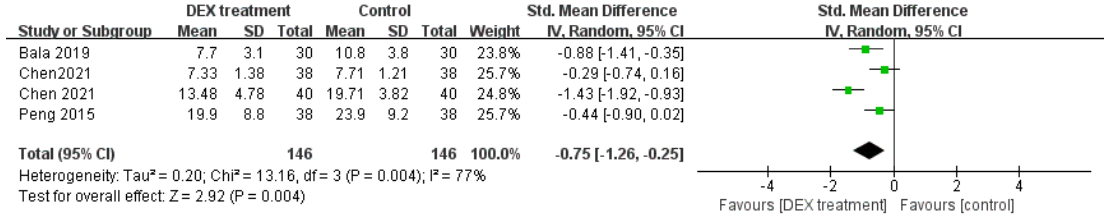

Figure 6 The effect of DEX on the extubation time. DEX, dexmedetomidine.

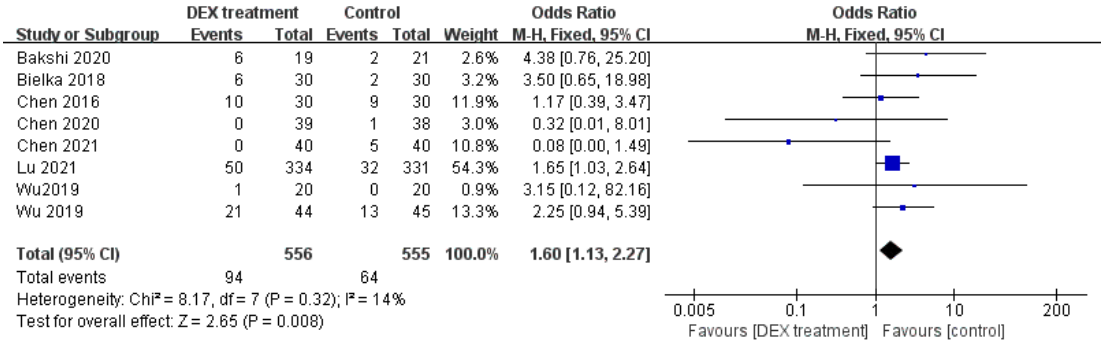

Figure 7 Incidence of bradycardia in DEX and control group. DEX, dexmedetomidine.

compared with regional anaesthesia.[13] The pathophysiology process of PONV is very elusive. A study suggested that injuries from operation, anaesthesia, visceral nerve stimulation, hypoxia, hypotension and pain were the major irritants, which could trigger the vomiting response when they reach the cortical/thalamic, cerebellar and vestibular nuclei and the chemoreceptor triggering band outside of the blood–brain barrier.[14] Although there are multiple methods and drugs to prevent PONV in clinical practice, the efficacy of PONV prophylaxis remains unsatisfactory especially in high-risk patients.[1]

DEX exerts the anxiolytic, sedative and analgesic effects by reducing the release of norepinephrine induced by α2 adrenergic receptors in the spinal cord and locus coeruleus. However, it could not result in excessive sedation or respiratory depression as the results of accumulation.[15] Therefore, DEX was used as an appropriate short-acting sedative for patients under general anaesthesia in perioperative period. Previous articles indicated that DEX reduced the occurrence of PONV, which were similar to our result. For instance, a study reported that DEX administered could decrease the occurrence of PONV in patients experiencing intestinal surgery,[16] another study discovered that intraoperative use of DEX could be a valid measure to prevent the PONV in patients after laparoscopic radical prostatectomy.[17] But the mechanisms for the effect of DEX on PONV are still obscure. Previous articles reported DEX could decrease the occurrence of PONV by modulating 5-hydroxytryptamine (5-HT) and dopamine release, suppressing the histamine-induced expression of interleukin-6 and reducing sympathetic outflow and total catecholamine release.[18 19] So, one of the key mechanisms about the effect of DEX on PONV might be attributable to the regulation of neurotransmitters. Moreover, it is well known to us that the amount of intraoperative opioid use directly influenced the frequency and degree of PONV.[13]

