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Efficacy of dexmedetomidine in children during cleft lip and palate repair: a system review and meta-analysis

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ABSTRACT

Objective Dexmedetomidine was increasingly used in many areas and pediatric anesthesia setting for various indications. However, the efficacy of this intervention on pediatric patients in cleft lip and palate (CLP) repair was still unknown. We aimed to systematically assess the efficacy and safety of dexmedetomidine as an anesthesia adjuvant during CLP repair in children.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase, Cochrane library, CNKI, VIP, and Wanfang (up to Oct 2020). Studies in languages other than English and Chinese were excluded.

Eligibility criteria for selecting studies Randomized controlled trials evaluating the impact of dexmedetomidine on emergence agitation (EA), the need for postoperative rescue analgesics, postoperative nausea and vomiting (PONV), and other adverse events in pediatric patients during CLP repair.

Data extraction and synthesis Data were screened, extracted and assessed by two independent authors. Outcomes reported as a risk ratio (RR) with 95% confidence interval (CI). Random effects model was used when heterogeneity was detected, otherwise fixed effects model was chosen.

Results Thirteen studies included 1040 children met the inclusion criteria. The incidence of EA was significantly decreased in the dexmedetomidine group (RR, 0.19; 95% CI, 0.10 to 0.36; P<0.00001; I^2=56%) as compared to the control group. Pediatric patients receiving dexmedetomidine had lower postoperative analgesic requirements (RR, 0.27; 95% CI, 0.10 to 0.73; P=0.01; I^2=84%) and less incidence of respiratory adverse events (RR, 0.49; 95% CI, 0.31 to 0.78; P=0.002; I^2=0%). There were no significant differences in the risk of PONV and

cardiovascular adverse events.

Conclusions There was a lack of high-quality study in this field. Perioperative administration of dexmedetomidine reduced the need for postoperative rescue analgesics and the incidence of EA in children without side effects undergoing CLP repair. However, further verification with larger samples and more high quality RCTs would be needed.

Keywords children, dexmedetomidine, cleft lip and palate repair, pain, agitation

ARTICLE SUMMARY

Strengths and limitations of this study

This is a comprehensive systematic review which identified the benefits of dexmedetomidine in children during CLP repair.

Different evaluation methods were used for the outcomes, even partial of which missed data on the definition detail, that would influence reliability in future recommended guide for dexmedetomidine interventions.

Unfortunately, low quality of the included studies impedes us to draw firm conclusions.

Word account: 2632

INTRODUCTION

Cleft lip and palate (CLP) were widespread congenital disfigurement requiring surgical correction early in life.[1] Early surgery was important to alleviate feeding difficulty, reduce airway complications and improve phonation problem.[2] However, cleft palate repair needed to dissect the soft and hard palates and would result in significant postoperative oropharyngeal pain and bleeding. High-dose opioids with sevoflurane anesthesia were commonly used to block the autonomic response.[3] Due to above factors, many pediatric patients suffered from a high risk of respiratory depression, postoperative emergence agitation (EA), postoperative nausea and vomiting (PONV), a prolonged hospital stay and increased hospital costs.[4-6]

Dexmedetomidine was a potent α2 adrenoreceptor agonist with sedative, anxiolytic, sympatholytic and analgesic properties. It also ensured a stable hemodynamic state and no significant respiratory depression.[7] Study[8] had demonstrated that it is proved helpful as a valuable adjunct in many diverse areas and increasingly used in pediatric anesthesia setting. A meta-analysis[9] recently showed that perioperative administration of dexmedetomidine can provide pain and agitation relief without side effects in children undergoing adenotonsillectomy. Another meta-analysis[10] found that intranasal dexmedetomidine provided more satisfactory sedation at parent separation and reduced the need for postoperative rescue analgesics in pediatric patients. However, evidence in the existing literature was insufficient to fully support the effectively and safely use of dexmedetomidine in CLP repair in children.

Therefore, our study was aimed to identify the effects of administration with dexmedetomidine in children during CLP repair. We performed a meta-analysis of randomized-controlled trials comparing dexmedetomidine with controls.

METHODS

We evaluated the efficacy and safety of dexmedetomidine administration following CLP repair in children. A systematic approach based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Cochrane Review Methods was used. [11]

Search strategy and selection criteria

We searched the following databases: PubMed, Embase, Cochrane library, CNKI, VIP, and Wanfang) from inception to October 1, 2020.The main keywords were used: dexmedetomidine, randomized controlled trial (RCT), cleft palate, cleft lip, infant, children. Reference lists of identified studies were scanned for additional material.

Inclusion and exclusion criteria

Two authors (LP and YG) systematically and independently identified all the studies with predefined selection criteria. A third author (XL) arbitrated disagreements when conflicting selections occurred. Studies were included in this meta-analysis if they satisfied the following criteria: 1) Literature type: prospective, randomized-controlled studies; 2) Language: both English and Chinese; 3) Subjects: children undergoing CLP repair; 4) Interventions: dexmedetomidine by any route of administration compared with any controls(including placebo and other drugs); 5) Outcomes: the primary outcome was the incidence of EA, secondary outcome was the need for postoperative rescue analgesia, and third outcomes were the incidence of adverse effects: PONV, respiratory adverse effects (breath holding, cough, desaturation and airway spasm), and

cardiovascular respiratory adverse effects (hypotension, bradycardia and postoperative bleeding).

Data collection and study appraisal

Two authors (JL and FL) independently extracted all the relevant information with a pre-specified data abstraction form. The following variables were collected: the name of the first author, publication year, country, publication language, number of patients, the protocol for administration method and dose, and outcomes. If the variables were not reported, we emailed the original authors to ask for the data.

Two authors (JL and FL) independently assessed the risk of bias basing on the Cochrane risk of bias tool, which considers adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessor, incomplete reporting of outcome data, free of selective reporting, and free of other bias. In case of the conflicting evaluations, the third author (XL) was arranged to arbitrate disagreements.

Quality of the evidence

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE)**.** We used GRADE profiler software version 3.2 to create the ‘‘Summary of findings’’ table, which includes the following outcomes: 1) Emergence agitation;2) Respiratory adverse events;3) The need for postoperative rescue analgesics; 4) Cardiovascular adverse events; and 5) Postoperative Nausea and vomiting.

Risk of Bias Across Studies

Publication bias was assessed by using a funnel plot.

Statistical analysis

The meta-analysis was performed using the Cochrane Collaboration Review Manager Software (RevMan version 5.1, https://training.cochrane.org/). We reported binary data as a risk ratio (RR) with 95% Confidence Interval (CI). Chi square test (Mantel Haenszel method) was used to assess the heterogeneity between studies. An I^2 >50% and a P value <0.10 was considered to indicate statistical heterogeneity. Subgroup analysis or sensitivity analysis was performed to analyze reasons of heterogeneity. Random effects model (Dersimonian and Laird method) was used when significant statistical or clinical heterogeneity was detected. P≤0.05 was considered to indicate a statistically significant difference for testing values of overall effect.

Patient and public involvement

There was no patient or public involvement in this study.

