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The effect of dexmedetomidine on postoperative nausea and vomiting in patients under general anesthesia: an updated meta-analysis of randomized controlled trials

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1 **The effect of dexmedetomidine on postoperative nausea and**
2 **vomiting in patients under general anesthesia: an updated meta-**
3 **analysis of randomized controlled trials**

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18 **Keywords:** Dexmedetomidine, Perioperative period, Postoperative nausea and
19 vomiting, Side effects, Meta-analysis

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1 ABSTRACT

2 **Objectives:** To explore the effect of dexmedetomidine on postoperative nausea and vomiting in
3 adult patients after general anesthesia.

4 **Design:** Systematic review and meta-analysis.

5 **Data Sources:** We searched the PubMed, the Web of Science, the Cochrane Library and Embase
6 (January 1, 2000, to June 30, 2022) to find the relevant randomized controlled trials (RCTs) using
7 the following search terms: dexmedetomidine and postoperative nausea and vomiting. All studies
8 included the primary outcome of interest: the incidence of postoperative nausea and vomiting.

9 **Data analysis:** All the relevant data were performed by using RevManV.5.4. Heterogeneity was
10 tested for each outcome, and random effect or fixed effect models were selected according to the
11 level of heterogeneity.

12 **Results:** In total of 18 trials involving 2018 patients were involved in this meta-analysis. The
13 incidence of postoperative nausea and vomiting in dexmedetomidine group was obviously lower
14 than that in control group (odds ratio [OR] =0.49, 95% CI 0.36 to 0.67) and the perioperative opioid
15 consumption in dexmedetomidine group was also decreased significantly (standard mean difference
16 [SMD] = -1.04, 95% CI -1.53 to -0.54). Moreover, the length of hospitalization (SMD= -2.29, 95%
17 CI -4.31 to -0.28) and the extubation time (SMD= -0.75, 95% CI -1.26 to -0.25) in
18 dexmedetomidine group were shorter. Whereas, higher number of patients receiving
19 dexmedetomidine occurred bradycardia (OR=1.60, 95% CI 1.13 to 2.27).

20 **Conclusions:** Dexmedetomidine can decrease the occurrence of postoperative nausea and vomiting
21 in adult patients under general anesthesia and promote the recovery after surgery. However,
22 dexmedetomidine may increase the occurrence of bradycardia.

1 PROSPERO registration number: CRD 42022341548

2 **Strengths and limitations of this study**

- 3 ● This is an update meta-analysis of 18 published articles to investigate the effect of
4 dexmedetomidine on postoperative nausea and vomiting in adult patients under general
5 anesthesia.
6 ● A thorough systematic review and meta-analysis provide confidence in the findings.
7 ● The main limitation of this review is that varied quality and heterogeneity of included studies
8 may limit the certainty of the findings of meta-analysis

9 **INTRODUCTION**

10 Postoperative nausea and vomiting (PONV), as a familiar negative events after operation, is
11 known as nausea, vomiting, or retching within one day after operation(1), which may be due to the
12 effect of anesthetics on the emetic control center in the medulla oblongata(2). The incidence of
13 PONV is about 30% and even rising to 60%-80% in high-risk populations. PONV, an extreme poor
14 medical experience for patients undergoing general anesthetic surgery, leads to many adverse
15 influences including stomach discomfort, dehydration, water-electrolyte disorders, wound
16 dehiscence, esophageal injury, reflux and aspiration, which extend the time of hospitalization and
17 increase the medical costs(3). Fortunately, prophylactic antiemetic agents can decrease the
18 happening of PONV, such as antihistamines, corticosteroids, dopamine antagonists, anticholinergics
19 and 5-HT₃ receptor antagonists. However, these drugs have some side effects including headache,
20 restlessness, dry mouth, hypotension and cardiovascular complications, which limit its use in some
21 cases(4). Therefore, exploring suitable drugs and methods to prevent and treat PONV is necessary.

22 Dexmedetomidine (DEX), as a new adrenal α_2 receptor agonist with high selectivity, has

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4 1 sedation, hypnosis and analgesia effects without respiratory depression, which is widely used in
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6 2 perioperative period. A previous study reported that DEX can decrease perioperative catecholamine
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9 3 release, maintain hemodynamic stability, reduce intraoperative analgesic and anesthetic
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11 4 requirements, and improve the quality of recovery(5). These characteristics have enabled DEX to
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14 5 be a multifunctional drug in the presentments of numerous negative events during anesthesia. There
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17 6 were two meta-analyses found that DEX significantly alleviated the postoperative pain intensity and
18
19 7 decreased the opioid consumption(6; 7). For the last few years, the effect of DEX on PONV has
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22 8 attracted increasing attention from anesthesiologists. One clinical study has reported that
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25 9 postoperative administration of DEX, as patient-controlled analgesia (PCA) regimen, produced
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28 10 early antiemetic effects(8). Another research indicated that intravenous DEX could prevent the
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31 11 occurrence of PONV in adult patients after laparoscopic hysterectomy(9). While different results
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34 12 were observed in the similar articles(10; 11). Therefore, it is still disputed whether intraoperative
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37 13 use of DEX can ameliorate the occurrence of PONV in patients after general anesthesia.

38 14 As far as we know, no updated analysis of the data about the effect of DEX on PONV was
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41 15 performed during general anesthesia. Therefore, in order to obtain the most recent proof, we
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44 16 thoroughly evaluated the effect of intraoperative use of DEX on PONV in adult patients
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47 17 experiencing general anesthesia according to the results from the 18 randomized controlled trials
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49
50 18 (RCTs) in our meta-analysis. We hope these consequences will provide suggestions for
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52
53 19 anesthesiologists and surgeons to make better prevention plans in the future.

54 20 **METHODS**

55 56 21 **Patient and public involvement**

57
58 22 No patient involved.
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1 **Registration**

2 This meta-analysis was conducted by following the criteria as outlined in the PRISMA
3 guidelines(12) (Supplementary document 1). The meta-analysis was registered on PROSPERO
4 (registry number: CRD 42022341548).

5 **Search strategy**

6 Two investigators independently searched for articles published in PubMed, the Web of
7 Science, Embase, and the Cochrane Library without any restrictions. The basic search words
8 included: (“Dex” OR “dexmedetomidine”) AND (“PONV” OR “postoperative nausea and vomiting”
9 OR “nausea” OR “vomiting” OR “nausea and vomiting” OR “postoperative emesis” OR
10 “postoperative vomiting” OR “postoperative nausea”). The complete search strategy protocol was
11 shown in Supplementary document 2. The literature search was updated on June 30, 2022.

12 **Inclusion and exclusion criteria**

13 The inclusion criteria: (1) RCTs; (2) Adult participants undergoing general anesthetic surgery;
14 (3) The administration of DEX intraoperatively; (4) The outcomes in the included articles included
15 nausea and vomiting; (5) DEX versus placebo or a single agent.

16 The exclusion criteria: (1) Reviews, abstracts, case reports or duplicates; (2) Drug/drugs
17 (including DEX) versus combinational drugs; (3) Adult patients undergoing surgery under local or
18 spinal-epidural anesthesia; (4) Full text not available.

19 **Data extraction and analysis**

20 All the information of the articles was collected independently by two researchers using
21 standardized forms. Any problems were decided by a third author in order to discuss and reach an
22 agreement. The corresponding data were collected: first author, type of surgery, publication year,

1 number of patients, administrations for patients, the incidence of PONV and bradycardia, the
2 perioperative opioid consumption, the extubation time and the length of hospitalization. A
3 standardized Excel file was used to save the extracted data.

4 **Risk of bias assessment**

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

9 **Statistical analysis**

10 We used the Review Manager 5.4 software to perform statistical analysis. For dichotomous
11 data, we calculated odds ratios (ORs) with 95% confidence intervals (CIs). And we use standardized
12 mean difference (SMD) and 95% CIs to analyze continuous outcomes. We used the *I*-square (I^2)
13 test to evaluate the heterogeneity on included studies. A random effects model was chosen when I^2
14 $\geq 50\%$, otherwise a fixed effect model was selected. Funnel plots were used for quality assessment
15 of bias. And the sensitivity analysis was performed for this meta-analysis involving at least 10 trials.

16 **RESULTS**

17 **Study selection**

18 The procedure of article screening, selection of articles, and the causes for exclusion were
19 displayed in the flow diagram (Figure 2). The initial search included 2659 documents, and after
20 taking out the duplicates and checking the abstracts and titles, 33 trials were considered potentially
21 eligible. After carefully reading the full-text studies, 18 studies were eventually included.

22 **Study characteristics**

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4 1 The main characteristics of the 18 articles were summed up in Table 1. 16 articles in the
5
6 2 included articles investigated the efficacy of DEX compared to saline, 1 trial examined the efficacy
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8 3 of DEX compared to clonidine, and 1 trial compared to dexamethasone. The 18 articles in this meta-
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10 4 analysis were published from 2015 to 2021 with sample sizes varying from 19 to 334 participants
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12 5 and a total of 2018 patients.
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17 6 **Table 1:** Characteristics of the included trials.
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Author	Year	Number	Participants	Type of surgery	Administration	Nausea and Vomiting
Bakri	2015	43/43	Adults	Laparoscopic cholecystectomy	DEX/Dexa	9/12
Peng	2015	38/38	Adults	Craniotomy	DEX/Saline	16/28
Chen	2016	30/30	Adults	Laparoscopic resection of colorectal cancer	DEX/Saline	6/6
Bielka	2018	30/30	Adults	Laparoscopic cholecystectomy	DEX/Saline	2/8
Das	2018	50/50	Adults	Breast cancer surgery	DEX/Saline	2/8
Wu	2019	44/45	Adults	Laparoscopic radical prostatectomy	DEX/Saline	2/10
Bala	2019	30/30	Adults	Transsphenoidal Pituitary Surgery	DEX/Saline	2/6
Wu	2019	20/20	Adults	Cholangiojejunostomy or radical resection of tumor	DEX/Saline	1/3
Bakshi	2020	19/21	Adults	Robotic-assisted laparoscopic oncosurgeries	DEX/Saline	4/3
Chen	2020	39/38	Adults	Radical resection of gastric cancer	DEX/Saline	1/3
Asri	2020	21/21	Adults	Thoracic Surgery	DEX/Saline	0/5
Pi	2021	121/96	Adults	Thoracoscopic radical resection of lung cancer	DEX/Saline	0/1
Lu	2021	334/331	Adults	Abdominal Surgery	DEX/Saline	16/17
Bafna	2021	35/35	Adults	Endoscopic sinus surgery	DEX/Clonidine	4/1
Prashantha	2021	40/40	Adults	Laparoscopic cholecystectomy	DEX/Saline	5/14

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2							
3	Chen	2021	38/38	Adults	Thoracoscopic pulmonary segmentectomy	DEX/Saline	1/1
4							
5	Yan	2021	50/50	Adults	Total Hip Arthroplasty	DEX/Saline	5/4
6							
7							
8	Chen	2021	40/40	Adults	Intestinal Surgery	DEX/Saline	1/6
9							

11 1 Abbreviations: DEX, dexmedetomidine; Dexa, dexamethasone.

