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Perioperative dexmedetomidine administration to prevent delirium in adults after non-cardiac surgery: A systematic review and meta-analysis

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ABSTRACT

Study objective: To evaluate the efficacy of perioperative dexmedetomidine (DEX) administration for preventing delirium in adults after non-cardiac surgery.
Design: Systematic review and meta-analysis of randomized controlled trials (RCTs).
Interventions: Perioperative administration of DEX to prevent delirium in adults following non-cardiac surgery.
Measurements: The incidence of postoperative delirium (POD).
Methods: The databases of PubMed, Embase and Cochrane Central Register were searched from inception to Mar 4, 2021 for all available RCTs that assessed DEX for POD in adults after non-cardiac surgery. Risk ratio (RR) with a 95% confidence interval (CI) was calculated for dichotomous data. Standardized mean difference (SMD) was calculated for continuous data. Risk of bias was assessed using the second version of the Cochrane risk-of-bias tool for RCTs (RoB 2.0), and the level of certainty for main outcomes were assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.
Main results: Thirteen studies, including the meta-analysis with a total of 4015 patients (DEX group: 2050 patients; placebo group: 1965 patients), showed that DEX significantly reduced the incidence of POD in adults after non-cardiac surgery compared with control group (RR: 0.60; 95%CI: 0.46 to 0.77, $P = 0.0001$, $I^2 = 55\%$, GRADE = moderate). Meanwhile, there was a statistical difference by the subgroup analysis between the mean age $\geq$ 65 years group and the mean age<65 years group. There were no statistical differences in length of hospital stay following surgery (SMD: -0.36; 95%CI: −0.80 to 0.07, $P = 0.1$, $I^2 = 97\%$, GRADE = low) and all-cause mortality rate (RR:0.57; 95%CI: 0.25 to 1.28, $P < 0.17$, $I^2 = 0\%$, GRADE = moderate) compared with placebo group. However, Meta-analysis showed that DEX administration significantly resulted in intraoperative bradycardia when compared with placebo group (RR: 1.39; 95%CI: 1.14 to 1.69, $P = 0.0009$, $I^2 = 0\%$, GRADE = high), and as well as intraoperative hypotension (RR: 1.25; 95%CI: 1.11 to 1.42, $P = 0.0004$, $I^2 = 0\%$, GRADE = high).
Conclusion: This systematic review and meta-analysis suggests that perioperative administration of DEX could significantly reduce the incidence of POD in patients elder than 65 years following non-cardiac surgery. However, there was no definite evidence that perioperative DEX could reduce the incidence of POD in patients younger than 65 years of age after non-cardiac surgery. In addition, perioperative DEX administration was associated with an elevated risk of bradycardia and hypotension.

1. Introduction

Postoperative delirium (POD) is an acute attentional deficit that typically occurs during the initial postoperative days and manifests with hypoactive, hyperactive, or mixed symptoms, which is associated with increased length of hospital stay, higher morbidity and mortality and long-term cognitive decline [1,2]. The incidence of delirium ranges from 12% to 51% in patients after noncardiac surgery [3,4]. Meanwhile, studies showed that elderly patients are at greater risk of POD [5,6]. It is essential for the clinician to appropriately adjust perioperative care plans and manage patients from developing postoperative delirium in the perioperative period [7,8]. Dexmedetomidine (DEX) is a highly selective α2-adrenergic receptor agonist providing anxiolysis, sedation, analgesia and neuroprotective effects, and reveals some effect on postoperative delirium in clinical practice [9,10]. However, perioperative use of DEX to prevent delirium showed some mixed results. Two major

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studies [11,12] recently published in the Lancet and JAMA Surgery showed contradictory results of DEX for delirium following non-cardiac surgery, which caused increasing attention to this topic.

With more new studies to provide extensive new data into the potential effects of DEX administration on POD, therefore, we performed this systematic review and meta-analysis of RCTs to evaluate the efficacy of perioperative DEX for POD in adults after non-cardiac surgery, which might provide more effective and accurate strategies for postoperative delirium in clinical practice.

2. Methods

2.1. Search strategy

This systematic review and meta-analysis followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [13], and it was registered in the PROSPERO database (CRD42021231811).

The databases of PubMed, Embase and Cochrane Central Register were systematically searched for all relevant studies from inception to Mar 4, 2021. We combined MeSH terms with free-text terms for this search strategy. The PubMed basic search strategy as follows: ("delirium" [MeSH] OR "delirium" [All Fields]) AND ("dexmedetomidine" [MeSH] OR "dexmedetomidine" [All Fields]). The search strategy was limited to randomized controlled trials (RCTs) and language restriction was not applied. We also manually searched the grey literature and conference proceedings followed with all cross-references screened.

2.2. Study selection criteria

This systematic review and meta-analysis mainly involved adult males and females (age $\geq$ 18 years older) who have undergone non-cardiac surgery. All published full-article RCTs compared the effect of perioperative DEX with placebo for prevention of delirium following non-cardiac surgery were eligible for inclusion. The pre-specified primary outcome was the incidence of POD following non-cardiac surgery. Secondary outcomes were also examined including hypotension(systolic blood pressure less than 90 mmHg or a decrease in systolic blood pressure $>$ 20% from baseline), hypertension(systolic blood pressure more than 180 mmHg or a increase in systolic blood pressure $>$ 20% from baseline), bradycardia(heart rate less than 45 beats per minute or a decrease of more than 20% from baseline), length of hospital stay and all-cause mortality follow surgery and other side effects.