RESULTS

Study selection

A total of 63 potentially relevant studies were identified. After excluding 50 studies, 13 studies including 1040 children aged 3 months to 12 years were finally considered in this analysis.[12-24] The flow diagram of the literature search strategy was shown in Figure1.

Description of studies

The included studies were undertaken from 2012-2020 in four different countries: Egypt (three)[12-14], Japan (one)[16], India (one)[17], and China (eight)[15,18-24]. Seven studies[12-18] were published in English, the other six studies[19-24] were published in Chinese. In all of the included studies, dexmedetomidine is administered for its sedative effect in the form of intravenous[15-21,23,24], intranasal[22] and perineural[12-14] administration.

Eleven studies[12,14-19,21-24] compared the effects of intravenous dexmedetomidine with saline, one study[20] compared the effects of intravenous dexmedetomidine with those of ketamine and fentanyl. One study[22] compared the effects of intranasal dexmedetomidine with saline. Two studies[12,14] compared the effects of perineural dexmedetomidine administration with placebo, and one study[13] compared the effects of perineural dexmedetomidine administration with those of dexamethasone. The characteristics of included studies were summarized in Table1.

Quality of the included studies

Nine studies[12,13,15-19,22,24] used a random allocation method. Four studies [13-15,17]described the allocation concealment in detail. Four studies[12,16-18] concretely explained their blinding methods. The risk of random allocation method was high in one study[20], and were unclear in the other three studies[14,21,23]. The risk of allocation concealment were unclear and the risk of blinding were high in the other studies. The risk of free of selective reporting were low in eight studies[12,14,17-20,22,23], unclear in one study[16] and high in other studies. For incomplete outcome data and free of other bias, most trials were judged as low risk of bias. The quality of included trials was summarized in Table 2 and supplementary file 1.

Risk of Bias Across Studies

The funnel plot was applied for assessing publication bias of studies in this meta-analysis in supplementary file 2. Due to the small number of studies, most of the publication bias of outcomes was unclear.

The overall quality of evidence based on the GRADE system was judged as moderate (The need for postoperative rescue analgesics, Respiratory adverse events, and Cardiovascular adverse events), or low (EA and PONV) (Table 3).

Emergence Agitation

Eight trials[15,18-24] including 684 patients reported the incidence of EA. EA was evaluated by Ramsay score, behavior score, Pediatric Anesthesia Emergence Delirium scale, or Aonos four-point scale. Dexmedetomidine administration(including intravenous and intranasal administration) showed a significant evidence of reducing EA when compared with saline[15,18,19,21-24] (RR, 0.19; 95% CI, 0.12 to 0.38; P<0.00001; I^2 = 62%) and all control groups[15,18-24] (RR, 0.19; 95% CI, 0.10 to 0.36; P<0.00001; I^2 =56%). We found different administration method of dexmedetomidine increased the clinical heterogeneity. Excluding the Yun2016 study[22] (intranasal administration), intravenous dexmedetomidine administration showed a significant evidence of reducing emergence agitation when compared with saline[15,18,19,21,23,24] (RR,0.24;95% CI, 0.13 to 0.44; P<0.00001; I^2=40%), and when compared with all control groups [15,18-21,23,24] (RR, 0.24;95% CI, 0.14 to 0.41; P<0.00001; I²=29%). However, subgroup analysis showed no difference when dexmedetomidine was compared with intravenous fentanyl[20] (RR, 0.14; 95% CI, 0.01 to 2.58; P=0.19) and intravenous ketamine[20] (RR, 0.14; 95% CI, 0.01 to 2.58; P=0.19). (Fig.2).

The need for postoperative rescue analgesics

Five studies[12,14,17,18,23] including 293 pediatric patients reported that dexmedetomidine had a greater analgesic effect as compared to saline

postoperatively (RR, 0.27; 95% CI, 0.10 to 0.73; P=0.01; I^2=84%). Basing on the two studies[12,14], there was no difference when perineural dexmedetomidine was compared with saline in the incidence of need for rescue analgesics at postoperative 24h (RR, 0.16; 95% CI, 0.00 to 33.36; P=0.50).

Respiratory adverse events

Eight studies[15-21,23] including 794 pediatric patients reported the number of respiratory adverse events. We found that intravenous dexmedetomidine administration showed a significant lower incidence of respiratory adverse events when compared with saline (RR, 0.49; 95% CI, 0.31 to 0.78; P=0.002; I^2=0%). Only one study[19] (n=60) reported that dexmedetomidine showed a significant lower incidence of cough when compared with saline (RR, 0.45; 95% CI, 0.25 to 0.82; P=0.009). There were no differences when dexmedetomidine was compared with saline in the incidence of breath holding[18,19,21] (RR, 1.29; 95% CI, 0.33 to 5.08; P=0.72), desaturation[16,17,19-21,23] (RR, 0.41; 95% CI, 0.16 to 1.08; P=0.07) and airway spasm[15,19,21] (RR, 0.33; 95% CI, 0.07 to 1.54; P=0.16).

Cardiovascular adverse events

Three studies[17,18,24] including 880 pediatric patients reported the number of cardiovascular adverse events. We found that no differences when dexmedetomidine was compared with saline in the incidence of hypotension[17,24] (RR, 0.78; 95% CI, 0.30 to 2.07; P=0.62), bradycardia[17,24] (RR, 1.18; 95% CI, 0.61 to 2.28; P=0.62) and postoperative bleeding[18,24] (RR, 0.44; 95% CI, 0.18 to 1.11; P=0.08).

Postoperative Nausea and vomiting

Eight trials[13-15,17-20,23] including 524 patients reported the incidence of PONV. Patients who received intravenous dexmedetomidine administration

experienced no statistically significant increase in PONV when compared with saline [14,15,17-19,23] (RR, 0.90; 95% CI, 0.40 to 2.06; P=0.81), and when compared with all control groups[13-15,17-20,23] (RR, 0.92; 95% CI, 0.47 to 1.80; P=0.80). Also, subgroup analysis showed no difference when dexmedetomidine was compared with fentanyl[20] (RR, 0.50; 95% CI, 0.06 to 4.15; P=0.52) , ketamine [20] (RR, 0.50; 95% CI, 0.06 to 4.15; P=0.52) and dexamethasone[13] (RR, 1.33; 95% CI, 0.31 to 5.65; P=0.70) .

DISCUSSION

Main findings

This meta-analysis revealed that perioperative administration of dexmedetomidine reduced the incidence of EA in children undergoing CLP repair. Pediatric patients receiving dexmedetomidine had lower need for rescue analgesics postoperative and less incidence of respiratory adverse events. However, there were no significant differences in the risk of PONV and cardiovascular adverse events.

Although dexmedetomidine is not approved by U.S. Food and Drug Administration (FDA) for administration in children, it has been an authorized drug in Europe since September 2011.[25] It is increasingly used in the pediatric setting for various indications such as premedication, adjunct, sedative, intraoperative analgesia, and adjuvant, [8] but the efficacy was still controversial.