12 2 **The association between DEX and PONV**

13 3 All 18 trials involved the effect of DEX on the incidence of PONV. There was no heterogeneity
 14 4 between the articles ($P < 0.00001$, $I^2 = 26\%$, Fig. 3), so a fixed-effects model was chosen. The
 15 5 consequences revealed that the occurrence of PONV in DEX group was lower than the control group
 16 6 (OR=0.49, 95% CI 0.36 to 0.67, Fig. 3), which indicated that DEX notably prevent the happening
 17 7 of PONV in adult patients after general anesthetic surgery.

18 8 **The association between DEX and perioperative opioid consumption**

19 9 8 studies assessed the effect of DEX on perioperative opioid consumption. Because of a high
 20 10 heterogeneity ($P < 0.00001$, $I^2 = 91\%$, Fig. 4), a random effect model was selected. The consequences
 21 11 of this meta-analysis indicated that the perioperative opioid consumption was lower in DEX group
 22 12 (SMD= -1.04, 95% CI -1.53 to -0.54, Fig. 4). Our results suggested that DEX decreased the
 23 13 perioperative opioid consumption significantly.

24 14 **Other recovery outcomes**

25 15 4 literatures including 200 patients involved the length of hospitalization. The study
 26 16 heterogeneity was high ($P < 0.00001$, $I^2 = 96\%$, Fig. 5), so a random effect model was selected. The
 27 17 consequence found that the length of hospitalization in DEX group was shorter (SMD= -2.29, 95%
 28 18 CI -4.31 to -0.28, Fig. 5). 4 trials including 292 subjects referred to the extubation time. A random
 29 19 effect model was chosen since the high heterogeneity ($P = 0.004$, $I^2 = 77\%$, Fig. 6). There was a shorter

1 time to extubation in DEX group (SMD= -0.75, 95% CI -1.26 to -0.25, Fig. 6). Therefore, meta-
2 analysis of the 8 literatures indicated that DEX could accelerate the recovery of patients after
3 anesthesia.

4 **Side effects**

5 8 trials described the incidence of bradycardia. A fixed effect model was selected considering
6 the little heterogeneity ($P=0.32$, $I^2=14\%$, Fig. 7). Compared to the control group, the number of
7 participants developed bradycardia in the DEX group was higher (OR=1.60, 95% CI 1.13 to 2.27,
8 Fig. 7). The consequences from this meta-analysis revealed that DEX may increase the occurrence
9 of bradycardia.

10 **Publication bias**

11 Publication bias of literatures that included in our meta-analysis was assessed by funnel plots.
12 No publication bias was found (Fig. 8). We removed each study one by one for sensitivity analysis
13 and found that the results did not change (Supplementary document 3).

14 **DISCUSSION**

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

18 PONV is unsatisfactory experience and painful adverse event for patients, especially in the
19 first day after surgery. Its incidence is approximately 30% and up to 80% without prevention(2; 13).
20 Moreover, there may be some surgical types were associated with the high occurrence of PONV,
21 especially in gynecological surgery, otolaryngology surgery and neurosurgery(4). There are many
22 risk factors that can increase the incidence of PONV by 20% respectively in patients, including

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4 1 anesthetic factors, surgical factors, female sex, non-smokers, and the medical history of motion
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6 2 sickness or/and PONV(14). These risk factors might also change with the premedication, anesthetic
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9 3 technique, postoperative management(15). Among the factors of anesthesia, general anesthesia is
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11 4 more likely to cause PONV compared with regional anesthesia(16). The pathophysiology process
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14 5 of PONV is very elusive. A study suggested that injuries from operation, anesthesia, visceral nerve
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17 6 stimulation, hypoxia, hypotension, and pain are the major irritants, which could trigger the vomiting
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20 7 response when they reach the cortical/thalamic, cerebellar and vestibular nuclei, and the
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23 8 chemoreceptor triggering band outside of the blood-brain barrier(17). Although there are multiple
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26 9 methods and drugs to prevent PONV in clinical practice, the efficacy of PONV prophylaxis remains
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29 10 unsatisfactory especially in high-risk patients(2).

30 11 Our meta-analysis found that DEX could notably decrease the happening of PONV in adult
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33 12 patients undergoing general anesthesia. DEX exerts the anxiolytic, sedative and analgesic effects by
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36 13 reducing the release of norepinephrine induced by α_2 adrenergic receptors in the spinal cord and
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39 14 locus coeruleus. However, it could not result in excessive sedation or respiratory depression as the
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42 15 results of accumulation(18). Therefore, DEX was used as an appropriate short-acting sedative for
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45 16 patients under general anesthesia in perioperative period. Previous articles indicated that DEX
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48 17 reduced the occurrence of PONV, which were similar to our result. For instance, a study has reported
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51 18 that DEX administered could decrease the occurrence of PONV in patients experiencing intestinal
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54 19 surgery(19), another study discovered that intraoperative use of DEX could be a valid measure to
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57 20 prevent the PONV in patients after laparoscopic radical prostatectomy(20). But the mechanisms for
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60 21 the effect of DEX on PONV are still obscure. Previous articles reported DEX could decrease the
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24 22 occurrence of PONV by modulating 5-HT and dopamine release, suppressing the histamine-induced

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4 1 expression of IL-6, and reducing sympathetic outflow and total catecholamine release(21; 22). So,
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6 2 one of the key mechanisms about the effect of DEX on PONV might be attributable to the regulation
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9 3 of neurotransmitters. It is well known to us that the amount of intraoperative opioid use directly
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11 4 influenced the frequency and degree of PONV(16). In our meta-analysis, we revealed that DEX
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14 5 could decrease the perioperative opioid consumption, which might explain the antiemetic effect of
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17 6 DEX.

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19 7 DEX also can prevent perioperative stress response by regulating heart rate and blood pressure,
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22 8 which are the most common adverse events especially in patient with atrioventricular block or
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25 9 hypovolemia(23). In this meta-analysis, the incidence of perioperative bradycardia was increased in
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28 10 patients with DEX. Similar consequence was found in a meta-analysis of 3638 patients from 9 high-
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31 11 quality RCTs(24). Bradycardia may be due to presynaptic α -2 receptor stimulation by DEX, which
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33
34 12 results in decreasing norepinephrine release.

35
36 13 Nausea and vomiting are two distinguishing phenomena. A study has shown that DEX reduced
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38 14 early postoperative nausea but not vomiting in adult patients undergoing general anesthesia(25).
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41 15 However, nausea and vomiting usually coexist with patients, and the occurrence of postoperative
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44 16 vomiting (POV) or postoperative nausea (PON) clearly consistent with PONV, so a number of
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47 17 studies do not attempt to distinguish between these two variables(26-28). Therefore, we just
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50 18 explored the influence of DEX on PONV in this meta-analysis.

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52 19 In fact, there have been two previous meta-analyses also reported that DEX could low the
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54 20 occurrence of PONV compared to the placebo group(15; 29). However, PONV has been rapidly
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57 21 developed and there are the increasing numbers of studies about it in the last few years. Therefore,
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60 22 an up-date meta-analysis is necessary to assess whether the consequences of newly updated or

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4 1 published studies can alter the previous meta-analysis. Overall, DEX did decrease the occurrence of
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6 2 PONV and accelerated the recovery of adult patients after general anesthesia in this meta-analysis.
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9 3 **LIMITATIONS**

10 4 There were several limitations to this meta-analysis. Firstly, the included articles did not give
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12 5 consistent doses of DEX, the influence of diverse doses of DEX on PONV in adult patients after
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14 6 general anesthesia needs to be further explored. Secondly, the severity degree of PONV was not
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16 7 quantified using a formal scale, so further study is required to explore the effect of DEX on different
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18 8 severity degree of PONV.
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24 9 **CONCLUSION**

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27 10 In a word, DEX can decrease the occurrence of PONV in adult patients who experiencing
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29 11 general anesthesia, and accelerate postoperative recovery. Thus, DEX can be used as an adjuvant
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31 12 drug for general anesthesia to prevent the development of PONV in clinical practice. However, it is
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33 13 essential to be vigilant the occurrence of bradycardia during surgery. The results of this meta-
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35 14 analysis may offer a new testimony to expand the clinical significance of DEX apart from its
36
37 15 conventional usage for sedation and analgesia.
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43 16 **Author Contributions** WZ and JL were involved in the conception and design of this meta-analysis. NW and ZW
44
45 17 conducted the data extraction. HZ and ML contributed to statistical analysis. WZ analyzed the data and drafted the
46
47 18 manuscript. JH, DY and MZ offered major comments and revised the manuscript. All authors have read and
48
49 19 approved the manuscript.
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52

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56
57 22 analysis, interpretation of data, and writing of the manuscript.
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4 1 **Ethics approval statement** This study was a meta-analysis of previously published literatures, ethical approval
5
6 2 was not necessary.
7
8
9 3 **Competing interests** None declared.
10
11 4 **Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting,
12
13 5 or dissemination plans of this research.
14
15 6 **Patient consent for publication** Not applicable.
16
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18
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21 9 information.
22
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16 **Figure legends**

17 **Figure 1:** The risk of bias of included studies.