DEX also can prevent the perioperative stress response by regulating heart rate and blood pressure, however, DEX might produce some adverse events like bradycardia especially in patients with atrioventricular block or hypovolaemia.[20] Similar consequence with our article, a meta-analysis of 3638 patients from nine high-quality RCTs reported that DEX could increase the incidence of bradycardia,[21] which might be due to presynaptic α2 receptor stimulation by DEX results in decreasing norepinephrine release.

Additionally, it was interesting to find that DEX could shorten the time to extubation in this meta-analysis, which was similar to the result of one previous meta-analysis.[22] However, because of the limited data and the high heterogeneity among the studies, the pooled result should be interpreted cautiously and further investigations were needed to support the conclusion.

In fact, there were two previous meta-analyses also reported that DEX could low the occurrence of PONV compared with the control group.[12 23] The included population of these two meta-analyses was the children and adults, and one study did not limit the methods of anaesthesia and the administration of DEX. Notably, we mainly focused on the adult patient population under general anaesthesia, and the intervention was perioperative intravenous DEX, which differed from the two previous meta-analyses. Moreover, the RCTs that DEX comparing with opioids agents were excluded in our meta-analysis to eliminate the effect of opioids on PONV. Additionally, our study involved a number of updated RCTs and added some indicators about the recovery after surgery. Ultimately, our results suggested that DEX did decrease

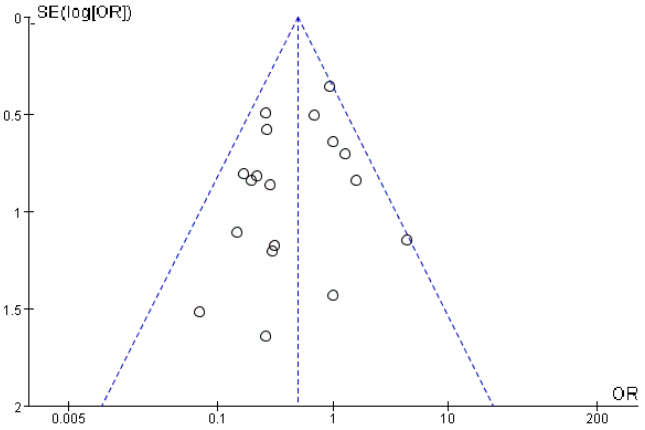

Figure 8 Test for publication bias of the studies included in the incidence of postoperative nausea and vomiting.

the occurrence of PONV, and accelerated the recovery of adult patients after general anaesthesia.

Clinical significance

The results of this meta-analysis might help the doctors and nurses to formulate plans to prevent PONV and offer a new testimony to expand the clinical significance of DEX apart from its conventional usage for sedation and analgesia.

Limitations

There were several limitations to this meta-analysis. First, the included articles did not give consistent doses of DEX, the influence of diverse doses of DEX on PONV in adult patients after general anaesthesia needs to be further explored. Second, the severity degree of PONV was not quantified using a formal scale, so further study is required to explore the effect of DEX on different severity degrees of PONV.

CONCLUSION

In a word, DEX could decrease the occurrence of PONV in adult patients who experience general anaesthesia, and accelerate postoperative recovery. Thus, DEX can be used as an adjuvant drug for general anaesthesia to prevent the development of PONV in clinical practice. However, it is essential to be vigilant as DEX might increase the occurrence of bradycardia during surgery.

Contributors The author acting as guarantor was JL. WZ and JL were involved in the conception and design of this meta-analysis. NW and ZW conducted the data extraction. HZ and ML contributed to statistical analysis. WZ analysed the data and drafted the manuscript. JH, DY and MZ offered major comments and revised the manuscript. All authors have read and approved the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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