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Original Article

Meta-analysis on clinical efficacy and safety of dexmedetomidine for perioperative anesthesia

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Abstract: Objective: To evaluate the clinical efficacy and safety of dexmedetomidine (DEX) for perioperative anesthesia by meta-analysis. Methods: The cochrane library, pubMed, proQuest, medline, springerLink, CBM, CNKI, CSTJ (VIP) and WANFANG DATA were searched for randomized controlled trials concerning the clinical efficacy and safety of DEX for perioperative anesthesia in patients. Literature published on these databases between Jane 2000 and June 2018 were collected and were screened according to the inclusion and exclusion criteria. After extracting data and appraising the quality of the literature, a meta-analysis was performed by stata 14.0. Primary outcome measures included cognitive impairment, Mini-Mental State Examination (MMSE) score, and related adverse reactions such as nausea, vomiting, bradycardia, hypotension and shivering. Thirty articles appraised as qualified ones were included in this meta-analysis. Results: A total of 3,183 patients were included, of which 1,454 were in the study group and 1,729 in the control group. Compared with the control group, meta-analysis showed that DEX could reduce the incidences of postoperative nausea and vomiting (RR=0.47, 95% CI (0.35, 0.63)), and shivering (RR=0.49, 95% CI (0.38, 0.63)) as well as delirium and agitation (RR=0.38, 95% CI (0.27, 0.55)), and could at the same time increase the incidences of bradycardia (RR=1.46, 95% CI (1.13, 1.87)) and hypotension (RR=1.32, 95% CI (1.12, 1.55)) in the study group. Besides, DEX increased the MMSE scores at postoperative day 1 (WMD=1.63, 95% CI (1.43, 1.82)), day 2 (WMD=1.41, 95% CI (1.17, 1.65)), day 3 (WMD=1.39, 95% CI (1.16, 1.61)) and day 7 (WMD=0.63, 95% CI (0.38, 0.88)). Conclusion: Compared with the control group, DEX used for perioperative anesthesia in the study group can reduce postoperative nausea and vomiting, agitation and delirium, and shivering, and can improve hemodynamic balance. In addition, DEX can effectively reduce the risk of postoperative cognitive impairment and improve postoperative MMSE scores.

Keywords: Dexmedetomidine, perioperative period, anesthesia, meta-analysis, cognitive dysfunction, MMSE score

Introduction

In order to reduce the fluctuation of vital signs caused by surgical noxious stimulation, nervousness or fear, and to lessen the adverse reactions after postoperative anesthesia, drugs are often administrated to patients during the perioperative period for anesthesia induction or sedation [1]. The clinical application of several drugs such as midazolam, clonidine, ketamine and fentanyl is helpful to accelerate postoperative recovery of muscle strength for early walking as well as prolong the analgesic and sedative effects, but the overall efficacy of those drugs is not very satisfactory [2].

Dexmedetomidine (DEX) is a highly selective α2-adrenoceptor agonist, which can produce sedative, anxiolytic, hypnotic, analgesic, and sympatholytic effects, and stabilize hemodynamics [3]. There are many relevant clinical reports, but the conclusions of the studies vary in a large range because of the differences in anesthesia method, subject, dosage and sample size [3-5]. This study was designed to evaluate the clinical efficacy and safety of DEX for perioperative anesthesia by meta-analysis, and to provide a reference for making a better medication scheme for patients during perioperative period.

Materials and methods

Search strategy

The Cochrane Library, PubMed, ProQuest, Medline, SpringerLink, CBM, CNKI, CSTJ (VIP) and WANFANG DATA were searched for ran-