18 **Figure 2:** Flow diagram.

19 **Figure 3:** The total effect of dexmedetomidine on PONV.

20 **Figure 4:** Perioperative opioid consumption in dexmedetomidine and control group.

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4 1 **Figure 5:** The effect of dexmedetomidine on the length of hospitalization.
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8 2 **Figure 6:** The effect of dexmedetomidine on the extubation time.
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11 3 **Figure 7:** Incidence of bradycardia in dexmedetomidine and control group.
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15 4 **Figure 8:** The funnel plot.
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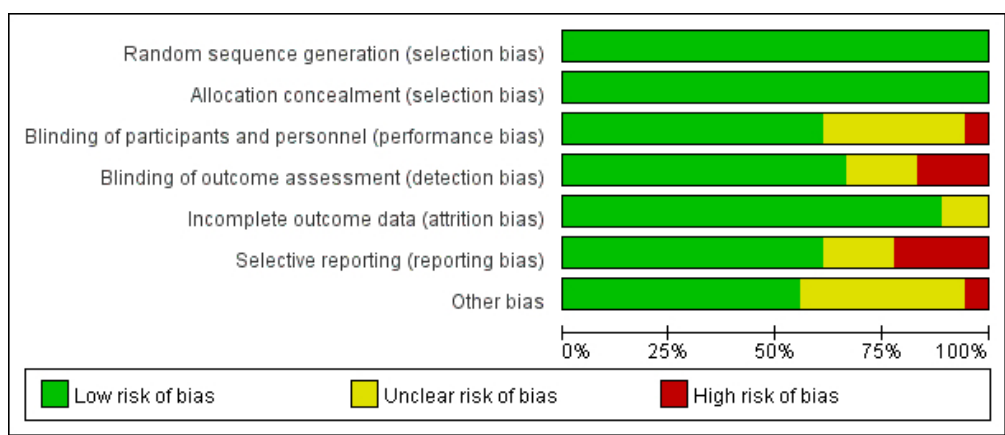


Figure 1: The risk of bias of included studies.

213x90mm (72 x 72 DPI)

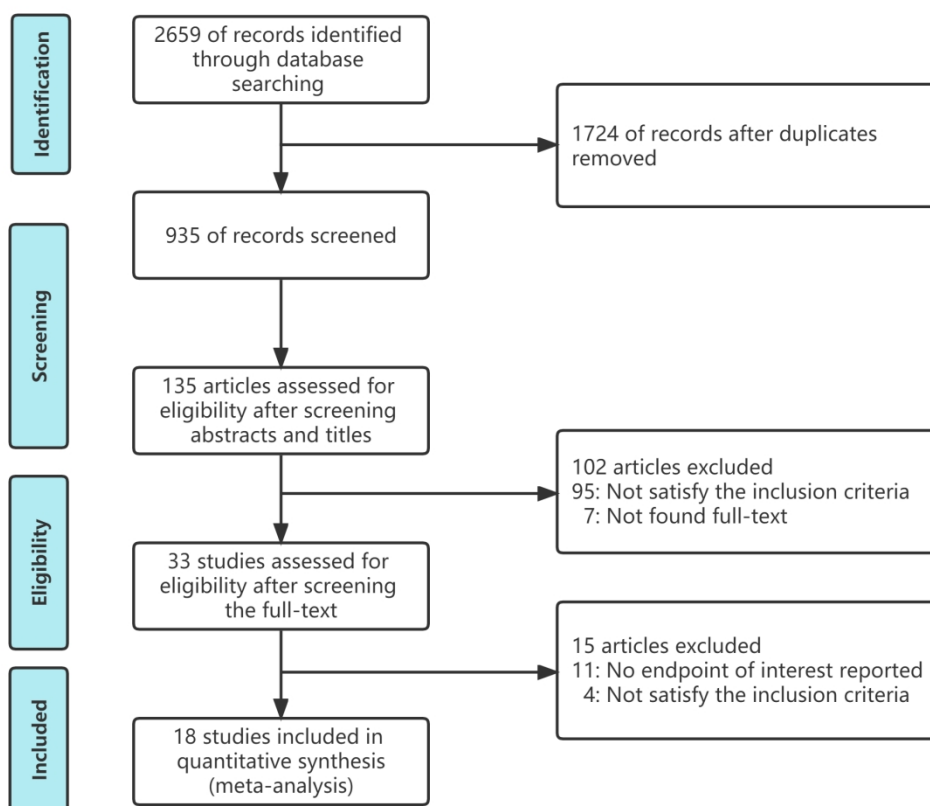


Figure 2: Flow diagram

735x638mm (72 x 72 DPI)

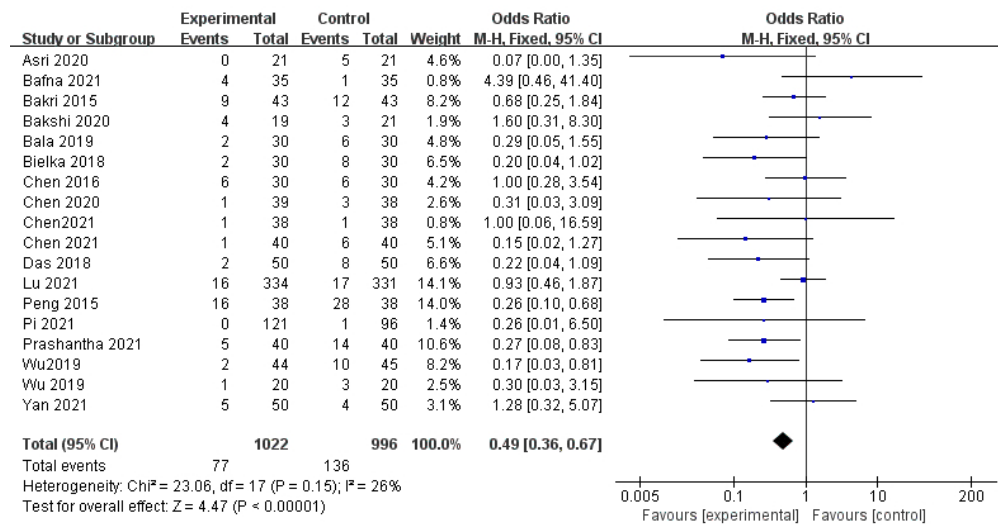


Figure 3: The total effect of dexmedetomidine on postoperative nausea and vomiting.

277x146mm (72 x 72 DPI)

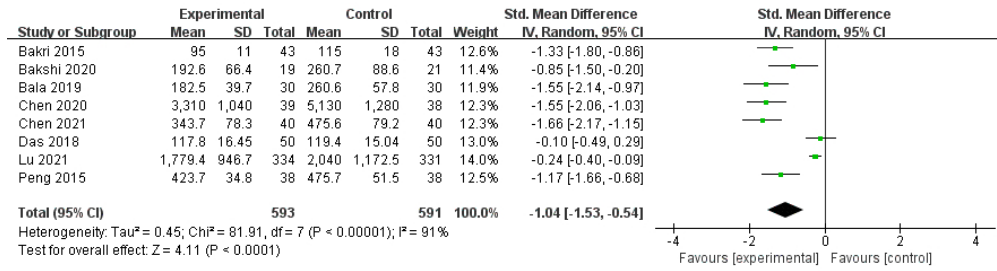


Figure 4: Perioperative opioid consumption in dexmedetomidine and control group.

311x84mm (72 x 72 DPI)

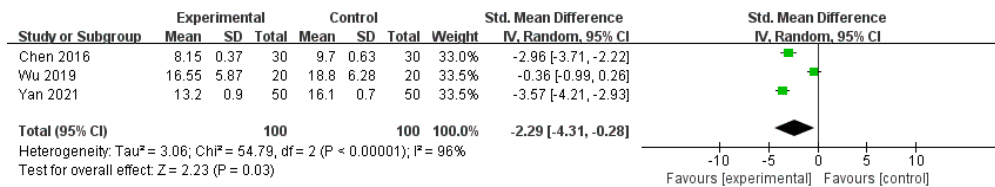


Figure 5: The effect of dexmedetomidine on the length of hospitalization.

300x56mm (72 x 72 DPI)

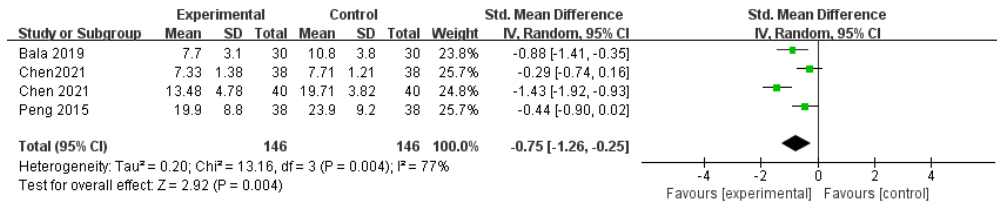


Figure 6: The effect of dexmedetomidine on the extubation time.

300x62mm (72 x 72 DPI)

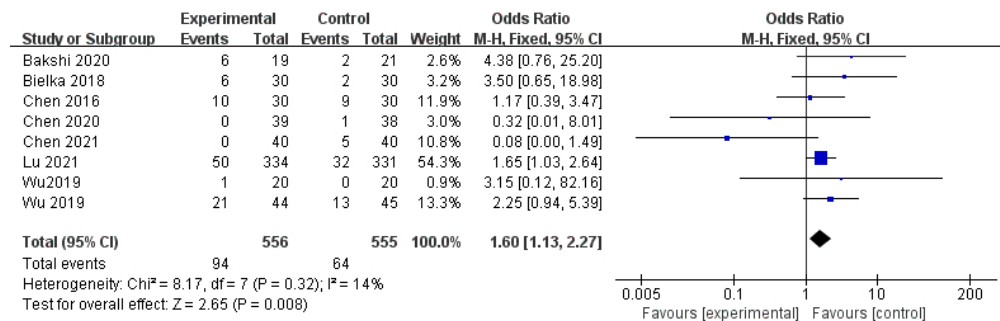


Figure 7: Incidence of bradycardia in dexmedetomidine and control group.