Our results found that both incidence of EA and the need for rescue analgesics postoperative were statistically decreased in the dexmedetomidine group as compared to the saline group. This was consistent with previous studies. [4,6,9,10] Two recent meta-analyses[30,31] found that the effects of dexmedetomidine in reducing risk of EA in children was superior to other drugs (including fentanyl, propofol, ketamine), which were inconsistent with our study. Numerous etiological factors (such as pre-existed anxiety, pain, age, type of surgical procedures, rapid awakening

and anesthetic technique) were considered to cause EA.[26] All of the included studies used sevoflurane anesthesia. It is widely believed that pain relief decreased the incidence of EA associated with sevoflurane general anesthesia. [9,26] It is known that dexmedetomidine shows dose-dependent effects on pain control and sedation. Reliable analgesic, sedative and neuroprotective effects could be main explanations for the effects of dexmedetomidine on EA.

Respiration is slightly affected by dexmedetomidine.[7-9] Our meta-analysis showed that dexmedetomidine would not influence the incidence of breath holding, desaturation and airway spasm. On the contrary, the incidence of cough and total respiratory adverse events were decreased in dexmedetomidine group. It was attributed to the residual sedation caused by the sedative effect of dexmedetomidine. Due to the rapid decreasing of concentration of sevoflurane during the recovery period, the fast awaken pediatric patients were in a highly sensitive state. It has minimal respiratory changes from the residual sedation, even extubation during the infusion of dexmedetomidine, in contrast to other sedatives.[7] However, we should pay attention to that the strength of residual sedation was related to the early phase of post-anesthesia recovery time in postoperative anesthesia care unit.

As a selective α2-agonist, dexmedetomidine acted on the autonomic ganglia and performed its cardiovascular effect by decreasing sympathetic outflow and augmenting vagal activity, thus low infusion rates could cause bradycardia and hypotension while high doses could cause hypertension and aggravated bradycardia.[7,8] Besides the dose, rapid injection may result in excessive hemodynamic alterations, it is recommended that dexmedetomidine be administered slowly. Only two of thirteen included studies reported the incidence of bradycardia and hypotension. One study administrated dexmedetomidine as a loading dose over 10 min and followed by a maintenance infusion of 0.5 ug/kg/h until the last suture was applied, while the other study administrated dexmedetomidine as a maintenance infusion of 0.5ug/kg/h intravenously after induction of anesthesia

until 20 min before the surgery finished. There was no significant difference in dexmedetomidine group as compared to placebo group. The hemodynamic stability owed to the method of low dose, slow injection and continuous infusion.

Few studies were focused on the effect of dexmedetomidine on PONV. Dexmedetomidine did not affect the incidence of PONV in our meta-analysis. This was consistent with a recent systematic review[27] in which dexmedetomidine intraoperative administration had no effect upon PONV during pediatric surgery, but it was inconsistent with a recent systematic review[28] in which dexmedetomidine was superior to placebo with a reduction in the need for an antiemetic in adults undergoing gynecological surgery. Another study also showed dexmedetomidine appeared to prevent postoperative vomiting after sevoflurane anesthesia for pediatric strabismus surgery. In their opinion, it is difficult to estimate the true incidence of nausea in younger children.[29] It may be the explanation for the difference effect of dexmedetomidine on PONV between children and adults.

Limitations

There were still some limitations in our meta-analysis. First, only one study was designed with low risk of bias, the others were of moderate risk of bias. Second, more than ten dosages were used in the thirteen studies, including three methods of intranasal, perineural and intravenous administration. However, we did not use subgroup analysis for the administration doses. Third, not all studies reported in enough detail on their outcome measures which may prevent us from performing our analysis more formal.

CONCLUSIONS

Our findings demonstrate that perioperative administration of dexmedetomidine in children undergoing CLP repair efficiently decrease pain, EA, and respiratory adverse events. However, standardized usage and dosage need further investigation, and larger rigorous studies need to be included.

Author Contributions

LP, YG and XL helped read and screen abstracts and titles of potentially relevant studies. JL, FL and XL helped read the retained papers and were responsible for extracting data and assessing their quality independently. DL helped design the study, conduct the study, analyse the data, and write the manuscript. JQ helped revise the paper with language. CH and CL helped design the study, conduct the study, analyse the data, and revise the manuscript. All authors contributed to conceptualize ideas, interpret findings and reviewed drafts of the manuscript.

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Figure captions:

Figure 1: Flow diagram of the literature search strategy

Figure 2: Perioperative dexmedetomidine versus control groups for emergence agitation (EA). CI: confidence interval; RR: risk ratio.

Table1 Characteristics of the included randomized-controlled trials.

Study(year)	Country	Language	Age (month/year)	N (Dex/Control)	Administration method	Comparison	Outcomes
Mostafa2020[12]	Egypt	English	1-5y	15/15	perineural	Dex:0.5ug/kg Control: saline	the incidence of need for rescue analgesia
El-Emam2019[13]	Egypt	English	3-6m	50/50	perineural	Dex:0.5ug/kg Control: 0.1mg/kg DA	the incidence of PONV
Obayah2010[14]	Egypt	English	11.7±2.4m 12±2.7m	15/15	perineural	Dex:1ug/kg Control: saline	the incidence of PONV, need for rescue analgesia
Peng2015[15]	China	English	3-24m	20/20	intravenous	Dex:0.8ug/kg/min (continuous intravenous infusion after induction) Control: saline	the incidence of EA, PONV, airway spasm
Boku2015[16]	Japan	English	10-14m	35/35	intravenous	Dex:6ug/kg/h (10 min before the end of the surgery for 10 min) +0.4ug/kg/h (continuous	the incidence of desaturation

						intravenous infusion until 15min before extubate) Control: saline	
Surana2017[17]	India	English	6m-12y	30/30	intravenous	Dex:1ug/kg, 0.5ug/kg/h(continuous intravenous infusion) Control: saline	the incidence of need for rescue analgesia, PONV, desaturation, hypotension, bradycardia
Luo2017[18]	China	English	1-5y	50/50	intravenous	Dex:0.5ug/kg (prior to induction of anesthesia) Control: saline	the incidence of EA, need for rescue analgesia, PONV, breath-holding, postoperative bleeding
Mei2014[19]	China	Chinese	8m-3y	30/30	intravenous	Dex:0.5ug/kg (30min before surgery finish for 10min) Control: saline	the incidence of EA, PONV, breath-holding, cough, desaturation, airway spasm
Xiao2012[20]	China	Chinese	1.22±0.22y	18/18/18	intravenous	Dex:2ug/kg during	the incidence of

			1.26±0.24y 1.25±0.23y			induction) +0.5ug/kg/h (continuous intravenous infusion after intubation) Control 1:2mg/kg (during induction) +0.5mg/kg/h (continuous intravenous infusion after intubation) ketamine Control 2:3mg/kg (during induction) + 1ug/kg (intermittent administration twice) fentanyl	EA, PONV, desaturation
Xi2012[21]	China	Chinese	1-3y	15/15	intravenous	Dex:1ug/kg (30min before surgery finish for10min) Control: saline	the incidence of EA, breath-holding, desaturation, airway spasm
Yun2016[22]	China	Chinese	6m-3y	60/60	intranasal	Dex:2ug/kg (30min before surgery finish) Control: saline	the incidence of EA
Ju2013[23]	China	Chinese	4m-3y	40/40	intravenous	Dex:0.5ug/kg (10min before surgery start for 10min)	the incidence of EA, need for

							Control: saline	rescue analgesia, PONV, Desaturation
Jun2018[24]	China	Chinese	1.71±0.61y 1.74±0.62y	110/110	intravenous	Dex:0.5ug/kg/h (20min before surgery finished) Control: saline		the incidence of EA, hypotension, Bradycardia, postoperative bleeding

dexmedetDA dexamethasoneagitation; PONV: postoperative nausea and vomiting.