2.3. Data extraction

Two authors (Qin C·S and Lin C) independently extracted the data using the established standard data collection table. Disagreements were resolved by discussion with the thirdauthor (Liu J.C). The extracted data were as follows: the first author's name, the year of publication, basic characteristics of the participants, type of surgery, assessment method of POD, the strategy of DEX infusion, and the primary and secondary outcomes mentioned above.

2.4. Assessment of trial quality

Two authors (Qin C·S and Lin C) independently assessed the quality of the included trials using the second version of the Cochrane risk-of-bias tool for RCTs (RoB 2.0) [14], which included five domains: Randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Risk of overall bias were graded as (1) "low risk of bias" when a low risk of bias was determined for all domains; (2) "some concerns" if at least one domain was assessed as raising some concerns, but not to be at high risk of bias for any single domain; or (3) "high risk of bias" when high risk of bias was reached for at least one domain or the study judgement included some concerns in multiple domains. The disagreements were resolved by discussion with another author (Liu J. C).

2.5. Statistical analysis

We used the Review Manager software (RevMan version5.3.5; The Cochrane Collaboration 2014) and STATA software (Version 13.0 StataCorp) to perform all statistical analyses. Risk ratio (RR) with a 95% confidence interval (CI) was calculated for dichotomous data. Mean differences (MD) was calculated for continuous data while studies all report the outcome using the same scale;otherwise, we chosed the standardized mean difference (SMD) for continuous data.The I^2 statistics used to evaluate heterogeneity were divided into the following three levels [15]: low ($I^2 < 50\%$), moderate ($I^2 = 50$–75%) and high ($I^2 > 75\%$). When the heterogeneity was low, we used fixed effects model to pooled the data; otherwise, we chose random effects model. Two predetermined subgroups analysis were conducted according to DEX administration strategy (preoperative, intraoperative or postoperative period) and the age range (age $\geq$ 65 years older or <65 years older). Publication bias was assessed through visual inspection of funnel plots and Egger's regression asymmetry test to evaluate the small-study effects.The influence of a potential publication bias on findings was explored by using the Duval and Tweedie trim-and-fill procedure. Sensitivity analysis was performed by omitting one study each time to detect the influence of a single study on the overall pooled results. Finally, the level of certainty for main outcomes were assessed by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [16]. A p-value of <0.05 was considered statistically significant.

3. Results

3.1. Search results

In total, 787 potentially eligible studies were identified through the literature search. We excluded 196 duplicate records by checking author name, publication date and journal title. In addition, a further 573 records were excluded based on the title and abstract. After review of the remaining 18 articles in full, 13 RCTs [11,12,17–27] ultimately met the inclusive criteria and were included in the meta-analysis. A flowchart of this process, including the reasons for excluding studies, is shown in Fig. 1.

3.2. Characteristics of trials

Ultimately included trials in this review were published between 2013 and 2020, totaling 4015 patients (2050 in the DEX group and 1965 in the placebo group). 10 trials [11,12,17–20,23–26] were published in English and 3 trials [21,22,27] was published in Chinese. The detailed characteristics of the included trials are presented in Table 1.

3.3. Risk of bias in included studies

According to the primary outcome, thirteen RCTs were assessed using the Cochrane risk-of-bias tool (RoB 2.0), of which four trials [21,22,25,27] were assessed as "high risk of bias", two trials [19,23] assessed as "some concerns" and seven trials[11, 12, 17, 18, 20, 24, 26] as "low risk of bias"(Fig. 2).And according to the secondary outcomes, the methodological results of the Cochrane risk-of-bias tool (RoB 2.0) are summarized in supplementary Fig.S1-S4.