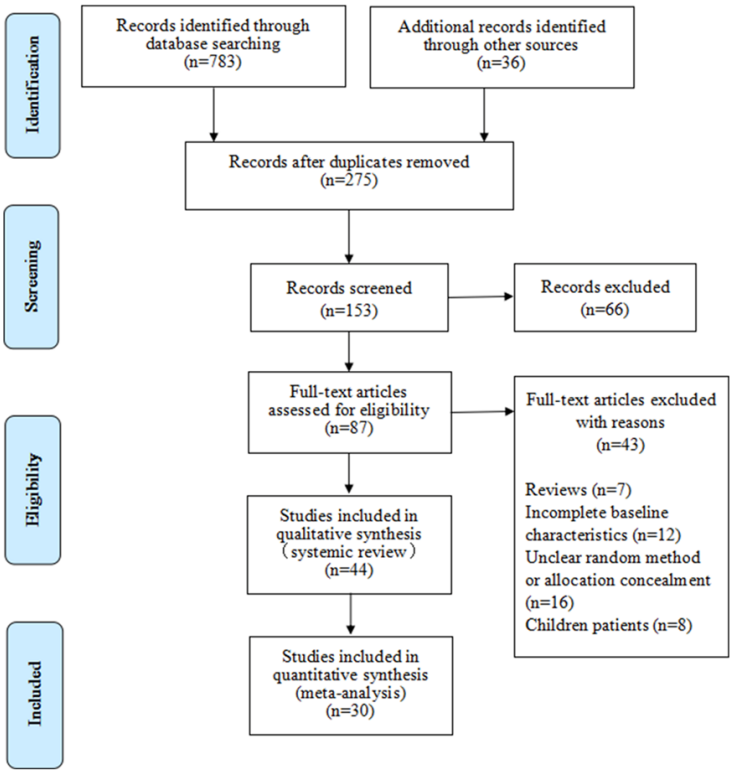

Figure 1. PRISMA flow diagram.

domized controlled literature concerning the clinical efficacy and safety of DEX for perioperative anesthesia in patients. Literatures published on these databases between Jane 2000 and May 2018 were collected. Search terms in this study were "DEX", "postoperative shivering", "agitation", "delirium", "postoperative cognitive dysfunction (POCD)", "nausea and vomiting", "hypotension" and "bradycardia". And those terms were searched using Chinese and English, respectively [6]. Search syntaxes like "AND" and "OR" were used between those search terms.

Study selection

Two authors independently examined titles and abstracts, and reviewed articles to select eligible studies. Inclusion criteria were: 1) study design: randomized controlled trial (RCT); 2) language: Chinese or English; 3) participants: patients undergoing some kinds of surgeries; and 4) outcomes: cognitive dysfunction, nausea, vomiting, agitation, delirium, bradycardia, hypotension, and shivering [7]. Exclusion criteria were: 1) study design other than RCT; 2) reviews, comments, abstracts, letters, research reports, abstracts from conferences, and duplicate publications; 3) pediatric and neuropathic patients; 4) animal researches or basic researces; 5) studies with only abstracts; 6) studies that reported insufficient data; and 7) average age, sex ratio, average body weight or body mass index, or average operation time were not clear.

Data extraction

Two authors independently extracted relevant data from all eligible RCTs. Extracted data included the followings: name of the first author; publication year; average age of participants; sex ratio; average body weight or body mass index; average operation time; random method; intervention; allocation concealment; comparison method; and follow-up method [8]. Outcome measures included intraoperative blood pressure, heart rate, cognitive dysfunction, MMSE score, and related adverse reactions such as nausea, vomiting, bradycardia, hypotension, agitation, delirium, and shivering.

Quality assessment

The quality of each included study was evaluated by two authors. The risk of bias in the included studies were evaluated from the following aspects: 1) completeness of baseline characteristics such as gender, age, weight or body mass index, and duration of operation; 2) correctness of random method; 3) sufficiency of allocation concealment; 4) clarity of intervention method; 5) clarity of follow-up (whole course, loss of follow-up) and dropout number; 6) completeness of data of measures. If the above methods were in line with the assessment, the study was considered to have less bias [9].