Table 2 Individual Randomized Controlled Trial Methodological Quality.

Study (year)	Adequate sequence generation	Allocation concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Mostafa2020[12]	yes	?	yes	yes	yes	yes	yes
El-Emam2019[13]	yes	yes	No	yes	yes	No	yes
Obayah2010[14]	?	yes	No	No	yes	yes	yes
Peng2015[15]	yes	yes	No	No	No	No	yes
Boku2015[16]	yes	?	yes	yes	yes	?	yes
Surana2017[17]	yes	yes	yes	yes	yes	yes	yes
Luo2017[18]	yes	?	yes	yes	yes	yes	No
Mei2014[19]	yes	?	No	No	yes	yes	yes
Xiao2012[20]	No	?	No	No	yes	yes	yes
Xi2012[21]	?	?	No	No	yes	No	yes
Yun2016[22]	yes	?	yes	No	yes	yes	yes
Ju2013[23]	?	?	No	No	yes	yes	yes
Jun2018[24]	yes	?	No	No	yes	No	yes

Yes=low risk of bias; No=high risk of bias; ?=unclear risk of bias.

Table 3 Summary of findings for the main outcomes

Dexmedetomidine for cleft lip and palate repair						
Patient or population: patients with cleft lip and palate repair **Settings:** surgery **Intervention:** Dexmedetomidine						
Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **Control**	 Corresponding risk **Dexmedetomidine**	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Emergence agitation	**Study population**		**RR 0.19** (0.10 to 0.36)	684 (8 studies)	⊕⊕⊖⊖ **low**[1,2,3,4,5]	
	458 per 1000	**87 per 1000** (46 to 165)				
Respiratory adverse events	**Study population**		**RR 0.49** (0.31 to 0.78)	794 (8 studies)	⊕⊕⊕⊖ **moderate**[1,6]	
	103 per 1000	**50 per 1000** (32 to 80)				
The need for postoperative rescue analgesics	**Study population**		**RR 0.27** (0.1 to 0.73)	293 (5 studies)	⊕⊕⊕⊖ **moderate**[1,2,6]	
	592 per 1000	**160 per 1000** (59 to 432)				

Cardiovascular adverse events	**Study population**		**RR 0.83**	880	⊕⊕⊕⊖
	105 per 1000	**87 per 1000** (55 to 138)	(0.52 to 1.31)	(3 studies)	**moderate**[1]
Postoperative Nausea and vomiting	**Study population**		**RR 0.92**	524	⊕⊕⊖⊖
	63 per 1000	**58 per 1000** (30 to 113)	(0.47 to 1.80)	(8 studies)	**low**[1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Allocation concealment and/or blinding of outcome assessors unclear/inadequate in 50% or more of the included studies

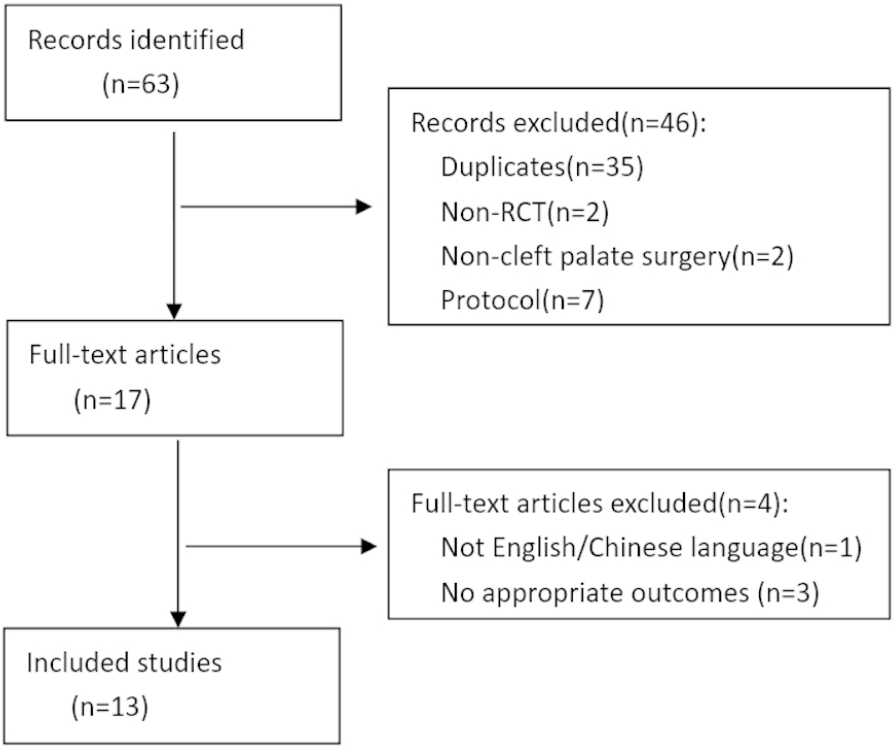
[2] Significant heterogeneity (I 2 > 50%) is partially explained by different administration method ,dose and comparators.

[3] Use of several different scoring criterias to evaluate emergence agitation.

[4] a dose response gradient was present

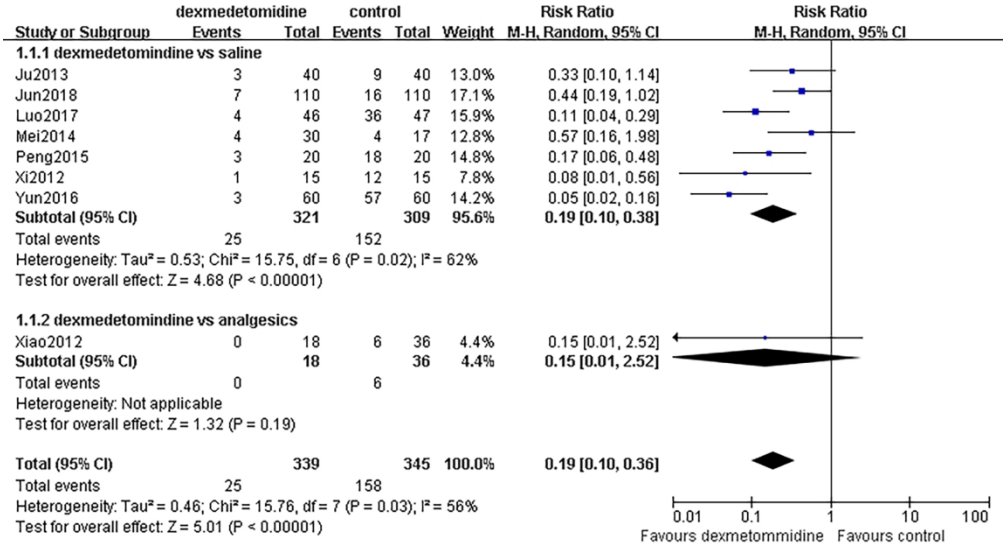
[5] RR >5 or <0.2

[6] RR >2 or <0.5



Flow diagram of the literature search strategy

82x73mm (300 x 300 DPI)



Perioperative dexmedetomidine versus control groups for emergence agitation (EA). CI: confidence interval; RR: risk ratio.