3.4. Effect of interventions

3.4.1. Primary outcomes

Thirteen studies, including the meta-analysis with a total of 4015

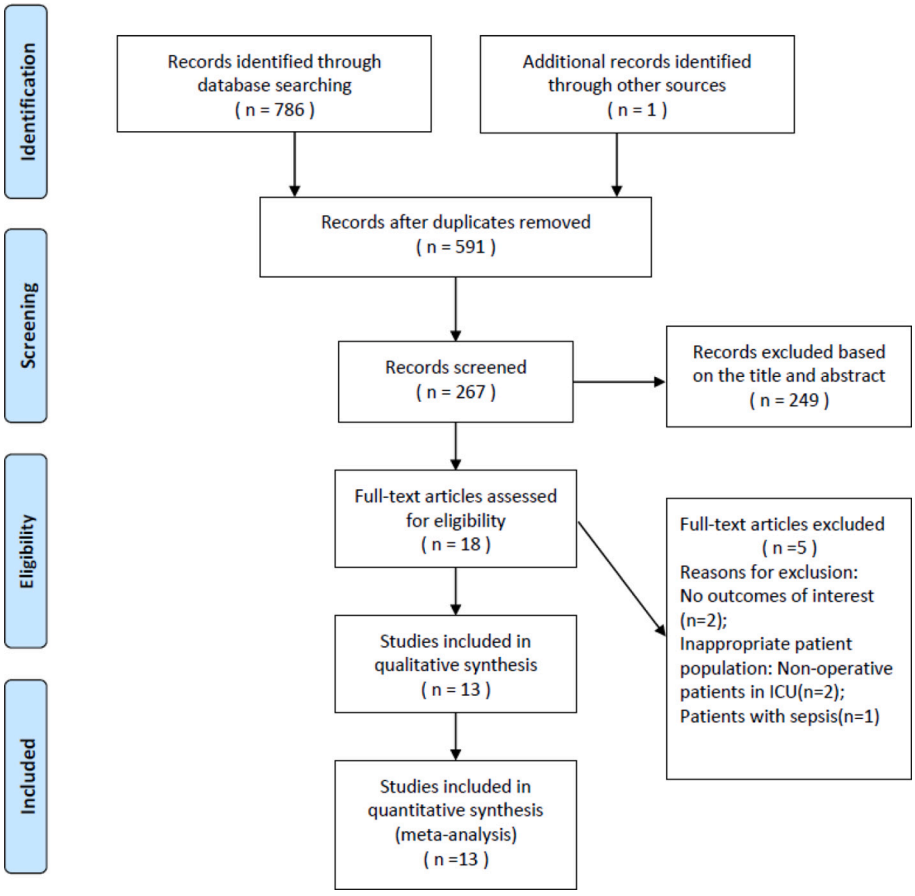

Fig. 1. Flow diagram showing results of search and reasons for exclusion of studies.

patients, showed that DEX significantly reduced the incidence of POD in adults after non-cardiac surgery compared with control group (13 trials [11,12,17–27], RR: 0.60; 95%CI: 0.46 to 0.77, $P = 0.0001$, $I^2 = 55\%$) (Fig. 3. 4). Similarly, the finding was consistent in subgroup analysis between intraoperative(7 trials [12,20,22–26], RR: 0.64; 95%CI: 0.47 to 0.87, $P = 0.004$, $I^2 = 49\%$) and postoperative(6 trials [11,17–19,21,27], RR: 0.54; 95%CI: 0.32 to 0.89, $P = 0.02$, $I^2 = 63\%$) infusion strategy (Fig. 3). In addition, we conducted another subgroup analysis based on the age of patients. We distributed the subgroups according to the mean age of the patients in the respective study. However, there was a statistical difference between the mean age $\geq$ 65 years group (10 trials [11,12,18,21–27], RR: 0.54; 95%CI: 0.41 to 0.74, $P < 0.0001$, $I^2 = 55\%$) and the mean age <65 years group (3 trials [17,19,20], RR: 1.02; 95%CI: 0.62 to 1.67, $P = 0.95$, $I^2 = 0\%$) compared with control groups(Fig. 4).

3.4.2. Secondary outcomes

Six studies, including the meta-analysis with a total of 2083 patients (DEX group: 1037 patients; placebo group: 1046 patients), showed that DEX administration significantly resulted in intraoperative bradycardia when compared with placebo group (6 trials [11,12,17–19,21], RR: 1.39; 95%CI: 1.14 to 1.69, $P = 0.0009$, $I^2 = 0\%$)(Fig. 5), and as well as intraoperative hypotension (6 trials [11,12,17–19,21], RR: 1.25; 95%CI: 1.11 to 1.42, $P = 0.0004$, $I^2 = 0\%$)(Fig. 6). Six studies reported the length of hospital stay following surgery, the results of meta-analyses revealed no statistical differences (6 trials [11,12,18,19,24,26], SMD: -0.36; 95%CI: −0.80 to 0.07, $P = 0.10$, $I^2 = 97\%$)(Fig. 7). In addition, six studies, with a total of 3002 patients examined all-cause mortality rate following surgery, showed there was no significant difference between the DEX group and placebo group (6 trials [11,12,18,19,24,26], RR:0.57; 95%CI: 0.25 to 1.28, $P = 0.17$, $I^2 = 0\%$)(Fig. 8). Two trials reported the occurrence of postoperative respiratory failure. In study of Deiner et al. [12], three patient in the DEX group and two patient in control group developed respiratory failure after surgery. In study of Cheng et al. [26], two patients in the control group developed respiratory failure postoperatively while no patient in DEX group. In both of their studies, there was no significant difference of postoperative respiratory failure between DEX and control groups. Two trials [12,18] reported perioperative hypertension, however, we were unable to performe further meta-analyses due to these insufficient data.

3.5. Sensitivity analysis and publication bias

Sensitivity analysis was performed by excluding all high risk studies (evaluated by RoB2.0) or omitting one study each time from including studies, and the pooled results of meta-analyses for the primary and secondary outcomes were still robust. Meawhile, there was no significant publication bias evidenced by visual inspection of funnel plot (Fig. 9) and Egger's tests($P = 0.933$) for the effects of DEX administration on POD. Similarly, the results of evaluation using the duval and tweedie's trim and fill method showed low publication bias.

3.6. Level of certainty for outcomes (GRADE)

Basing on methodology of GRADE, we evaluated the level of certainty for our major outcomes. The level of certainty for these main outcomes varied from low to high, the detailed information were shown in Table 2.