Statistical analysis

Statistical analyses were performed using STATA 14.0. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated for dichot-

Table 1. Baseline characteristics of included studies

Studies	Sample size	Anesthetic method	Interventions	Random method	Blind method	Outcomes
Megalla et al. 2017 [11]	25/25/25	2	DEX^T/Nalbuphine^C/Normal Saline^C	Y	Y	②③④⑤
Venkatraman et al. 2018 [12]	30/30/30	2	DEX^T/Clonidine^C/Tramadol^C	Y	Y	②③④⑤
Aksua et al. 2018 [13]	31/31	1	Bupivacaine + DEX^T/Bupivacaine^C	Y	Y	⑤
Mohamed et al. 2015 [14]	50/55	2	DEX^T/Nefopam^C	Y	Y	②
Mohamed et al. 2016 [15]	80/80/80/80	2	DEX^T/Granisetron^C/Tramadol^C/Normal Saline^C	Y	Y	②③④⑤
Corredor et al. 2016 [16]	33/40/38/45	2	DEX^T/Pethidine^C/Clonidine^C/Normal Saline^C	Y	Y	②④⑤⑥
Aksu et al. 2009 [17]	20/20	1	DEX^T/Fentanyl^C	Y	Y	②③⑤⑥
Tekin et al. 2007 [18]	30/30	2	DEX^T/Normal Saline^C	Y	Y	①②⑤
Kong et al. 2018 [19]	60/60	1	DEX^T/Normal Saline^C	Y	NA	⑥⑦
Yin et al. 2016 [20]	50/50	1	DEX^T/Normal Saline^C	Y	NA	⑦
Liao et al. 2017 [21]	30/30	1	DEX^T/Normal Saline^C	Y	NA	⑥⑦
Liu et al. 2014 [22]	30/30	1	DEX^T/Normal Saline^C	Y	NA	⑦
Hassan et al. 2015 [23]	25/25	1	DEX^T/Clonidine + Propofol^C	Y	Y	⑤⑥
Liu et al. 2016 [24]	29/32	1	DEX^T/Propofol^C	Y	Y	③④⑤⑥
Mai et al. 2015 [25]	30/30	2	DEX^T/Clonidine^C	Y	Y	⑤⑥
Mohamed et al. 2015 [26]	24/24	2	Lidocaine + DEX^T/Lidocaine^C	Y	Y	④⑥
Samantaray et al. 2015 [27]	20/20	2	DEX^T/Normal Saline^C	Y	Y	②③④⑤
Nethra et al. 2015 [28]	20/20	2	DEX^T/Normal Saline^C	Y	Y	①②④⑤
Naaz et al. 2016 [29]	20/20	2	DEX^T/Normal Saline^C	Y	Y	②③④
Gupta et al. 2011 [30]	30/30	2	DEX^T/Normal Saline^C	Y	Y	②③④⑤
Kermany et al. 2016 [31]	50/50	2	DEX^T/Remifentanil^C	Y	Y	⑦
Li et al. 2015 [32]	50/50	2	DEX^T/Normal Saline^C	Y	Y	⑥⑦
Guo et al. 2015 [33]	76/73	1	DEX^T/Normal Saline^C	Y	Y	③④⑦
Zhang et al. 2014 [34]	20/20	1	DEX^T/Normal Saline^C	Y	Y	③④⑦
Chen et al. 2013 [35]	59/63	1	DEX^T/Normal Saline^C	Y	Y	⑥⑦
Kilic et al. 2011 [36]	25/25	1	DEX^T/Midazolam^C	Y	Y	⑤⑦
Su et al. 2016 [37]	350/350	2	DEX^T/Normal Saline^C	Y	Y	③④⑥
Liu et al. 2015 [38]	39/39/38	2	1 μg/kg DEX^T/0.5 μg/kg DEX^T/Normal Saline^C	Y	Y	⑤
Wang et al. 2017 [39]	40/40	2	DEX^T/Propofol^C	Y	Y	⑤
Qi et al. 2016 [40]	39/40/39	2	DEX^T/Morphine^C/Normal Saline^C	Y	Y	①②③④⑤

Note: ^{T}: Observation group, ^{C}: control group; 1: general anesthesia, 2: local anesthesia or local nerve block anesthesia; Y: the implementation is clear, NA: the implementation is not clear; ①: anesthetic dosage, ②: bradycardia, ③: hypotension, ④: postoperative nausea and vomiting, ⑤: shivering, ⑥: agitation, delirium, COPD, ⑦: mini-mental state examination (MMSE) score.