277x90mm (72 x 72 DPI)

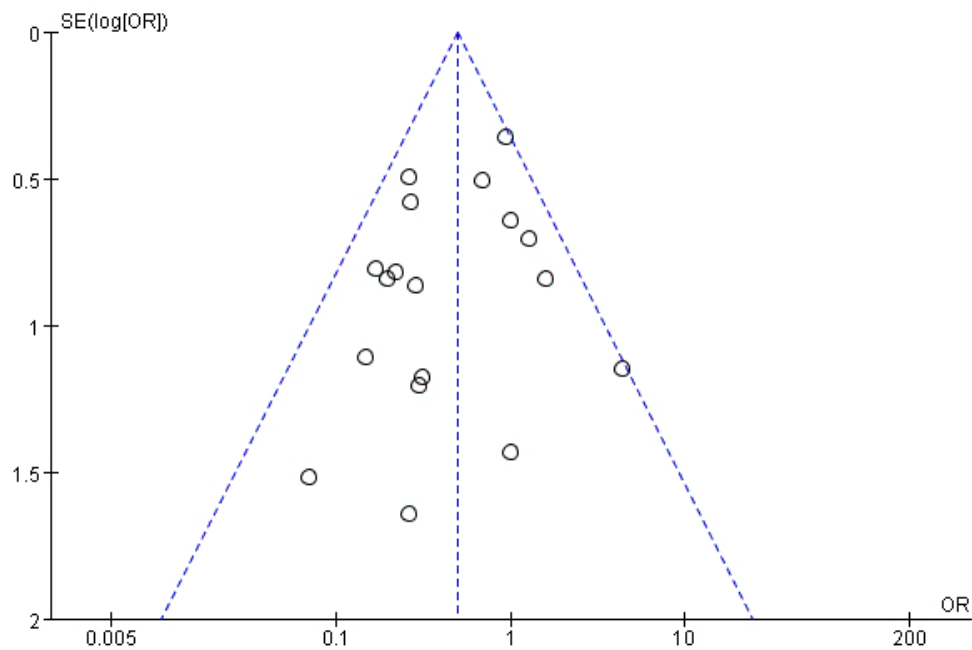


Figure 8: The funnel plot

211x141mm (72 x 72 DPI)

Supplementary document 1



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	3
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3,Supplementary document 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3,Supplementary document 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	3-4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	3-4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	4
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Table 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	4

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	4
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	4
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	4
Study characteristics	17	Cite each included study and present its characteristics.	4
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6, Figure 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5-6
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	5-6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	5-6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplementary document 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	6
	23b	Discuss any limitations of the evidence included in the review.	8

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Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	8
	23d	Discuss implications of the results for practice, policy, and future research.	8
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	-
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Title page
Competing interests	26	Declare any competing interests of review authors.	Title page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Title page

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

Supplementary document 2: The search strategy

Pubmed

Search: (DEX[Title/Abstract]) OR ("Dexmedetomidine"[Mesh]) OR (Dexmedetomidine[Title/Abstract]) AND ("Postoperative Nausea and Vomiting"[Mesh]) OR (((((((((PONV[Title/Abstract]) OR (Nausea[Title/Abstract] AND Vomiting, Postoperative[Title/Abstract])) OR (Vomiting, Postoperative[Title/Abstract])) OR (Postoperative Emesis[Title/Abstract])) OR (Postoperative Vomiting[Title/Abstract])) OR (Emesis, Postoperative[Title/Abstract])) OR (Emeses, Postoperative[Title/Abstract])) OR (Postoperative Emeses[Title/Abstract])) OR (Postoperative Nausea[Title/Abstract])) OR (Nausea, Postoperative[Title/Abstract]))

Embase

- #1 Dexmedetomidine
- #2 'mpv-1440':ab,ti OR 'mpv 1440':ab,ti OR 'mpv1440':ab,ti OR 'precedex':ab,ti OR 'dexmedetomidine hydrochloride':ab,ti OR 'hydrochloride, dexmedetomidine':ab,ti
- #3 #1 OR #2
- #4 postoperative AND nausea AND vomiting
- #5 'ponv':ab,ti OR 'nausea and vomiting, postoperative':ab,ti OR 'vomiting, postoperative':ab,ti OR 'postoperative emesis':ab,ti OR 'postoperative vomiting':ab,ti OR 'emesis, postoperative':ab,ti OR 'emeses, postoperative':ab,ti OR 'postoperative emeses':ab,ti OR 'postoperative nausea':ab,ti OR 'nausea, postoperative':ab,ti
- #6 #4 OR #5
- #7 #3 AND #6

Cochrane

- #1 Dexmedetomidine
- #2 (MPV-1440):ti,ab,kw OR (MPV 1440):ti,ab,kw OR (MPV1440):ti,ab,kw OR (Precedex):ti,ab,kw OR (Dexmedetomidine Hydrochloride):ti,ab,kw OR (Hydrochloride, Dexmedetomidine):ti,ab,kw
- #3 #1 OR #2
- #4 Postoperative nausea and vomiting
- #5 (PONV):ti,ab,kw OR (Nausea and Vomiting, Postoperative):ti,ab,kw OR (Vomiting, Postoperative):ti,ab,kw OR (Postoperative Emesis):ti,ab,kw OR (Postoperative Vomiting):ti,ab,kw OR (Emesis, Postoperative):ti,ab,kw OR (Emeses, Postoperative):ti,ab,kw OR (Postoperative Emeses):ti,ab,kw OR (Postoperative Nausea):ti,ab,kw OR (Nausea, Postoperative):ti,ab,kw
- #6 #4 OR #5
- #7 #3 AND #6

Supplementary document 3: The sensitivity analysis of effect of dexmedetomidine on PONV

Study	Odds Ratio	95% CI
Omitting Asri 2020	0.51	[0.37, 0.70]
Omitting Bafna 2021	0.46	[0.33, 0.63]
Omitting Bakri 2015	0.47	[0.34, 0.66]
Omitting Bakshi 2020	0.47	[0.34, 0.64]
Omitting Bala 2019	0.50	[0.36, 0.69]
Omitting Bielka 2018	0.51	[0.37, 0.70]
Omitting Chen 2016	0.47	[0.34, 0.65]
Omitting Chen 2020	0.49	[0.36, 0.68]
Omitting Chen2021	0.49	[0.35, 0.67]
Omitting Chen 2021	0.51	[0.37, 0.70]
Omitting Das 2018	0.51	[0.37, 0.70]
Omitting Lu 2021	0.42	[0.29, 0.60]
Omitting Peng 2015	0.53	[0.38, 0.73]
Omitting Pi 2021	0.49	[0.36, 0.68]
Omitting Prashantha 2021	0.52	[0.37, 0.72]
Omitting Wu2019	0.52	[0.38, 0.71]
Omitting Wu 2019	0.49	[0.36, 0.68]
Omitting Yan 2021	0.46	[0.34, 0.64]
Random effects model	0.48	[0.32, 0.73]

BMJ Open

The effect of dexmedetomidine on postoperative nausea and vomiting in patients under general anesthesia: an updated meta-analysis of randomized controlled trials

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Primary Subject Heading:	Anaesthesia
Secondary Subject Heading:	Anaesthesia, Surgery
Keywords:	ANAESTHETICS, Adult anaesthesia < ANAESTHETICS, Adult surgery < SURGERY, Adverse events < THERAPEUTICS

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1 **The effect of dexmedetomidine on postoperative nausea and**
2 **vomiting in patients under general anesthesia: an updated meta-**
3 **analysis of randomized controlled trials**

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19 vomiting, Side effects, Meta-analysis

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1 ABSTRACT

2 **Objectives:** To explore the effect of dexmedetomidine on postoperative nausea and vomiting in
3 adult patients after general anesthesia.

4 **Design:** Systematic review and meta-analysis.

5 **Eligibility criteria for selecting studies:** Randomized controlled trials comparing the efficacy of
6 dexmedetomidine with placebo or a single drug on postoperative nausea and vomiting in adult
7 patients after general anesthesia.

8 **Data Sources:** We searched the PubMed, the Web of Science, the Cochrane Library and Embase
9 (January 1, 2000, to June 30, 2022) to select the relevant randomized controlled trials (RCTs).

10 **Data analysis:** All the relevant data were analyzed by using RevManV.5.4. Heterogeneity was
11 tested for each outcome, and random effect or fixed effect models was selected according to the
12 level of heterogeneity. The primary outcome was the incidence of postoperative nausea and
13 vomiting. The second outcomes were the incidence of bradycardia, perioperative opioid
14 consumption, extubation time and the length of hospitalization.

15 **Results:** In total of 18 trials involving 2018 patients were included in this meta-analysis. Notably,
16 15 updated studies were not involved in the previous meta-analysis. The incidence of postoperative
17 nausea and vomiting in dexmedetomidine group was lower than that in control group (odds ratio
18 [OR] =0.49, 95% CI 0.36 to 0.67) and the perioperative opioid consumption in dexmedetomidine
19 group was also decreased significantly (standard mean difference [SMD] = -1.04, 95% CI -1.53 to
20 -0.54). Moreover, the length of hospitalization (SMD= -2.29, 95% CI -4.31 to -0.28) and the
21 extubation time (SMD= -0.75, 95% CI -1.26 to -0.25) in dexmedetomidine group were shorter.
22 Whereas, more number of patients receiving dexmedetomidine occurred bradycardia (OR=1.60, 95%

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4 1 CI 1.13 to 2.27).