205x114mm (300 x 300 DPI)

Risk of bias

Mostafa2020[12] (ClinicalTrials.gov ID: NCT03412474).

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated program of random numbers
Allocation concealment (selection bias)	unclear	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the doctors (investigators) nor the patients' guardians or even the children themselves were aware of the group al-location and the drug received. One anesthesiologist not involved in the block implementation or the data collection, prepared all the study solutions.
Blinding of outcome assessment (detection	Low risk	While a third, blinded to the previous protocol, was responsible

bias) All outcomes		only for data collection.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 80 patients
Other bias	Low risk	Groups well balanced

El-Emam2019[13] Clinical Trials.gov (NCT03480607)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated randomization numbers
Allocation concealment (selection bias)	Low risk	a closed-seal envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	The principal investigator prepared the drug and performed the block
Blinding of outcome assessment (detection bias) All outcomes	Low risk	the person observing and recording the parameters was blinded to the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	The primary outcome was to compare both groups regarding time to first rescue analgesic, while the primary outcomes in the pre-registration site were

		postoperative FLACC scale and postoperative sedation score.
Other bias	Low risk	Groups well balanced

Obayah2010[14]

Bias	Authors'	Support for judgement

	judgement	
Random sequence generation (selection bias)	Unclear risk	“randomly allocated”, no details
Allocation concealment (selection bias)	Low risk	The randomization was achieved by the opening of a sealed envelope by the attending physician
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 30 patients
Other bias	Low risk	Groups well balanced

Peng2015[15] Chinese Clinical Trial Register (ChiCTR-TRC-13003865).

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Randomly divided with a computer-generated sequence of numbers
Allocation concealment (selection bias)	Low risk	a sealed envelop
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	The actual sample was 40 while the planned sample in the pre-registration site was 60.
Selective reporting (reporting bias)	High risk	The primary outcome was to compare both groups regarding emergence agitation and time about recovery parameters while the primary outcomes in the pre-registration site were heart rate and blood pressure.

Other bias	Low risk	Groups well balanced

Boku2015[16] (UMIN 000009869) http://upload.umin.ac.jp.

Bias	Authors'	Support for judgement

	judgement	
Random sequence generation (selection bias)	Low risk	A computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The patient's parents and the attending anesthesiologist were blinded to the group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data for each patient were obtained by the blinded anesthesiologist.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Do not get the protocol
Other bias	Low risk	Groups well balanced

Surana2017[17]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection	Low risk	a computer-generated randomized chart

bias)		
Allocation concealment (selection bias)	Low risk	The random group assignments were enclosed in a sealed opaque envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	the surgeons, the patients, and the anesthesiologist in the post-anesthesia care unit (PACU) were all blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data was recorded by a blinded observer.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 60 patients
Other bias	Low risk	Groups well balanced

Luo2017[18]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a computer-generated table of random numbers

Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All pharmacological agents used in the present study were prepared and administrated by the anesthesiologists who were blinded to the details of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pediatric Anesthesia Emergence Delirium and CHIPPS scores were documented by a well-trained PACU nurse who was blinded to the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 patients from group DS and 3 patients from group SF were excluded from the analysis
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 93 patients
Other bias	High risk	Groups well balanced. Not in intention-to-treat: Of the 100 patients admitted to the study, 7 were later excluded by the authors for the reasons listed in table II,

		leaving data from 93 patients for consideration

Mei2014[19]

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	a table of random numbers, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 60 patients
Other bias	Low risk	Groups well balanced.

Xiao2012[20]

Bias	Authors' judgement	Support for judgement
Random sequence	High risk	randomized according to the operation

generation (selection bias)		time sequence
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 54 patients
Other bias	Low risk	Groups well balanced.

Xi2012[21]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection	Unclear risk	Random mentioned, no detail

bias)		
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	High risk	Lack of complications, such as postoperative hoarseness, nausea and vomiting
Other bias	Low risk	Groups well balanced.

Yun2016[22]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a table of random numbers, no detail
Allocation concealment	Unclear risk	Not mentioned.

(selection bias)		
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A blinded anesthesia nurse prepared and administrated drugs
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 120 patients
Other bias	Low risk	Groups well balanced.

Ju2013[23]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentioned random, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants	High risk	Not mentioned.

and personnel (performance bias) All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 80 patients
Other bias	Low risk	Groups well balanced.

Jun2018[24]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Compute randomized
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias)	High risk	Not mentioned.

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	High risk	The secondary outcomes were to compare both groups regarding extubation time and incision bleeding which were not mentioned in method.
Other bias	Low risk	Groups well balanced.

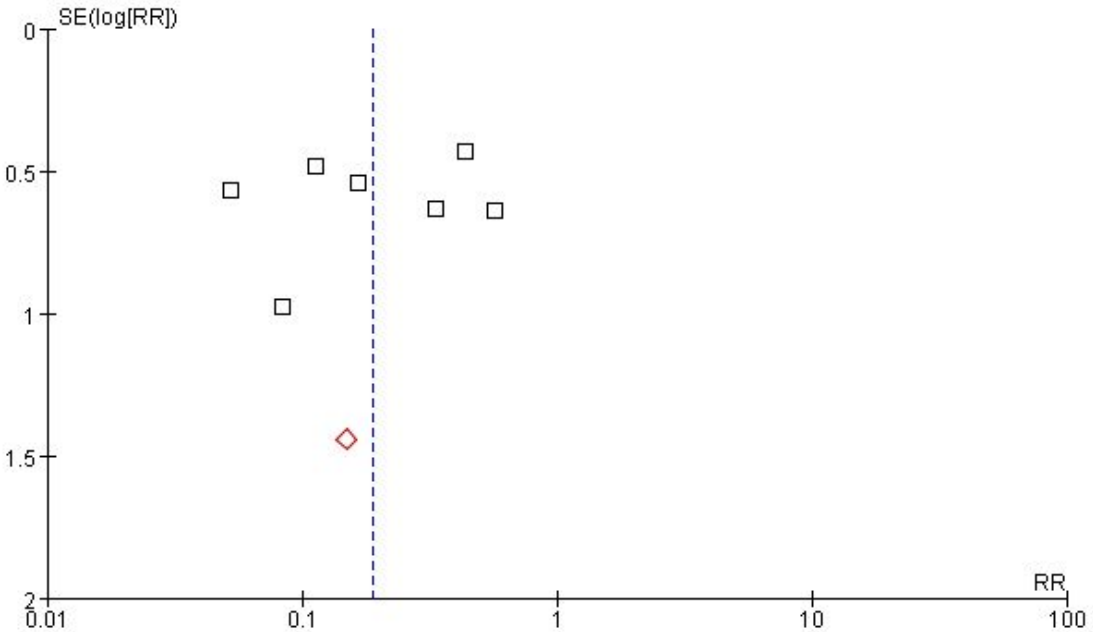


Figure1 Funnel plot of comparison: dexmedetomidine vs control, outcome: 1.1 emergence agitation.