4. Disscussion

This systematic review and meta-analysis, with a moderate level of certainty, suggested that the perioperative administration of DEX could

Table 1
Characteristics of included randomized controlled studies.

Author /Year	Group (N)	Age/ mean age (yr)	Grade of ASA	Anesthsia depth momotoring	Timing of administering DEX	Type of surgery	Strategy of DEX	Delirium assessment	Primary outcome	Secondary outcomes
Ma [22]	DEX (30) Control (30)	≥60/67	I-III	NO	Intra	Orthopedic surgery	Loading dose of DEX 1 μg/kg before induction of anaesthesia and followed by a continuous infusion (0.5 μg/kg/h) until 30 min before the end of surgery	CAM	Delirium incidence	Serum interleukin levels: IL-6; Patients recovery time
Liu [23]	DEX (99) Control (98)	≥65	II-III	BIS	Intra	Total hip joint or knee joint or shoulder joint replacement surgery	DEX 0.2–0.4 μg/kg/h continuous infusion during the surgery , and stopped 20 min before the end of surgery	CAM	Delirium incidence	Delirium duration
Deiner [12]	DEX (189) Control (201)	>70	I-IV	NO	Intra	Non-cardiac surgery (thoracic, orthopedic, spine,Urologic General,others)	DEX 0.5 μg/kg/h infusion once patients entered the operating room and continued for 2 h in the recovery room	CAM	Delirium incidence	Length of hospital stay, in-hospital mortality, bradycardia, hypotension, hypertension, serious adverse events
Lee [25]	DEX-1 (95) DEX-2 (114) Control (109)	>65	/	BIS	Intra	Laparoscopic or robot assisted radical cystectomy; Partial or total nephrectomy/ colorectal surgery	DEX-1:1 μg/kg bolus after anaesthesia induation and followed by 0.2–0.7 μg/kg/h infusion until end of surgery DEX-2: 1 μg/kg diluted to a total volume of 10 mL in saline over 10 min period infusion before the end of surgery	CAM; CAM-ICU	Delirium incidence	Duration of delirium; cytokine (tumor necrosis factor-alpha: TNFα, interleukin: IL-1 β, IL-2, IL-6, IL-8, and IL-10) and cortisol levels
Li [24]	DEX (309) Control (310)	≥60/69	I-III	BIS	Intra	Thoracolaparoscopic surgery; Open thoracoabdominal and spinal surgery;	Loading dose of DEX 0.6 μg/kg was administered over 10 min before induction of anaesthesia and followed by a continuous infusion (0.5 μg/kg/h) until 1 h before the end of surgery	CAM; CAM-ICU	Delirium incidence	Postoperative pain scores and cumulative morphine; the need for ICU admission after surgery; durations of ICU and hospital stay; MMSE score; total non-delirium complications within 30 days, and all-cause 30 day mortality
Cheng [26]	DEX (269) Control (266)	≥65	I-IV	BIS	Intra	Gastro-intestinal laparotomy	DEX 0.5 μg/kg bolus before induction of anaesthesia and followed by 0.4 μg/kg/h infusion until 30 min before the end of surgery	CAM-ICU	Delirium &POCD	DEX infusion with changes in brain-derived neurotrophic factor
Yang [27]	DEX (46) Control (46)	≥68	I-III	NO	Intra+Post	Femoral fracture surgery	DEX 1 μg/kg bolus followed by a continuous infusion (0.2–0.4 μg/kg/h) until	CAM;	The incidence of delirium	Serum levels of cortisol and C-reactive protein

(*continued on next page*)

Table 1 (*continued*)

Author /Year	Group (N)	Age/ mean age (yr)	Grade of ASA	Anesthsia depth momotoring	Timing of administering DEX	Type of surgery	Strategy of DEX	Delirium assessment	Primary outcome	Secondary outcomes
							the end of the surgery,and DEX 200 μg PCIA after surgery for 48 h.			
Kim [20]	DEX (60) Control (60)	(18–75)/ 63	I-II	BIS	Intra	Thoracic surgery	DEX intravenouslyat a rate of 0.125–0.5 μg/kg/h before induction of anaesthesia until the end of the surgery.	CAM; CAM-ICU	Postoperative delirium	pro- and anti-inflammatory cytokines and catecholamines