omous data, and weighted mean differences (WMDs) with 95% CIs were calculated for continuous variables. Heterogeneity was measured and expressed as I^2, according to which a random effect model (I^2>50%) or a fixed effect model (I^2≤50%) was used to evaluate the overall effect. Subgroup analyses were conducted according to types of adverse effect and time points of POCD; and potential publication bias was evaluated using Egger regression [10]. Statistical significance level was set at α=0.05.

Results

Literature screening process

The systematic review based on the search strategy excluded 94 non-related and non-original studies by reading the titles and abstracts. Finally, after further examining of titles and abstracts, and review of articles according to inclusion and exclusion criteria, a total of 30 RCTs involving 3,183 patients (1,729 in the control group and 1,454 in the research group) were included in this meta-analysis [11-40]. The quality of the RCTs was generally good. The detailed process of literature screening (PRISMA flow diagram) is shown in **Figure 1**.

Quality assessment

The baseline characteristics involving average age, sex ratio, mean body weight or body mass index, and average operation time in the included studies were clear and of good comparability. All studies were randomized blinded controlled trails. Control interventions included positive drug controls such as clonidine, midazolam, propofol, and fentanyl. Blank control like normal saline was also included. The random methods and blind methods in most of the studies were clearly pointed out. The criteria for sedation score and the amount of anesthetics administered could not be systematically evaluated due to non-uniformity (**Table 1**).

Rate of adverse reaction

There were 17, 10, 5, 14 and 14 studies, respectively, reporting the incidence of nausea and vomiting, shivering, agitation and delirium, bradycardia, and hypotension at different time points after DEX. Perioperative application of DEX, compared with control interventions, could reduce the incidence of postoperative nausea and vomiting (RR=0.47, 95% CI (0.35, 0.63)), shivering (RR=0.49, 95% CI (0.38, 0.63) w), agitation and delirium (RR=0.38, 95% CI (0.27, 0.55)), and increase the incidence of bradycardia (RR=1.46, 95% CI (1.13, 1.87)) and hypotension (RR=1.32, 95% CI (1.12, 1.55)). The results of the egger's test were -0.47, 0.12, -0.13, 0.60, and -0.67, respectively; and the corresponding *P* values were 0.30, 0.85, 0.79, 0.03, and 0.01, respectively. There was a significant publication bias in the studies involving the incidence of bradycardia and hypotension, which was probably due to the relatively high proportion of negative outcomes in terms of bradycardia and hypotension compared with other adverse reactions among the included studies. Subgroup analyses were conducted according to the control intervention methods. Compared with the positive controls, DEX showed no significant increase in the incidence of shivering (RR=0.76, 95% CI (0.53, 1.08)), agitation and delirium (RR=0.74, 95% CI (0.22, 2.51)), and hypotension (RR=1.24, 95% CI (0.92, 1.66)). See **Table 2**.

Impact on cognitive function

A total of 9 studies involving 710 patients in the observation group and 714 patients in the control group reported the effect of DEX on the incidence of postoperative cognitive dysfunction at different time points. The results of the heterogeneity analysis in all the studies were I^2=19.6%., DEX significantly reduced the incidence of postoperative cognitive dysfunction (RR=0.31, 95% CI (0.23, 0.42), P=0.00) through fixed model effect analysis. Subgroup analysis showed that DEX reduced the incidence of cognitive dysfunction in the patients on postoperative day 1 (RR=0.32, 95% CI (0.23, 0.44), P=0.00), day 3 (RR=0.19, 95% CI (0.06, 0.59), P=0.00), and day 7 (RR=0.48, 95% CI (0.12, 1.9), P=0.30) (**Figure 2**). The results of the heterogeneity analysis in all the subgroups were I^2<50%. The result of Egger's test was -0.66, and its corresponding *P* value was 0.10, indicating that there was no significant publication bias.