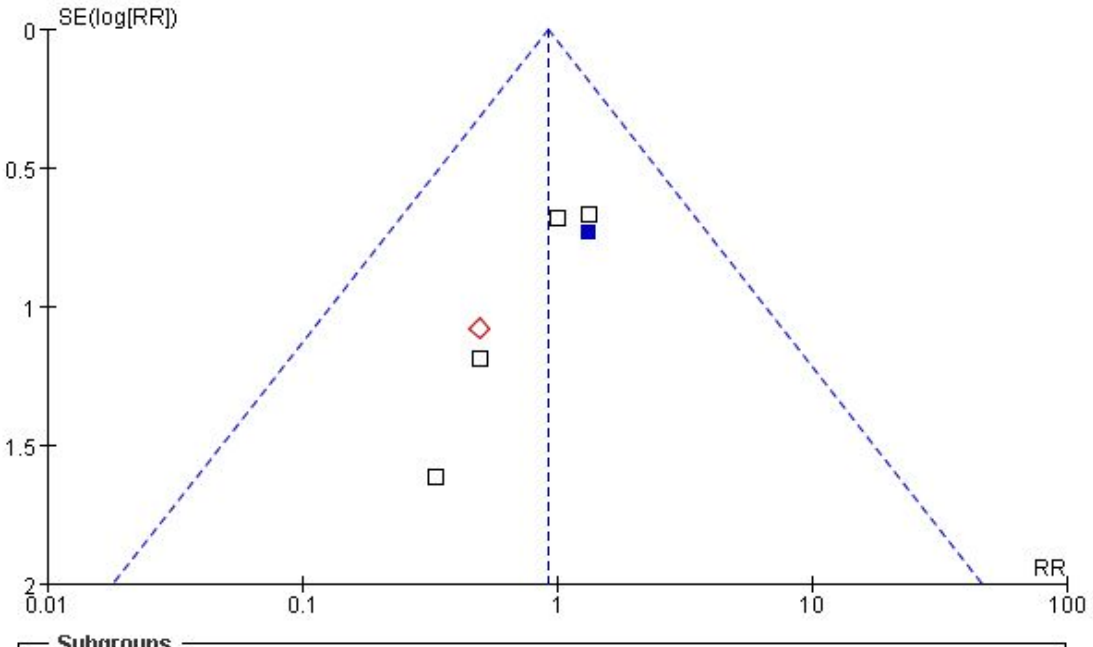


Figure 2 Funnel plot of comparison: dexmedetomidine vs control, outcome: 1.2 postoperative nausea and vomiting.

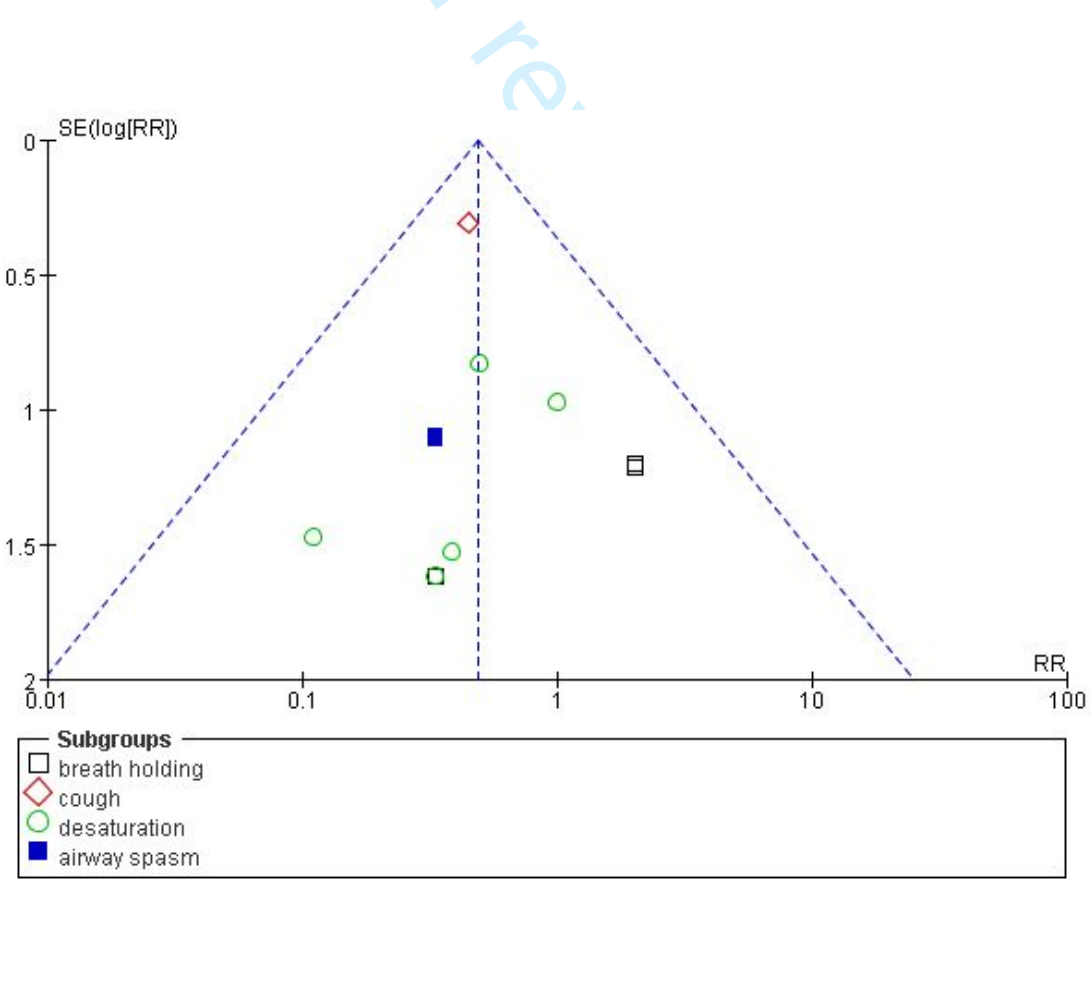


Figure 3 Funnel plot of comparison: dexmedetomidine vs control, outcome: 1.3 complication in respiration.