Author /Year	Group (N)	Age/ mean age (yr)	Grade of ASA	Anesthsia depth momotoring	Timing of administering DEX	Type of surgery	Strategy of DEX	Delirium assessment	Primary outcome	Secondary outcomes
Yang [17]	DEX (39) Control (40)	(18–80)/ 50	I-II	NO	Intra+Post	Microvascular Free Flap Surgery	DEX at a rate of 0.5 μg/kg/h 60 min before the end of surgery; and following by a continued infusions (0.2–0.7 μg/kg/h) until 6:00 am the next morning.	CAM-ICU	The incidence of agitation and postoperative delirium	Length of ICU stay, bradycardia, hypotension, revision surgery, infection, respiratory failure, sputum, headache, nausea, vomiting, VAS scores, sleep quality, comfort scores
Sun [18]	DEX (281) Control (276)	≥65	I-III	BIS	Post	Spine Surgery; Orthopedic Surgery; Urologic Surgery; Thoracic Surgery; General Surgery	DEX intravenously at a rate of 0.1 μg/ kg/h after surgery for 48 h	CAM; CAM-ICU	The incidence of delirium	postoperative pain scores, the percentage of patients requiring flurbipro-fen axetil for pain rescue, cumulative consumption of NSAIDs, and sleep quality
Su [11]	DEX (350) Control (350)	>65	/	NO	Post	Intra-abdominal Surgery; Intra-thoracic Surgery; Spinal and extremital; Superficial and transurethral Surgery	DEX intravenously at 0·1 μg/kg/h within 1 h after ICU admission until 8:00 am on the first day after surgery.	CAM-ICU	The incidence of delirium	Time to extubation, length of stay in the ICU; length of stay in the hospital after surgery; occurrence of non-delirium postoperative complications, and all-cause 30 day mortality
Lee [19]	DEX (100) Control (101)	(52–62)/ 56	I-III	BIS	Intra+Post	Living-Donor Liver Transplantation	DEX (0.1 μg/kg /h) was administered immediately after induction of anaesthesia and was continued until 48 h postoperatively.	CAM-ICU	The incidence of delirium	Duration of delirium after LT, mechanical ventilation duration, ICU length of stay, hospital length of stay, in-hospital mortality, and mortality at 3 months
Guo [21]	DEX (60) Control (78)	≥65	I-II	BIS	Post	Oral cancer	DEX intravenously at a rate of 0.2 μg/ kg/h after surgery for 12 h.	CAM-ICU	Delirium incidence	VAS, RASS scores, bradycardia, hypotension, respiratory depression, vomiting, nausea

DEX: Dexmedetomidine; N: Number; BIS: Bispectral index; ASA: American society of anesthesiologists; CAM: Confusion assessment method; ICU: Intensive care unit; POCD: Postoperative cognitive dysfunction; Intra: Intraoperative Post: Postoperative; PCIA: Patient controlled intravenous analgesia; VAS: visual analogue scale; RASS: Richmond Agitation Sedation Scale.

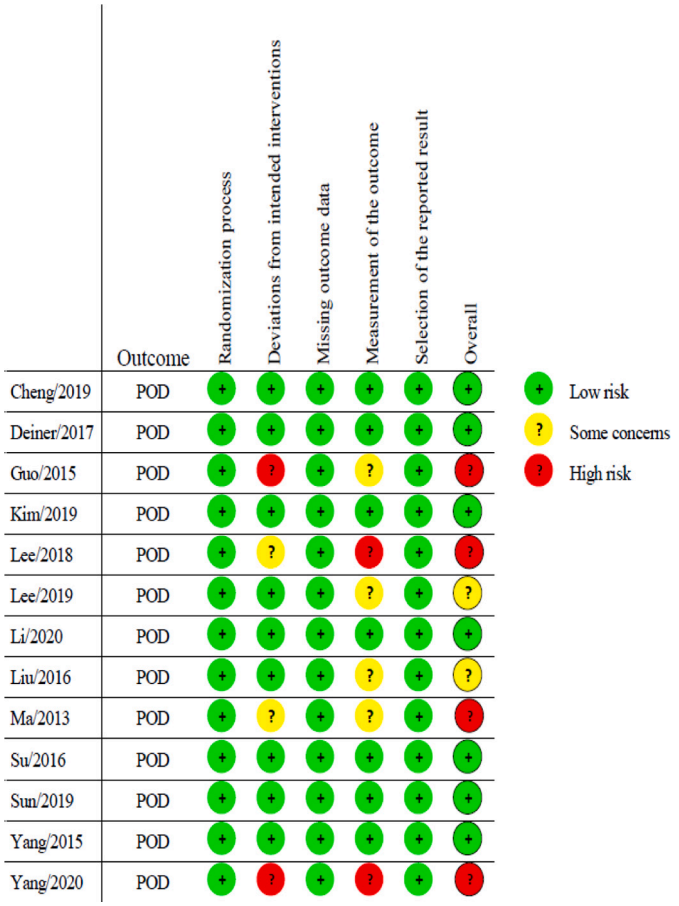

Fig. 2. Quality assessment according to the outcome of POD, using version 2.0 of the Cochrane risk-of-bias tool for RCTs (RoB 2.0).

significantly reduce the risks of POD in patients following non-cardiac surgery when compared with placebo. Furthermore, both intraoperative or/and postoperative infusion of DEX significantly reduced the incidence of POD. The results of meta-analysis for length of hospital stay and all-cause mortality rate showed no significant difference compared with placebo groups.

Prevention of delirium in the surgical patient is essential as postoperative delirium is an important health care issue [28]. Risk factors such as pre-existing cognitive dysfunction, postoperative pain, use of opioids and sedatives and surgical inflammation have been proved associated with postoperative delirium [29,30]. DEX's ability to reduce POD might be associated with its specific characteristics, which has a significant opioid-sparing effect due to high and specific α2-adrenergic receptor selectivity [10,31]. In addition, study revealed that DEX could attenuate the systemic inflammatory response processes through the downregulation of the HMGB1-TLR4-NF-κB signaling pathway [32–34], which play an important effect on patient's cognitive function following surgery.