A total of 10 studies involving 375 patients in the observation group and 376 patients in the control group reported MMSE scores, which showed significant heterogeneity (I^2=97.0%). The total WMD was 1.32, 95% CI (1.20, 1.43)

Table 2. Meta-analysis of perioperative adverse events using dexmedetomidine

Outcomes	Sample size (T/C)	I^2 (%)	RR	95% CI		P
Bradycardia	1108/1109	0.0	1.46	1.13	1.87	0.00
Positive control	469/470	0.0	1.92	1.04	3.52	0.04
Blank control	639/639	0.0	1.36	1.04	1.80	0.03
Hypotension	1136/1161	0.0	1.32	1.12	1.55	0.00
Positive control	515/528	0.0	1.24	0.92	1.66	0.16
Blank control	621/633	0.0	1.36	1.12	1.65	0.00
Postoperative nausea and vomiting	786/813	19.9	0.47	0.35	0.63	0.00
Positive control	409/425	0.0	0.55	0.37	0.81	0.01
Blank control	377/388	55.9	0.40	0.27	0.60	0.00
Shivering	667/692	49.5	0.49	0.38	0.63	0.00
Positive control	415/428	31.9	0.76	0.53	1.08	0.12
Blank control	252/264	19.2	0.29	0.20	0.44	0.00
Agitation and delirium	527/554	13.7	0.38	0.27	0.55	0.00
Positive control	120/135	7.3	0.74	0.22	2.51	0.62
Blank control	407/419	34.3	0.36	0.25	0.52	0.00

Note: T: observation group, C: control group.