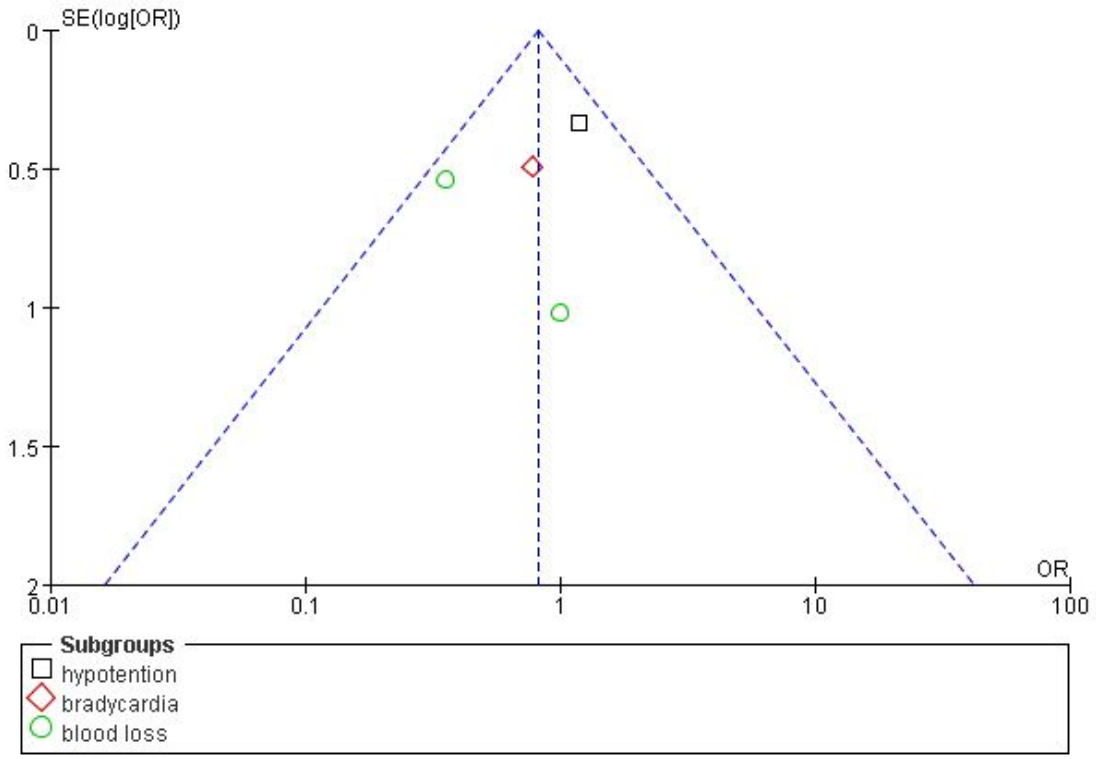


Figure 4 Funnel plot of comparison: dexmedetomidine vs control, outcome: 1.4 complication in circulation.

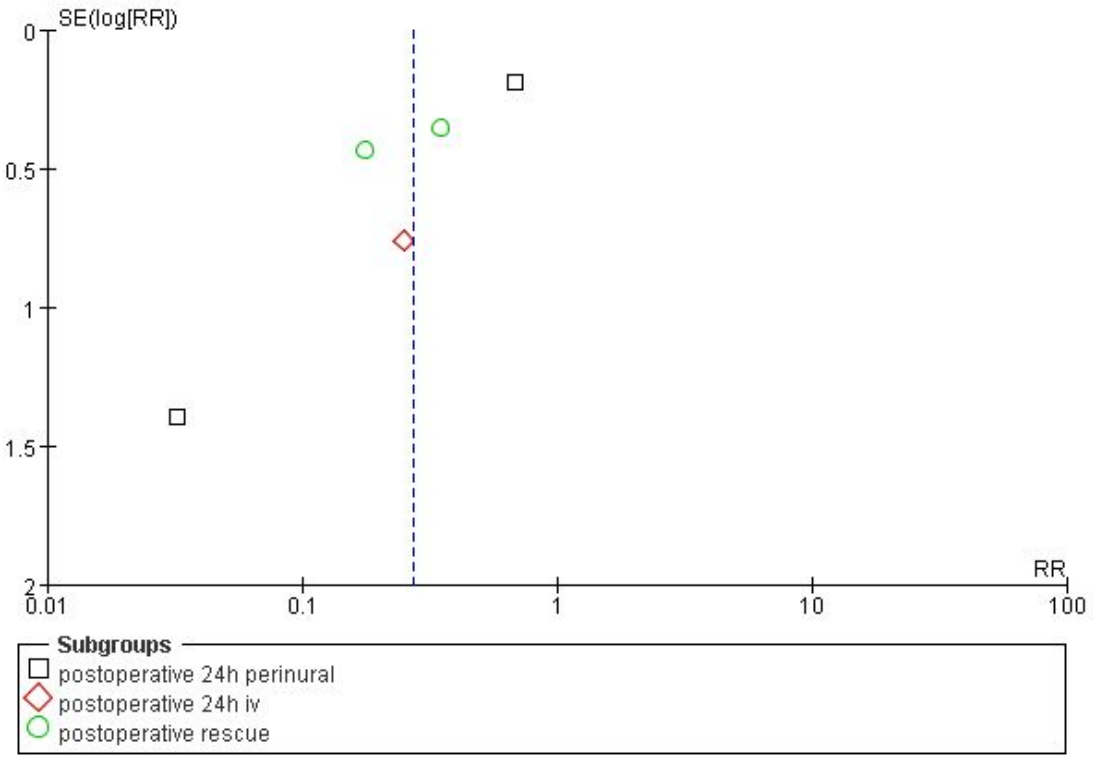


Figure 5 Funnel plot of comparison: dexmedetomidine vs control, outcome:1.5 postoperative analgesia rescue.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1-2
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			3-4
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			5
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			6-8
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	--
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	--
RESULTS			8-12,21-27
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9,21-24
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,25
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9,10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10,26-27
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	--
DISCUSSION			12-15
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14,15
FUNDING			15
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Efficacious of dexmedetomidine in children undergoing cleft lip and palate repair: a systematic review and meta-analysis

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Anaesthesia, Paediatrics, Dentistry and oral medicine
Keywords:	ORAL & MAXILLOFACIAL SURGERY, Paediatric anaesthesia < ANAESTHETICS, Pain management < ANAESTHETICS

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Efficacious of dexmedetomidine in children undergoing cleft lip and palate repair: a systematic review and meta-analysis

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ABSTRACT

Objective To systematically assess the efficacy and safety of dexmedetomidine as an anaesthesia adjuvant for cleft lip and palate (CLP) repair in children.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase, Cochrane, CNKI, VIP, and Wanfang (up to Oct 2020). Studies in languages other than English and Chinese were excluded.

Eligibility criteria for selecting studies Randomized controlled trials (RCTs) evaluating the impact of dexmedetomidine on emergence agitation (EA), the need for postoperative rescue analgesics, postoperative nausea and vomiting (PONV), and other adverse events in paediatric patients during CLP repair.

Data extraction and synthesis The quality of evidence was assessed by using the Cochrane Review Methods and the Grading of Recommendations Assessment, Development, and Evaluation approach. Data were screened, extracted and assessed by two independent authors. Outcomes reported as a risk ratio (RR) with a 95% confidence interval (CI). A random effects model was used when heterogeneity was detected.