Our subgroup analysis confirmed the result of a recent meta-analysis [35], which showed DEX administration reduced risk of POD in elderly patients following non-cardiac surgery. On the contrary, statistical analysis showed that perioperative administration of DEX could not reduce the incidence of POD in the mean age <65 years group when compared with the placebo group in this review. The elderly appeared to more benefit than younger patients from perioperative DEX administration. However, according to the data included, we should interpret this result with cautions. On the one hand, there were only three studies with a relative small samples were included in the mean age <65 years subgroup, which may be subject to small study effect bias; On the other hand, due to the data of age were insufficient in this review, we classified the subgroups according to the mean age values in studies, which might induce some misclassification of accurate age.

There were three studies [12,19,20] drew the opposite conclusion versus the other studies in this review. The study of Deiner et al. [12] included 390 patients reported no difference in POD incidence between the DEX and placebo group. In this study, there was a high proportion of patients with presurgical mild cognitive impairment existed on baseline levels (63.1%, 246 of 390), and it excluded patients with ASA classification of >III or planned postoperative admission to ICU, which maybe interfered with the analysis of the final results. Lee et al. [19] and Kim et al. [20] reported the same results as Deiner et al., however, two researcher included relatively small sample sizes respectively and used

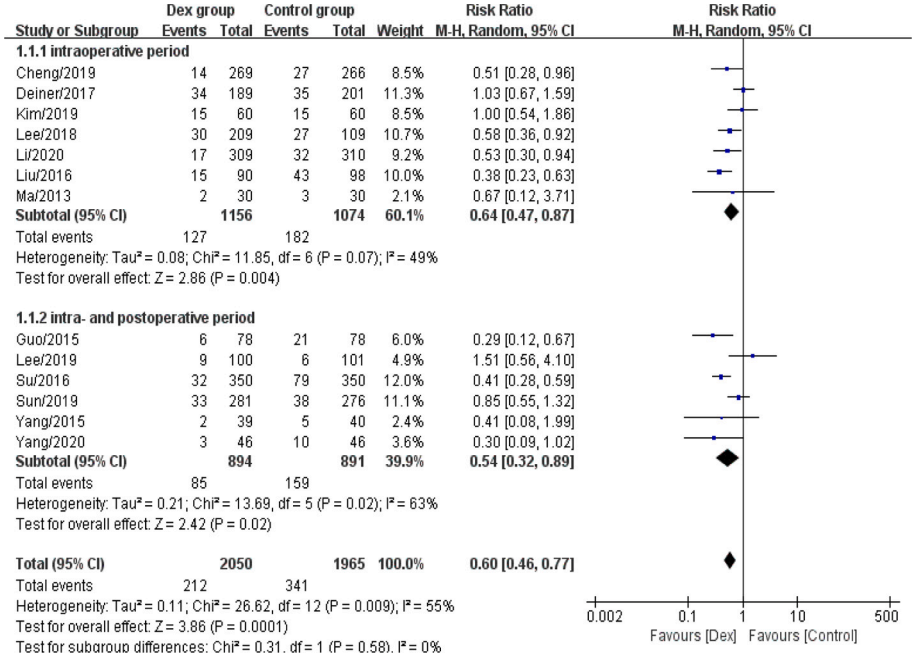

Fig. 3. Forest plot of postoperative delirium by subgroup base on dexmedetomidine administration strategy.

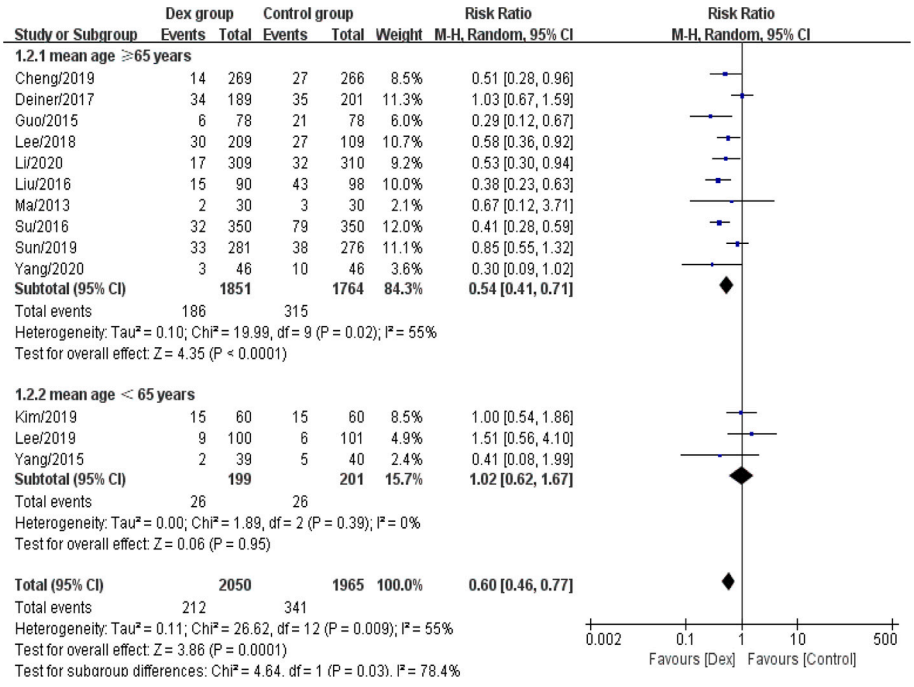

Fig. 4. Forest plot of postoperative delirium by subgroup base on age classification.