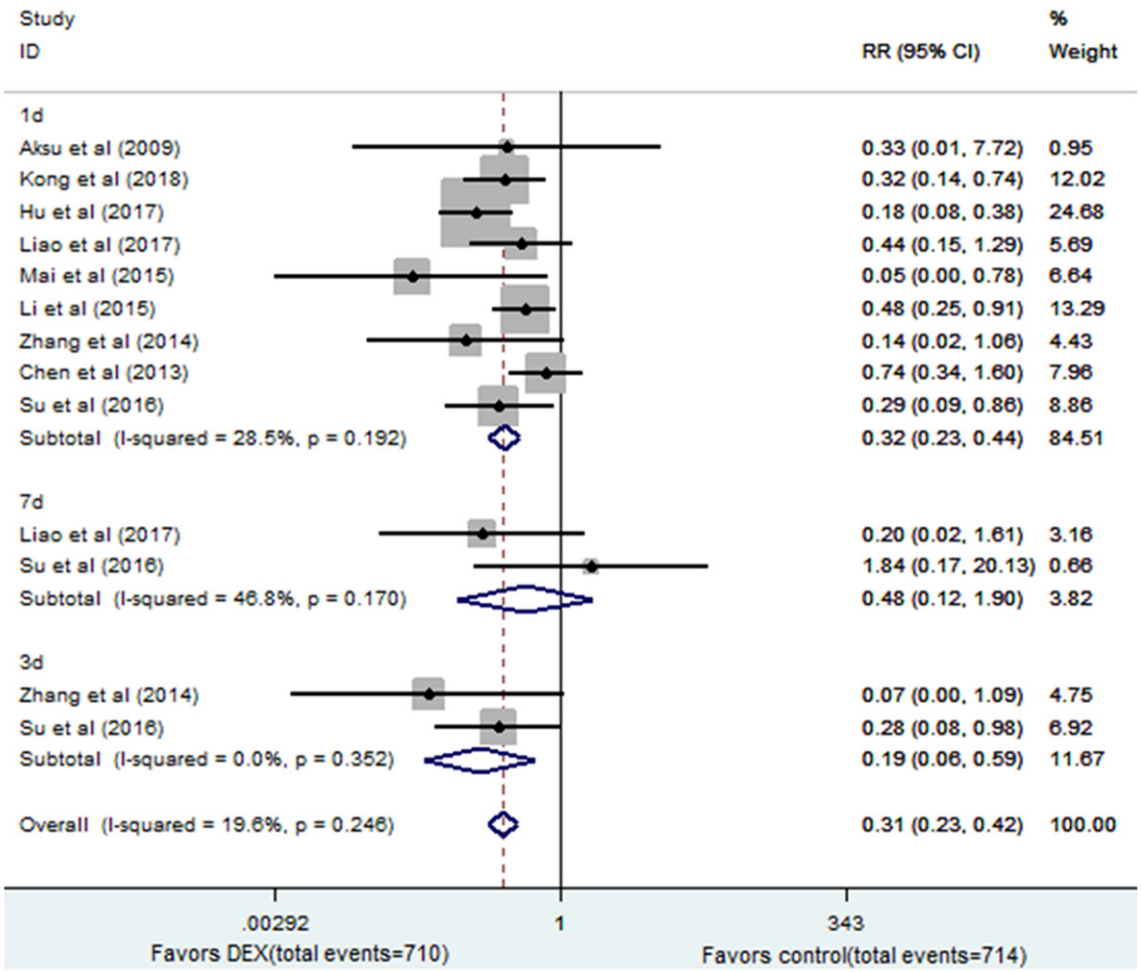

Figure 2. A forest plot about the effect of dexmedetomidine on the incidence of postoperative cognitive dysfunction.