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6 2 **Conclusions:** Dexmedetomidine could decrease the occurrence of postoperative nausea and
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9 3 vomiting in adult patients under general anesthesia and promote the recovery after surgery. However,
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11 4 dexmedetomidine might increase the occurrence of bradycardia.

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14 5 **PROSPERO registration number:** CRD 42022341548

15 16 17 6 **Strengths and limitations of this study**

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19 7 ● An up-to-date assessment of the effectiveness of dexmedetomidine on postoperative nausea
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21 8 and vomiting.
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23 9 ● We excluded studies that DEX compared with opioids agents in our meta-analysis to eliminate
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25 10 the effect of opioids on postoperative nausea and vomiting.
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27 11 ● The main limitation of this review was that varied quality and heterogeneity of included studies
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29 12 might affect the certainty of meta-analysis.

30 31 32 13 **INTRODUCTION**

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35 14 Postoperative nausea and vomiting (PONV), as a familiar negative events after operation, is
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37 15 known as nausea, vomiting, or retching within one day after operation, which may be due to the
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39 16 effect of anesthetics on the emetic control center in the medulla oblongata[1]. The incidence of
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41 17 PONV is about 30% and even rising to 60%-80% in high-risk populations. PONV, an extreme poor
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43 18 medical experience for patients undergoing general anesthetic surgery, leads to many adverse
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45 19 influences including stomach discomfort, dehydration, water-electrolyte disorders, wound
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47 20 dehiscence, esophageal injury, reflux and aspiration, which extend the time of hospitalization and
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49 21 increase the medical costs[2]. Fortunately, prophylactic antiemetic agents could decrease the
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51 22 happening of PONV. However, these drugs produce some side effects including headache,
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4 1 restlessness, dry mouth, hypotension and cardiovascular complications, which limit their use in
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6 2 some cases[3]. Therefore, exploring suitable drugs and methods to prevent and treat PONV is
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9 3 necessary.

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11 4 Dexmedetomidine (DEX), as a new adrenal α_2 receptor agonist with high selectivity, has
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14 5 sedation, hypnosis and analgesia effects without respiratory depression, which is widely used in
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17 6 perioperative period. These characteristics have enabled DEX to be a multifunctional drug in the
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20 7 presentments of numerous negative events during anesthesia. For the last few years, the effect of
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23 8 DEX on PONV attracted increasing attention from anesthesiologists. One clinical study reported
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26 9 that postoperative administration of DEX, as patient-controlled analgesia (PCA) regimen, produced
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29 10 early antiemetic effects[4]. Another research indicated that intravenous DEX could prevent the
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32 11 occurrence of PONV in adult patients after laparoscopic hysterectomy[5]. While different results
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35 12 were observed in the similar articles[6; 7]. Therefore, it is still disputed whether intraoperative use
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38 13 of DEX can ameliorate the occurrence of PONV in patients after general anesthesia.

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40 14 As far as we know, no updated analysis of the data about the effect of DEX on PONV was
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43 15 performed during general anesthesia. Therefore, in order to obtain the most recent proof, we
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46 16 thoroughly evaluated the effect of intraoperative use of DEX on PONV in adult patients
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49 17 experiencing general anesthesia according to the results from the 18 randomized controlled trials
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52 18 (RCTs) in our meta-analysis.

53 19 **METHODS**

54 20 **Patient and public involvement**

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56 21 No patient involved.

57 58 22 **Registration**

1 This meta-analysis was prepared by following the criteria as outlined in the PRISMA
2 guidelines[8] (Supplementary document 1). The meta-analysis was registered on PROSPERO
3 (registry number: CRD 42022341548).

4 **Search strategy**

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

9 **Inclusion and exclusion criteria**

10 The inclusion criteria were in accordance with PICO[9]:

11 Patients: Adult participants undergoing general anesthetic surgery;

12 Intervention: received a single or continuously-administered intravenous dose of intraoperative
13 DEX;

14 Comparison: received a single or continuously-administered intravenous injection of placebo
15 or comparator;

16 Outcomes: the incidence of PONV and bradycardia, the perioperative opioid consumption, the
17 extubation time and the length of hospitalization.

18 The reviews, abstracts, case reports or duplicates were excluded. Additionally, some RCTs
19 meeting the following criteria were also excluded (1) Drug/drugs (including DEX) versus
20 combinational drugs; (2) DEX compared with opioids agents; (3) Adult patients undergoing surgery
21 under local or spinal-epidural anesthesia; (4) Full text not available.

22 **Data extraction and analysis**

1 All information of the articles was collected independently by two researchers using
2 standardized forms. Any problems were decided by a third author in order to discuss and reach an
3 agreement. The corresponding data were collected: first author, type of surgery, publication year,
4 number of patients, administrations for patients, the incidence of PONV and bradycardia, the
5 perioperative opioid consumption, the extubation time and the length of hospitalization. A
6 standardized Excel file was used to save the extracted data. And all the data were pooled together.
7 Studies were excluded when the primary outcome was not clearly reported with quantifiable data or
8 it was not possible to extract and calculate the appropriate data from the published results.

9 **Risk of bias assessment**

10 In accordance with the Cochrane risk-of-bias tool[10], the risk of bias in the included articles
11 were evaluated by two authors independently (Figure 1). According to the following criteria: bias
12 from selection, performance, detection, attrition, reporting and other, we reviewed and scored each
13 study as "high", "unclear", and "low".

14 **Statistical analysis**

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

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1 **RESULTS**

2 **Study selection**

3 The procedure of article screening, selection of articles, and the causes for exclusion were
4 displayed in the flow diagram (Figure 2). The initial search included 2659 documents, and after
5 taking out the duplicates and checking the abstracts and titles, 33 trials were considered potentially
6 eligible. After carefully reading the full-text studies, 18 studies were eventually included, of which
7 15 studies were new articles appearing after the previously published meta-analyses.

8 **Study characteristics**

9 The main characteristics of the 18 articles were summed up in Table 1. 16 articles in the
10 included studies investigated the efficacy of DEX compared to saline, 2 trials examined the efficacy
11 of DEX compared to clonidine and dexamethasone, respectively. The 18 articles including a total
12 of 2018 patients in this meta-analysis were published from 2015 to 2021 with sample sizes varying
13 from 19 to 334 participants.

Table 1: Characteristics of the included trials.

Author	Year	Age (yr)		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 [11]	2015	31.1±2.4	32.3±2.1	15/71	43/43	Laparoscopic cholecystectomy	1µg/kg DEX IV	8 mg DEXa IV	9/12	A visual analogue scale (VAS) of 0–100 mm, 0 score meant no nausea, while 100 score meant the worst imaginable nausea
Peng [12]	2015	42.3±10.8	43.5±11.1	33/43	38/38	Craniotomy	Continuous infusion of DEX 0.5µg/kg/h IV	Equal volume of saline	16/28	0, absent; 1, nausea not requiring treatment; 2, nausea requiring treatment; and 3, vomiting.
Chen [13]	2016	56.67±2.705	60.17±1.644	29/31	30/30	Laparoscopic resection of colorectal cancer	Loading dose 1µg /kg DEX, continuous infusion of 0.3µg /kg/h IV	Equal volume of saline	6/6	Verbal rating scale scores: 0: no, 1–3: mild, 4–6: moderate, 7–10: severe
Bielka [14]	2018	55 (49–61)	53 (49–66)	7/53	30/30	Laparoscopic cholecystectomy	Continuous infusion of DEX 0.5µg/kg/h IV	Equal volume of saline	2/8	NR
Das[15]	2018	50.74±9.05	47.92±8.08	NR	50/50	Breast cancer surgery	Continuous infusion of DEX 0.6µg/kg/h IV	Equal volume of saline	2/8	NR
Wu[16]	2019	67	69	NR	NR	Laparoscopic radical prostatectomy	Loading dose 1µg /kg DEX, continuous infusion of 0.5µg /kg/h IV	Equal volume of saline	2/10	NR
Bala [17]	2019	37.2±11.0	41±13.4	33/27	30/30	Transsphenoidal Pituitary Surgery	Loading dose 1µg /kg DEX, continuous infusion of 0.5µg /kg/h IV	Equal volume of saline	2/6	NR
Wu[18]	2019	55.00±5.07	54.85±4.96	25/15	20/20	Cholangiojejunostomy or resection of tumor	Loading dose 0.5µg /kg DEX, continuous infusion of 0.5µg /kg/h IV	Equal volume of saline	1/3	NR
Bakshi [19]	2020	51.8±12	47.2±13	14/26	19/21	Robotic-assisted laparoscopic oncologies	Loading dose 1µg /kg DEX, continuous infusion of 0.2µg /kg/h IV	Equal volume of saline	4/3	NR
Chen [20]	2020	42.68±7.59	43.35±6.82	41/36	39/38	Radical resection of gastric cancer	Loading dose 0.6µg /kg DEX, continuous infusion of 0.4µg /kg/h IV	Equal volume of saline	1/3	NR
Asri [21]	2020	51±12	46±16	32/10	21/21	Thoracic Surgery	Continuous infusion of DEX 0.3µg/kg/h IV	Equal volume of saline	0/5	NR

Table 1: Characteristics of the included trials.