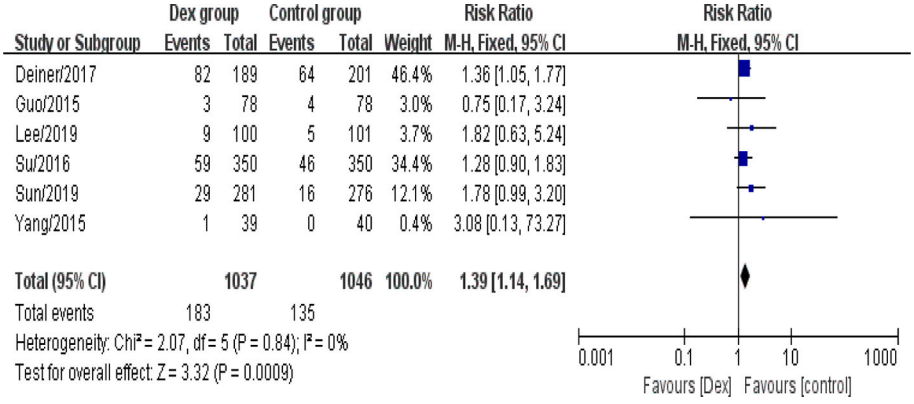

Fig. 5. Forest plot of intraoperative bradycardia.

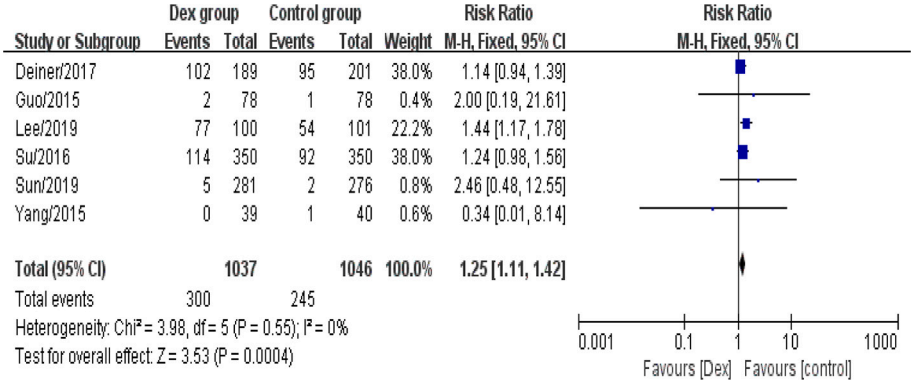

Fig. 6. Forest plot of intraoperative hypotension.

very low doses of DEX infusion strategy in their studies, which might have an underestimated the efficacy of the DEX infusion.

Notably, the maintenance infusion rate of perioperative DEX differed from 0.1 μg/kg/h to 0.7 μg/kg/h (with or without a loading dose) between included studies; Meanwhile, the mean value of the applied maintenance dose of DEX was not reported in any study of this review, the reliable optimal dose of DEX can not be finally concluded from our included studies. Therefore, we did not deliberately divide a dose point

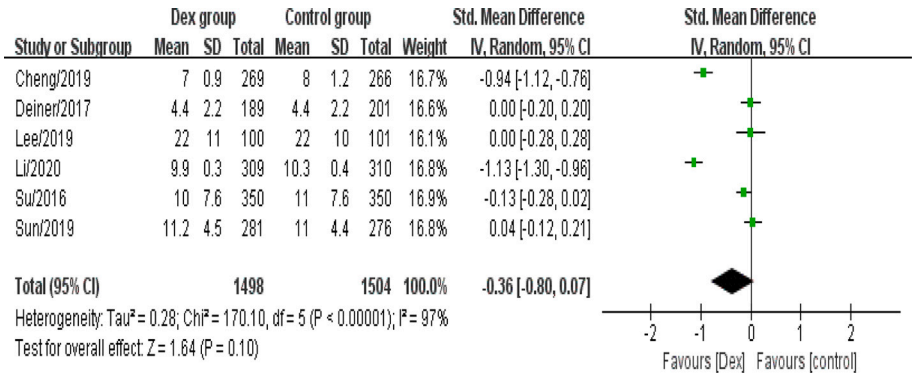

Fig. 7. Forest plot of length of hospital stay.

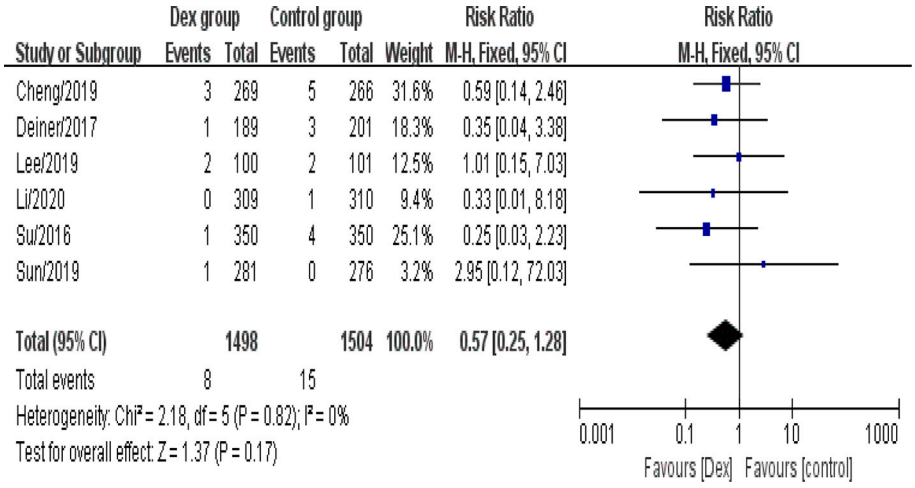

Fig. 8. Forest plot of all-cause mortality rate following surgery.