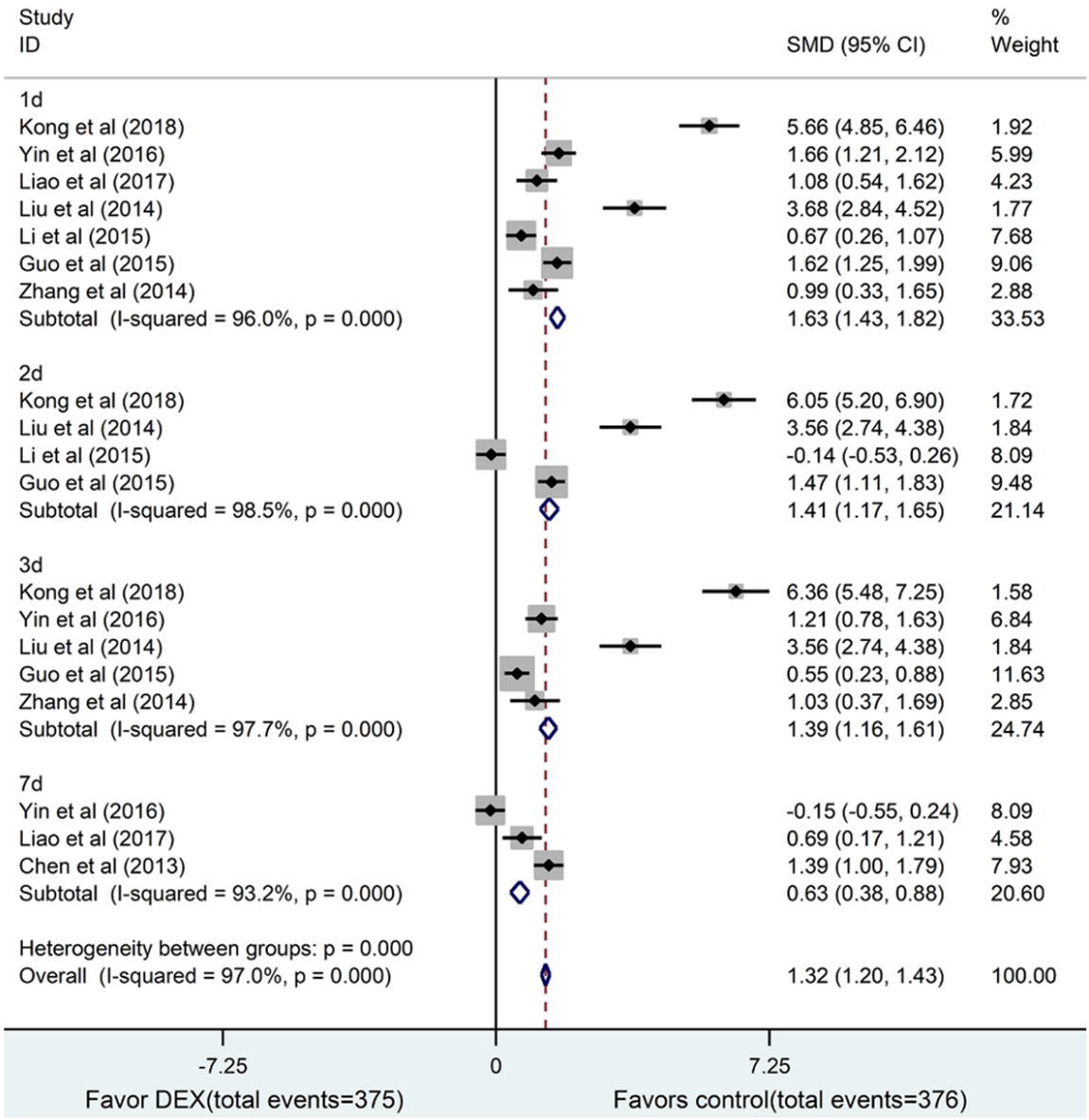

Figure 3. A forest plot about the effect of dexmedetomidine on postoperative MMSE scores.

through random effect model analysis. Subgroup analysis showed that the MMSE scores of the observation group at postoperative day 1 (WMD=1.63, 95% CI (1.43, 1.82)), day 2 (WMD=1.41, 95% CI (1.17, 1.65)), day 3 (WMD=1.39, 95% CI (1.16, 1.61)), and day 7 (WMD=0.63, 95% CI (0.38, 0.88)) were higher than the control group, which showed statistical significance (all P<0.01) (**Figure 3**). The result of egger's test was 13.85, and its corresponding *P* value was 0.00, indicating that there was significant publication bias.

Discussion

An appropriate anesthesia scheme is not only related to efficacy, but also to the occurrence and severity of adverse events. Opioids are the cornerstone of pain management. However, their application in patients is associated with a variety of adverse effects, such as respiratory depression, central nervous system toxicity, cognitive impairment, nausea, and vomiting [41]. Many adjuvant drugs for anesthesia such as midazolam and clonidine can be used for

anesthetic practices. Those drugs contribute to a good sedative and analgesic effect; but they may also induce adverse effects like hyperphasia, agitation, and spasm in some patients, which will affect the smooth operation of surgery [42]. Compared with placebos or other anesthetics, perioperative administration of DEX to pediatric patients undergoing cardiac surgery may shorten the duration of mechanical ventilation by 2.2 h, the length of intensive care unit stay by 0.47 days, and the length of hospital stay by 1.8 days [43]. Vorobeichik et al. identified 32 clinical trials (2,007 patients) and found that DEX reduced postoperative oral morphine consumption by 10.2mg after DEX group, improved pain control and enhanced satisfaction, and prolonged the duration of brachial plexus sensory blockade (at least 57%), motor blockade (at least 58%) and analgesia (at least 63%) [44]. Other studies have found that administration of DEX for conscious sedation in patients who undergo inguinal hernia repair, compared with the same dosage of fentanyl, decreased the requirement of opioids and the incidence of adverse events, but slightly prolonged the time to sedation and recovery [39, 45]. In conclusion, DEX as an adjunct to nerve block anesthesia showed rapid sensory and motor blockade with a longer duration of analgesia and hemodynamic stability; in terms of postoperative complications, DEX was also superior to the control group in reducing the incidences of postoperative nausea and vomiting, shivering and agitation [46].