Author	Year	Age (yr)		Gender male/female	Number	Type of surgery	Administration mode	Comparisons	Numbers of PONV DEX/Control DEX/Control	Scale used for assessing PONV
		DEX	Control							
Pi[22]	2021	42.15±1.34	41.88±1.56	162/55	121/96	Thoracoscopic radical resection of lung cancer	Loading dose 0.4µg/kg DEX, continuous infusion of 0.2µg/kg/h IV	Equal volume of saline	0/1	NR
Lu[23]	2021	70.1 ±5.8	70.4 ±6.5	445/230	344/331	Abdominal Surgery	Loading dose 0.5µg/kg DEX, continuous infusion of 0.2µg/kg/h IV	Equal volume of saline	16/17	10-point rating scale 0: no PONV and 10: maximal PONV
Bafna[24]	2021	27.23±7.75	27.49±8.68	38/32	35/35	Endoscopic sinus surgery	Loading dose 1µg/kg DEX, continuous infusion of 1µg/kg/h IV	Loading dose 2µg/kg clonidine, continuous infusion of 1µg/kg/h IV	4/1	NR
Prashantha [25]	2021	37.73 ± 7.24	35.63 ± 12.61	19/61	40/40	Laparoscopic cholecystectomy	DEX IV	Saline IV	5/14	NR
Chen[26]	2021	55.93 ± 11.14	55.64 ± 10.81	41/35	38/38	Thoracoscopic pulmonary segmentectomy	0.6µg/kg DEX infusion from 10 min before induction	Equal volume of saline	1/1	NR
Yan[7]	2021	73.2 ± 5.8	72.7 ± 4.3	42/58	50/50	Total Hip Arthroplasty	Continuous infusion of DEX 0.3µg/kg/h IV	Equal volume of saline	5/4	NR
Chen[27]	2021	50.76 ± 8.32	51.07 ± 9.43	44/36	40/40	Intestinal Surgery	Loading dose 1µg/kg DEX, continuous infusion of 0.4µg/kg/h IV	Equal volume of saline	1/6	NR

Abbreviations: DEX: dexmedetomidine; Dexa: dexamethasone; NR: not reported.

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67 **2 The association between DEX and PONV**

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9 3 All 18 trials involved the effect of DEX on the incidence of PONV. There was no heterogeneity
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11 4 between the articles ($P < 0.00001$, $I^2 = 26\%$, Fig. 3), so a fixed-effects model was chosen. The
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13 5 consequences revealed that the occurrence of PONV in DEX group was lower than the control group
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15 6 (OR=0.49, 95% CI 0.36 to 0.67, Fig. 3), which indicated that DEX notably prevent the happening
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17 7 of PONV in adult patients after general anesthetic surgery.
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22 **8 The association between DEX and perioperative opioid consumption**

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25 9 8 studies assessed the effect of DEX on perioperative opioid consumption. Because of a high
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27 10 heterogeneity ($P < 0.00001$, $I^2 = 91\%$, Fig. 4), a random effect model was selected. The consequences
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29 11 of this meta-analysis indicated that the perioperative opioid consumption was lower in DEX group
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31 12 (SMD= -1.04, 95% CI -1.53 to -0.54, Fig. 4). Our results suggested that DEX decreased the
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33 13 perioperative opioid consumption significantly.
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38 **14 Other recovery outcomes**

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40 15 4 literatures including 200 patients involved the length of hospitalization. The study
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42 16 heterogeneity was high ($P < 0.00001$, $I^2 = 96\%$, Fig. 5), so a random effect model was selected. The
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44 17 consequence found that the length of hospitalization in DEX group was shorter (SMD= -2.29, 95%
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46 18 CI -4.31 to -0.28, Fig. 5). 4 trials including 292 subjects referred to the extubation time. A random
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48 19 effect model was chosen since the high heterogeneity ($P = 0.004$, $I^2 = 77\%$, Fig. 6). There was a shorter
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50 20 time to extubation in DEX group (SMD= -0.75, 95% CI -1.26 to -0.25, Fig. 6). Therefore, meta-
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52 21 analysis of the 8 literatures indicated that DEX could accelerate the recovery of patients after
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54 22 anesthesia.
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1 Side effects

2 8 trials described the incidence of bradycardia. A fixed effect model was selected considering
3 the little heterogeneity ($P=0.32$, $I^2=14\%$, Fig. 7). Compared to the control group, the number of
4 participants developed bradycardia in the DEX group was higher (OR=1.60, 95% CI 1.13 to 2.27,
5 Fig. 7). The consequences from this meta-analysis revealed that DEX might increase the occurrence
6 of bradycardia.

7 Risk of bias

8 Publication bias of literatures including the incidence of PONV in our meta-analysis was
9 assessed by funnel plots, and no publication bias was found (Fig. 8). We removed each study one
10 by one for sensitivity analysis and found that the results did not change (Supplementary document
11 3).

12 DISCUSSION

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

16 PONV is unsatisfactory experience and painful adverse event for patients, especially in the
17 first day after surgery. Its incidence is approximately 30% and up to 80% without prevention[1; 28].
18 Moreover, some surgical types were associated with the high occurrence of PONV, especially in
19 gynecological surgery, otolaryngology surgery and neurosurgery[3]. There are many risk factors
20 that can increase the incidence of PONV by 20% respectively in patients, including anesthetic
21 factors, surgical factors, female, non-smokers, and the medical history of motion sickness or/and
22 PONV[29]. These risk factors might also vary with the premedication, anesthetic technique and

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4 1 postoperative management[30]. Among the factors of anesthesia, general anesthesia is more likely
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6 2 to cause PONV compared with regional anesthesia[31]. The pathophysiology process of PONV is
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9 3 very elusive. A study suggested that injuries from operation, anesthesia, visceral nerve stimulation,
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11 4 hypoxia, hypotension, and pain were the major irritants, which could trigger the vomiting response
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14 5 when they reach the cortical/thalamic, cerebellar and vestibular nuclei, and the chemoreceptor
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17 6 triggering band outside of the blood-brain barrier[32]. Although there are multiple methods and
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20 7 drugs to prevent PONV in clinical practice, the efficacy of PONV prophylaxis remains
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22 8 unsatisfactory especially in high-risk patients[1].

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25 9 DEX exerts the anxiolytic, sedative and analgesic effects by reducing the release of
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28 10 norepinephrine induced by $\alpha 2$ adrenergic receptors in the spinal cord and locus coeruleus. However,
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31 11 it could not result in excessive sedation or respiratory depression as the results of accumulation[33].
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34 12 Therefore, DEX was used as an appropriate short-acting sedative for patients under general
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37 13 anesthesia in perioperative period. Previous articles indicated that DEX reduced the occurrence of
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40 14 PONV, which were similar to our result. For instance, a study reported that DEX administered could
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43 15 decrease the occurrence of PONV in patients experiencing intestinal surgery[27], another study
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46 16 discovered that intraoperative use of DEX could be a valid measure to prevent the PONV in patients
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49 17 after laparoscopic radical prostatectomy[16]. But the mechanisms for the effect of DEX on PONV
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52 18 are still obscure. Previous articles reported DEX could decrease the occurrence of PONV by
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55 19 modulating 5-HT and dopamine release, suppressing the histamine-induced expression of IL-6, and
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58 20 reducing sympathetic outflow and total catecholamine release[34; 35]. So, one of the key
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60 21 mechanisms about the effect of DEX on PONV might be attributable to the regulation of
22 22 neurotransmitters. Moreover, it is well known to us that the amount of intraoperative opioid use

1 directly influenced the frequency and degree of PONV[31].

2 DEX also can prevent the perioperative stress response by regulating heart rate and blood
3 pressure, however, DEX might produce some adverse events like bradycardia especially in patient
4 with atrioventricular block or hypovolemia[36]. Similar consequence with our article, a meta-
5 analysis of 3638 patients from 9 high-quality RCTs reported that DEX could increase the incidence
6 of bradycardia[37], which might be due to presynaptic α -2 receptor stimulation by DEX results in
7 decreasing norepinephrine release.

8 Additionally, it was interesting to found that DEX could short the time to extubation in this
9 meta-analysis, which was similar to the result of one previous meta-analysis[38]. However, because
10 of the limited data and the high heterogeneity among the studies, the pooled result should be
11 interpreted cautiously and further investigations were needed to support the conclusion.

12 In fact, there were two previous meta-analyses also reported that DEX could low the
13 occurrence of PONV compared to the control group[30; 39]. The included population of these two
14 meta-analyses was the children and adults, and one study didn't limit the methods of anesthesia and
15 the administration of DEX. Notably, we mainly focused on the adult patient population under
16 general anesthesia, and the intervention was perioperative intravenous DEX, which differed from
17 the two previous meta-analyses. Moreover, the RCTs that DEX comparing with opioids agents were
18 excluded in our meta-analysis to eliminate the effect of opioids on PONV. Additionally, our study
19 was involved a number of updated RCTs and added some indicators about the recovery after surgery.
20 Ultimately, our results suggested that DEX did decrease the occurrence of PONV, and accelerated
21 the recovery of adult patients after general anesthesia.

22 **Clinical significance**

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4 1 The results of this meta-analysis might help the doctors and nurses to formulate plans to prevent
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6 2 PONV and offer a new testimony to expand the clinical significance of DEX apart from its
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9 3 conventional usage for sedation and analgesia.

10 4 **LIMITATIONS**

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14 5 There were several limitations to this meta-analysis. Firstly, the included articles did not give
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16 6 consistent doses of DEX, the influence of diverse doses of DEX on PONV in adult patients after
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19 7 general anesthesia needs to be further explored. Secondly, the severity degree of PONV was not
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22 8 quantified using a formal scale, so further study is required to explore the effect of DEX on different
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25 9 severity degree of PONV.

26 27 10 **CONCLUSION**

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30 11 In a word, DEX could decrease the occurrence of PONV in adult patients who experiencing
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32 12 general anesthesia, and accelerate postoperative recovery. Thus, DEX can be used as an adjuvant
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35 13 drug for general anesthesia to prevent the development of PONV in clinical practice. However, it is
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38 14 essential to be vigilant the occurrence of bradycardia during surgery.

39
40 15 **Author Contributions** WZ and JL were involved in the conception and design of this meta-analysis. NW and ZW
41
42 16 conducted the data extraction. HZ and ML contributed to statistical analysis. WZ analyzed the data and drafted the
43
44
45 17 manuscript. JH, DY and MZ offered major comments and revised the manuscript. All authors have read and
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48 18 approved the manuscript.

49
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53
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55 21 analysis, interpretation of data, and writing of the manuscript.