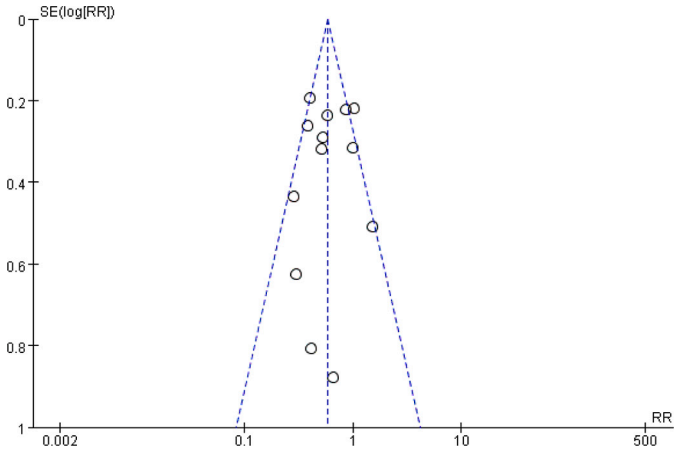

Fig. 9. Funnel plot of the primary outcome (postoperative delirium after non-cardiac surgery).

of DEX infusion for subgroup analysis, and the optimal dose-response effect of dexmedetomidine to prevent postoperative delirium needs to be explored in future studies.

In clinical practice, bradycardia and hypotension are the most commonly reported adverse events of DEX infusion, which were associating with its α2 adrenoreceptor agonist mechanism [36], It is not surprising that the results of this meta-analysis revealed the bradycardia and hypotension in DEX group were significantly higher when compared with placebo group, and we should take more attention on it during perioperative DEX administration.

This systematic review has several potential limitations. First, the time-point of postoperative delirium evaluation was not uniform among the included studies. Delirium was assessed within 3 to 5 day after surgery in most studies, however, some trials assessed delirium in the first 2 days after surgery, which may underestimate the the incidence of POD. Second, the strategy of DEX differ among the included studies. The maintenance dose of DEX could been adjusted based on hemodynamic changes or intraoperative anesthsia depth momotoring, while in other study the infusion rate of DEX was maintained by fixed dose. In addition, in order to effectively relieve postoperative pain, almost all patients received postoperative adjuvant analgesia therapy (fentanyl, sufentanil, morphine and other opioids) in these included study, however, these analgesia strategies are not universally standardized. Therefore, these variables produced the clinical heterogeneity and influenced the final results. Third, patients with preoperative delirium were not excluded carefully in studies, which might weakness of these studies. Therefore, further more structured and standardized perioperative DEX protocols should be developed for prevention of delirium following non-cardiac surgery.

5. Conclusion

In summary, this systematic review and meta-analysis suggests that perioperative administration of DEX could significantly reduce the incidence of POD in patients elder than 65 years following non-cardiac surgery. However, there were no definite evidence that perioperative DEX could reduce the risk of POD in patients younger than 65 years of

Table 2
GRADE evidence for main outcomes.

Outcomes	NO of participants (studies)	Relative effect (95% CI)		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of the evidence (GRADE)
		ESP-block	Non-block						
Postoperative dlirium	4015 (13 RCTs)	RR:0.6(0.46, 0.77)		Not Serious	Not Serious°	Not serious	Not serious	None	⊕⊕⊕⊖ Moderate
Intraoperative bradycardia	2083 (6 RCTs)	RR:1.39(1.14, 1.69)		Not Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕ Hight
Intraoperative hypotension	2047 (6 RCTs)	RR:1.25(1.11, 1.42)		Not Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕ Hight
Length of hospital	3002 (6 RCTs)	SMD:-0.36(−0.8, 0.07)		Not Serious	Serious°	Not serious	Serious△	None	⊕⊕⊖⊖ Low
All-cause mortality	3002 (6 RCTs)	RR:0.57(0.25, 1.28)		Not Serious	Not serious	Serious▽	Serious	None	⊕⊕⊕⊖ Moderate

° Quality was rated down for having high statistical heterogeneity; ▽ It may be influenced by the disease itself and surgical strategy; △ We used the median and quartile ranges to approximate the means and SD, which might decreased confidence in the estimate and the 95% CI.

age. In addition, perioperative DEX administration was associated with an elevated risk of bradycardia and hypotension. Further large high-quality standardized studies are still warranted to explore the optimal dose of dexmedetomidine for POD prevention and its side effects.

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Declaration of Competing Interest

The authors declare that they have no known competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2021.110308.

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