The pharmacological mechanism of DEX differs from that of clonidine, the latter of which is a central nervous system α-receptor agonist that strongly inhibits sympathetic nerve signals for exciting central nervous system, and inhibits peripheral sympathetic function [47]. The lipophilicity of DEX is about 8-10 times that of clonidine, which can rapidly pass the blood-brain barrier and bind to the α2-adrenergic receptors that widely distribute in the brain and spinal cord, and further inhibit the spontaneous discharge of neurons and rhythm of sympathetic nerves, and then play a calming and analgesic effect as well as reduce the patients' nervousness and the threshold of shivering; but there is no inhabitation in breathing [9, 39, 41]. This drug has a certain effect on the locus coeruleus. A large number of noradrenergic cells were found by scholars in the cerebellopontile angle, which seemed to have an agonistic effect on extracellular dopamine neurons [8]. Therefore, DEX is often used for sedation, preemptive analgesia, reduction of postoperative nausea and vomiting (PONV), and maintenance of stable hemodynamics during laparoscopic surgery [43]. Intravenous DEX can result in hyperpolarization of the nerve tissue by altering the transmembrane and ionic conductivity of the brainstem locus coeruleus, producing an analgesic effect and enhancing local anesthesia. In addition, DEX can enhance the stability of the sympathetic nervous system and improves hemodynamics, which is responsible for reducing the incidences of nausea and vomiting [41].

POCD is a common complication of the central nervous system in elderly patients and may be related to the severity of postoperative pain and the dosage of opioids [33-35]. In addition, stress response may occur in surgery and anesthesia operations; abnormally elevated inflammatory factors can cause cognitive impairment, and affect learning and memory. Perioperative administration of DEX could significantly improve the analgesic effect of opioids and decrease the requirement of opioids [25]. Continuous infusion of DEX after administration of a loading dose can effectively maintain the stability of postoperative hemodynamics and blood glucose, and reduce the body's stress response, which is beneficial to the patient' brain function. Parecoxib sodium combined with dexmedetomidine could reduce the incidence of early postoperative cognitive dysfunction in elderly patients, which might be related to the improvement of postoperative analgesia effect and cerebral oxygen metabolism in patients [48]. The improvement of postoperative cognitive dysfunction by infusion of DEX may involve the following mechanisms: 1) inhibition of inflammatory factor release; 2) improvement of analgesic effect; 3) protection of the central nervous system; 4) improvement of sleep quality.

For the administration of DEX, efficacy and increased risk should be weighed. Bradycardia and hypotension are among the most commonly reported adverse events in patients who received DEX [49]. DEX has a dual effect on hemodynamics, which is affected by dosage and rate of administration. Its ability to activate alpha adrenergic receptors in vascular smooth

muscle and then cause vasoconstriction and transient elevation of blood pressure accounts for the effect. It will cause moderate decreases in the mean arterial pressure and the heart rate when the α2 receptors in the central nervous system are excited [39]. In clinical infusions, microinjection with a small dose of slow continuous intravenous pumping is recommended other than a single injection, which can reduce hemodynamic effect [42]. A study by Vorobeichik et al. reported that DEX significantly increased the incidence of bradycardia (RR=3.3) and hypotension (RR=5.4) [44]. Another study showed that DEX-assisted application could improve sedative effects and reduce adverse effects of anesthetics without significant increases in the incidence of bradycardia and hypotension [7]. This article included 30 studies with a relatively high quality. Positive and blank controls, and general and local anesthesia were included in this study. Perioperative administration of DEX for anesthesia, compared with the control group, could reduce postoperative nausea and vomiting, agitation, and shivering, and improve hemodynamic balance. In addition, DEX could effectively reduce the risk of postoperative cognitive dysfunction and improve the postoperative MMSE score. Despite overall bradycardia and increase in hypotension, subgroup analyses showed no significant difference in the incidence of hypotension compared with the positive controls, which was consistent with the findings of Sun et al. [4].

This systematic review study has several limitations. First, there were differences in the dosage of DEX, intervention, anesthesia methods and the subjects among all the included studies, which influenced the heterogeneity of this study. Second, exclusion criteria in this study were strict, which limited the number of included studies. Finally, there were significant publication biases in some outcomes, which might affect the results of this trial [50]. Therefore, the interpretation for the results of this study should be prudent. In the following study, exclusion criteria can be appropriately adjusted to include more studies for analysis. A more detailed analysis should be conducted on the dose-response relationship and the type of subjects.

Disclosure of conflict of interest

None.

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