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4 1 **Ethics approval statement** This study was a meta-analysis of previously published literatures, ethical approval
5
6 2 was not necessary.
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9 3 **Competing interests** None declared.
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11 4 **Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting,
12
13 5 or dissemination plans of this research.
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15 6 **Patient consent for publication** Not applicable.
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17 7 **Provenance and peer review** Not commissioned; externally peer reviewed.
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19 8 **Data availability statement** All data relevant to the study are included in the article or uploaded as supplementary
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21 9 information.
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23 10 **Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing
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43 20 appropriate credit is given, any changes made indicated, and the use is non-commercial.
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45 21 See: <http://creativecommons.org/licenses/by-nc/4.0/>.
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9 3 **Figure legends**

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12 4 **Figure 1:** The risk of bias of included studies.

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15 5 **Figure 2:** Flow diagram of the inclusion and exclusion process.

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18 6 **Figure 3:** The total effect of dexmedetomidine on postoperative nausea and vomiting.

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22 7 **Figure 4:** Perioperative opioid consumption in dexmedetomidine and control group.

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25 8 **Figure 5:** The effect of dexmedetomidine on the length of hospitalization.

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28 9 **Figure 6:** The effect of dexmedetomidine on the extubation time.

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32 10 **Figure 7:** Incidence of bradycardia in dexmedetomidine and control group.

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37 11 **Figure 8:** Test for publication bias of the studies included in the incidence of postoperative nausea
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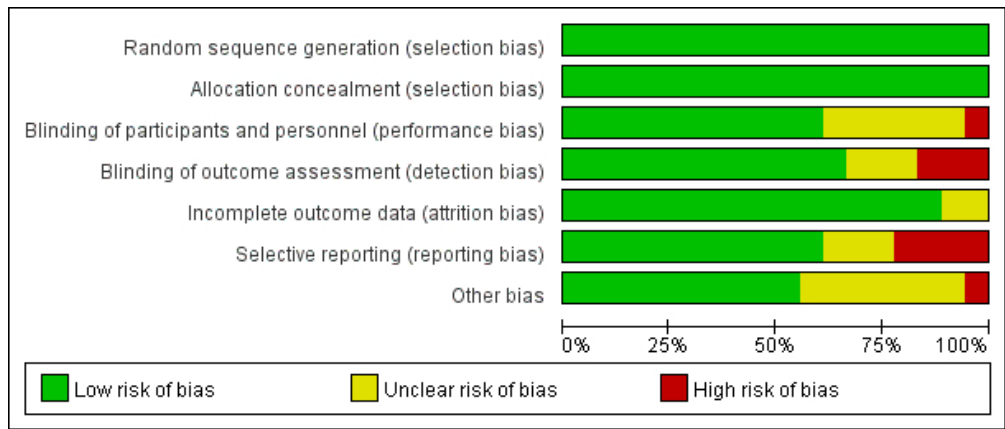


Figure 1: The risk of bias of included studies.

213x90mm (72 x 72 DPI)

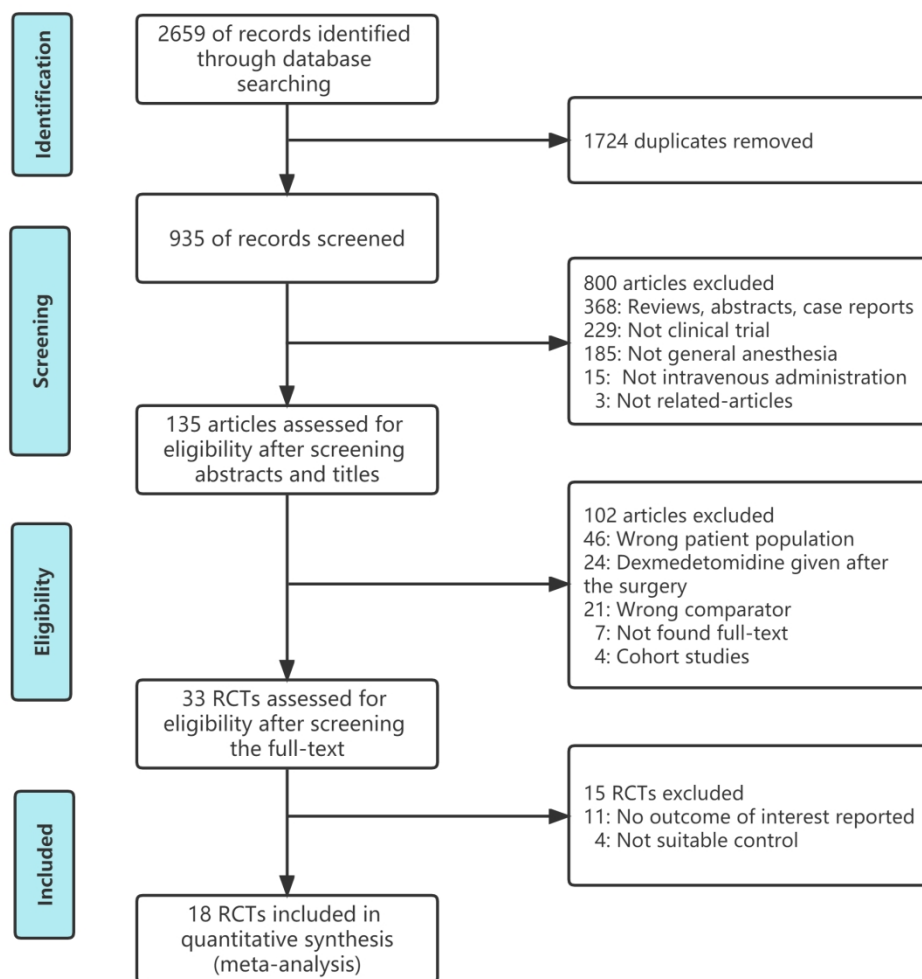


Figure 2: Flow diagram of the inclusion and exclusion process.

720x751mm (72 x 72 DPI)

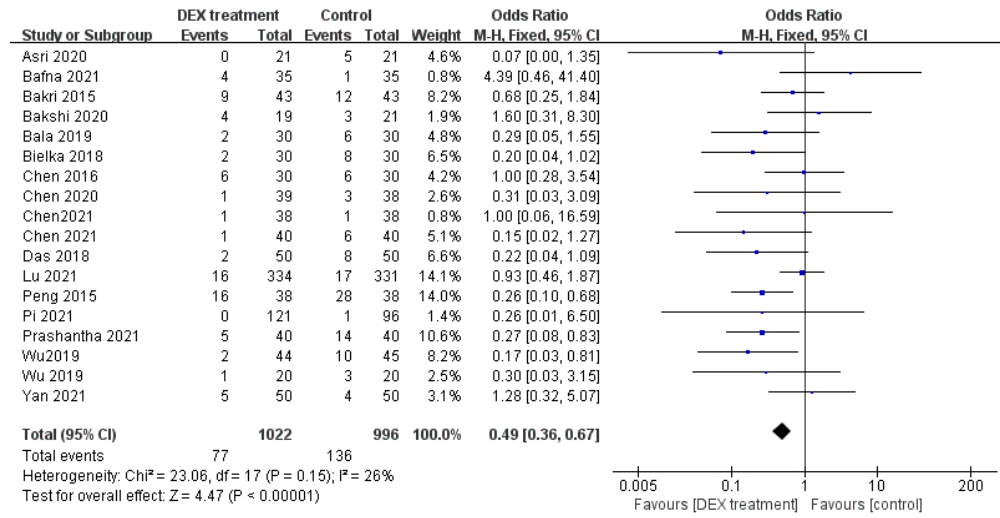


Figure 3: The total effect of dexmedetomidine on postoperative nausea and vomiting.

283x146mm (72 x 72 DPI)

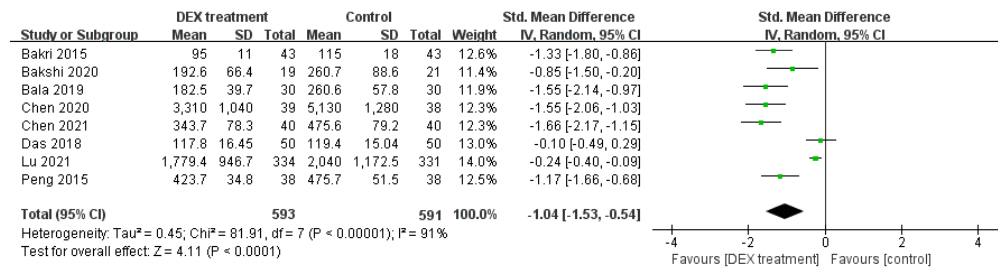


Figure 4: Perioperative opioid consumption in dexmedetomidine and control group.

314x84mm (72 x 72 DPI)

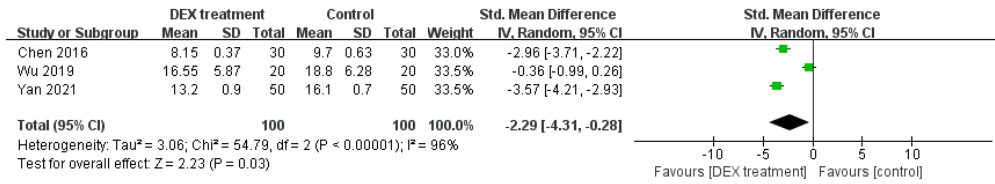


Figure 5: The effect of dexmedetomidine on the length of hospitalization.

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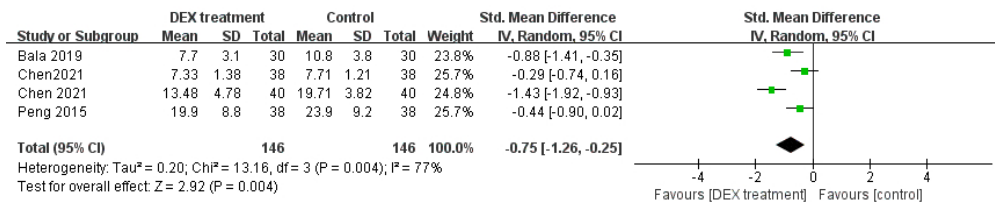


Figure 6: The effect of dexmedetomidine on the extubation time.

303x62mm (72 x 72 DPI)

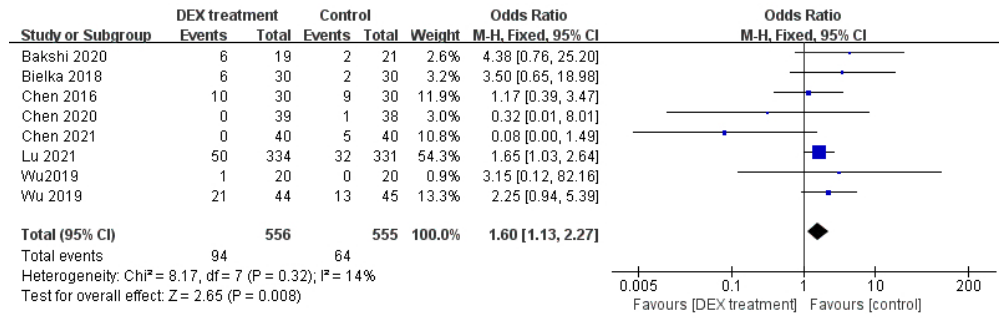


Figure 7: Incidence of bradycardia in dexmedetomidine and control group.

283x90mm (72 x 72 DPI)

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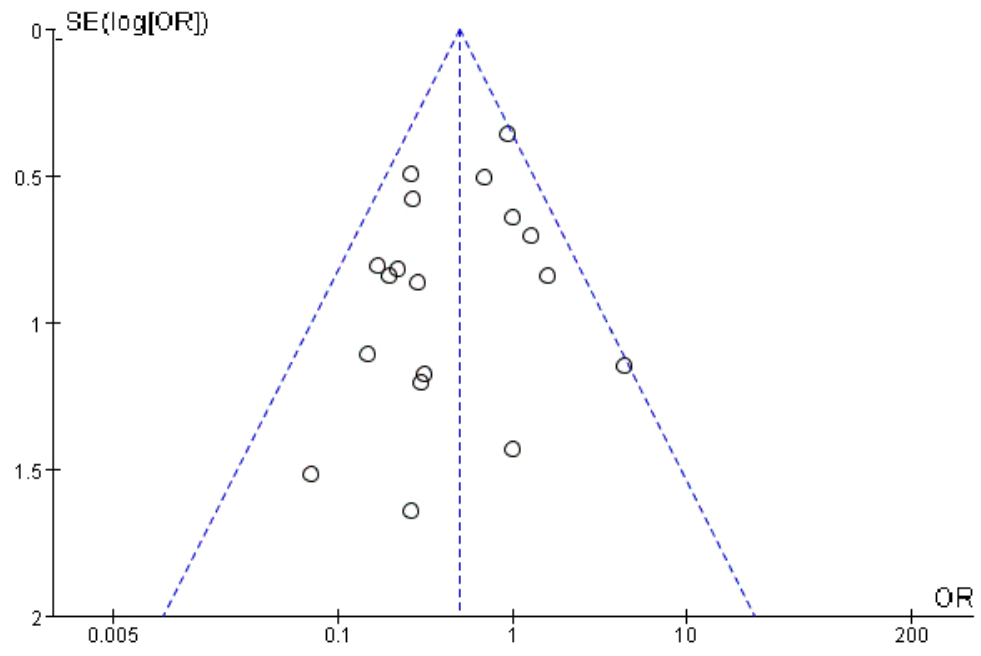


Figure 8: Test for publication bias of the studies included in the incidence of postoperative nausea and vomiting.

544x362mm (28 x 28 DPI)

Supplementary document 1



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3-4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 5 Supplementary document 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary document 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Table 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data	Page 6

Section and Topic	Item #	Checklist item	Location where item is reported
		conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 2
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 2
Study characteristics	17	Cite each included study and present its characteristics.	Page 7
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 11 Figure 8
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 10-11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 10-11
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 10-11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Supplementary document 3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 11
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 11-13
	23b	Discuss any limitations of the evidence included in the review.	Page 14

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	Page 14
	23d	Discuss implications of the results for practice, policy, and future research.	Page 13-14
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 5
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 5
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 14
Competing interests	26	Declare any competing interests of review authors.	Page 15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 15

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

Supplementary document 2: The search strategy

Pubmed (<https://pubmed.ncbi.nlm.nih.gov/>)

Search: (((((((Dexmedetomidine[MeSH Terms]) OR (Dexmedetomidine[Title/Abstract])) OR (MPV-1440[Title/Abstract])) OR (MPV 1440[Title/Abstract])) OR (MPV1440[Title/Abstract])) OR (Precedex[Title/Abstract])) OR (Dexmedetomidine Hydrochloride[Title/Abstract])) OR (Hydrochloride, Dexmedetomidine[Title/Abstract]) AND (("Postoperative Nausea and Vomiting"[Mesh]) OR (((((((PONV[Title/Abstract]) OR (Nausea[Title/Abstract]) AND Vomiting, Postoperative[Title/Abstract])) OR (Vomiting, Postoperative[Title/Abstract])) OR (Postoperative Emesis[Title/Abstract])) OR (Postoperative Vomiting[Title/Abstract])) OR (Emesis, Postoperative[Title/Abstract])) OR (Emeses, Postoperative[Title/Abstract])) OR (Postoperative Emeses[Title/Abstract])) OR (Postoperative Nausea[Title/Abstract]) OR (Nausea, Postoperative[Title/Abstract]))) AND (2000:2022[pdat])

Embase (<http://www.embase.com/>)

- #1 Dexmedetomidine
- #2 'mpv- 1440':ab,ti OR 'mpv 1440':ab,ti OR 'mpv1440':ab,ti OR 'precedex':ab,ti OR 'dexmedetomidine hydrochloride':ab,ti OR 'hydrochloride, dexmedetomidine':ab,ti
- #3 #1 OR #2
- #4 postoperative nausea and vomiting
- #5 'ponv':ab,ti OR 'nausea and vomiting, postoperative':ab,ti OR 'vomiting, postoperative':ab,ti OR 'postoperative emesis':ab,ti OR 'postoperative vomiting':ab,ti OR 'emesis, postoperative':ab,ti OR 'emeses, postoperative':ab,ti OR 'postoperative emeses':ab,ti OR 'postoperative nausea':ab,ti OR 'nausea, postoperative':ab,ti
- #6 #4 OR #5
- #7 [2000-2022]/py
- #8 #3 AND #6 AND #7

Cochrane (<https://www.cochranelibrary.com/>)

- #1 Dexmedetomidine
- #2 (MPV- 1440):ti,ab,kw OR (MPV 1440):ti,ab,kw OR (MPV1440):ti,ab,kw OR (Precedex):ti,ab,kw OR (Dexmedetomidine Hydrochloride):ti,ab,kw OR (Hydrochloride, Dexmedetomidine):ti,ab,kw
- #3 #1 OR #2
- #4 **Postoperative nausea and vomiting**
- #5 (PONV):ti,ab,kw OR (Nausea and Vomiting, Postoperative):ti,ab,kw OR (Vomiting, Postoperative):ti,ab,kw OR (Postoperative Emesis):ti,ab,kw OR (Postoperative

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3 Vomiting):ti,ab,kw OR (Emesis, Postoperative):ti,ab,kw OR (Emeses, Postoperative):ti,ab,kw
4 OR (Postoperative Emeses):ti,ab,kw OR (Postoperative Nausea):ti,ab,kw OR (Nausea,
5 Postoperative):ti,ab,kw
6
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- 8 • #6 #4 OR #5
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- 10 • #7 #3 AND #6 (with Publication Year from 2000 to 2022)
- 11
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13 **Web of Science (<http://apps.webofknowledge.com/>)**

- 14

- 15 • #1 TS= (Postoperative nausea and vomiting OR PONV OR Nausea and Vomiting,
16 Postoperative OR Vomiting, Postoperative OR Postoperative Emesis OR Postoperative
17 Vomiting OR Emesis, Postoperative OR Emeses, Postoperative OR Postoperative Emeses OR
18 Postoperative Nausea OR Nausea, Postoperative)
19
- 20 • #2 TS= (Dexmedetomidine OR MPV-1440 OR MPV 1440 OR MPV1440 OR Precedex OR
21 Dexmedetomidine Hydrochloride OR Hydrochloride, Dexmedetomidine)
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- 23 • #3 PY= (2000-2022)
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Supplementary document 3: The sensitivity analysis of effect of dexmedetomidine on PONV

Study	Odds Ratio	95% CI
Omitting Asri 2020	0.51	[0.37, 0.70]
Omitting Bafna 2021	0.46	[0.33, 0.63]
Omitting Bakri 2015	0.47	[0.34, 0.66]
Omitting Bakshi 2020	0.47	[0.34, 0.64]
Omitting Bala 2019	0.50	[0.36, 0.69]
Omitting Bielka 2018	0.51	[0.37, 0.70]
Omitting Chen 2016	0.47	[0.34, 0.65]
Omitting Chen 2020	0.49	[0.36, 0.68]
Omitting Chen2021	0.49	[0.35, 0.67]
Omitting Chen 2021	0.51	[0.37, 0.70]
Omitting Das 2018	0.51	[0.37, 0.70]
Omitting Lu 2021	0.42	[0.29, 0.60]
Omitting Peng 2015	0.53	[0.38, 0.73]
Omitting Pi 2021	0.49	[0.36, 0.68]
Omitting Prashantha 2021	0.52	[0.37, 0.72]
Omitting Wu2019	0.52	[0.38, 0.71]
Omitting Wu 2019	0.49	[0.36, 0.68]
Omitting Yan 2021	0.46	[0.34, 0.64]
Random effects model	0.48	[0.32, 0.73]