Results Thirteen studies including 1040 children met the inclusion criteria. The incidence of EA was significantly decreased in the dexmedetomidine group (RR, 0.19; 95% CI, 0.10 to 0.36; P<0.00001; I^2=56%) as compared to the control group. Paediatric patients receiving dexmedetomidine had lower postoperative analgesic requirements (RR, 0.27; 95% CI, 0.10 to 0.73; P=0.01; I^2=84%) and a lower incidence of respiratory adverse events (RR, 0.49; 95% CI, 0.31 to 0.78; P=0.003; I^2=0%). There were no significant differences in the risk of PONV and cardiovascular adverse events.

Conclusions There was a lack of high-quality studies in this field. Perioperative administration of dexmedetomidine reduced the need for postoperative rescue analgesics and the incidence of EA in children without side effects undergoing CLP repair. However, further verification with larger samples and more high quality RCTs are needed.

Keywords children, dexmedetomidine, cleft lip and palate repair, pain, emergence agitation

ARTICLE SUMMARY

Strengths and limitations of this study

Studies in both English language and Chinese language were included.

This is a comprehensive systematic review that identified the benefits of dexmedetomidine in children undergoing CLP repair.

Heterogeneity was observed in the doses, timing of administration and evaluation methods for the outcomes across studies.

For some comparisons, the numbers of trials included and outcomes reported were small.

The low quality of the included studies impedes us from drawing firm conclusions.

Word account: 3349

INTRODUCTION

Cleft lip and palate (CLP) are widespread congenital disfigurement requiring surgical correction early in life.[1] Early surgery is important to alleviate feeding difficulty, reduce airway complications and improve phonation problems.[2] However, cleft palate repair is needed to dissect the soft and hard palates and may result in significant postoperative oropharyngeal pain and bleeding. High-dose opioids with sevoflurane anaesthesia are commonly used to block the autonomic response,[3] while many paediatric patients suffer from a high risk of respiratory depression, postoperative emergence agitation (EA), postoperative nausea and vomiting (PONV), a prolonged hospital stay and increased hospital costs.[4-6]

Dexmedetomidine is a potent α2 adrenoreceptor agonist with sedative, anxiolytic, sympatholytic and analgesic properties. It alleviated the autonomic response to surgery and ensured a stable haemodynamic state without significant respiratory depression.[7] One previous study[8] had demonstrated that dexmedetomidine is helpful as a valuable adjunct for multiple applications and is increasingly used in paediatric anaesthesia settings. A meta-analysis[9] recently showed that perioperative administration of dexmedetomidine can provide pain and agitation relief without side effects in children undergoing adenotonsillectomy. Another meta-analysis[10] found that intranasal dexmedetomidine provided more satisfactory sedation at parent separation and reduced the need for postoperative rescue analgesics in paediatric patients. However, evidence in the existing literature was insufficient to fully support the effective and safe use of dexmedetomidine in children undergoing CLP repair.

Therefore, our study aimed to identify the efficacy and safety of dexmedetomidine in children during CLP repair. We performed a meta-analysis of randomized controlled trials comparing dexmedetomidine with controls.

METHODS

We evaluated the efficacy and safety of dexmedetomidine administration during CLP repair in children. A systematic review approach based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the Cochrane Review Methods was used. [11]

Search strategy and selection criteria

We searched the following databases from inception to October 1, 2020: PubMed, Embase, Cochrane Library, CNKI, VIP, and Wanfang. The main keywords used were: dexmedetomidine, randomized controlled trial (RCT), cleft palate, cleft lip, infant and children. The reference lists of identified studies were searched for additional eligible studies. (search strategy of PubMed as supplementary file1)

Inclusion and exclusion criteria

Two authors (LP and YG) systematically and independently identified all the studies using predefined selection criteria. A third author (XL) resolved disagreements when conflicting selections occurred. Studies were included in this meta-analysis if they met the following criteria: 1) Literature type: prospective, randomized controlled studies; 2) Language: both English and Chinese; 3) Subjects: children undergoing CLP repair; 4) Interventions: dexmedetomidine by any route of administration compared with any controls(including saline and other drugs); 5) Outcomes: the primary outcome was the incidence of EA, secondary outcome was the need for postoperative rescue analgesia, and third outcomes were the incidence of adverse effects: PONV, respiratory adverse effects (breath holding, cough, desaturation and airway spasm), and cardiovascular adverse effects (hypotension, bradycardia and postoperative bleeding).

Data collection and study appraisal

Two authors (JL and FL) independently extracted all the relevant information with a prespecified data abstraction form. The following variables were collected: the name of the first author, publication year, country, publication language, other anaesthetic agents, number of patients, protocol for administration method and dose, and outcomes. If the variables were not reported, we emailed the original authors to ask for the data.

Two authors (JL and FL) independently assessed the risk of bias based on the Cochrane risk of bias tool, which considers the following aspects: adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessor, incomplete reporting of outcome data, free of selective reporting, and free of other bias. In case of conflicting evaluations, a third author (XL) was consulted to resolve disagreements.

Quality of the evidence

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE)**.** We used GRADE profiler software version 3.2 to create the ‘‘Summary of findings’’ table, which includes the following outcomes: 1) EA; 2) respiratory adverse events; 3) the need for postoperative rescue analgesics; 4) cardiovascular adverse events; and 5) PONV.

Risk of bias across studies

Publication bias was assessed by using a funnel plot.

Statistical analysis

The meta-analysis was performed using Cochrane Collaboration Review Manager Software (RevMan version 5.1, https://training.cochrane.org/). We reported binary data as a risk ratio (RR) with a 95% confidence interval (CI). The chi square test (Mantel Haenszel method) was used to assess the heterogeneity between studies. An I^2 >50% and a P value <0.10 were considered to indicate statistical heterogeneity. Subgroup analysis or sensitivity analysis was performed to analyse reasons for heterogeneity. A random effects model (DerSimonian and Laird method) was used when significant statistical or clinical heterogeneity was detected. P≤0.05 was considered to indicate a statistically significant difference for testing values of overall effect.

Patient and public involvement

There was no patient or public involvement in this study.

RESULTS

Study selection

A total of 63 potentially relevant studies were identified. After excluding 50 studies, 13 studies including 1041 children aged 3 months to 12 years were finally included in this analysis.[12-24] The flow diagram of the literature search strategy is shown in Fig 1.

Description of studies

The included studies were undertaken from 2012-2020 in four different countries: Egypt (three)[12-14], Japan (one)[16], India (one)[17], and China (eight)[15,18-24]. Seven studies[12-18] were published in English, and the other six studies[19-24] were published in Chinese. In all of the included studies, dexmedetomidine was administered via intravenous[15-21,23,24], intranasal[22] and perineural[12-14] administration.

Eleven studies[12,14-19,21-24] compared the effects of intravenous dexmedetomidine with saline, and one study[20] compared the effects of intravenous dexmedetomidine with those of ketamine and fentanyl. One study[22] compared the effects of intranasal dexmedetomidine with saline. Two studies[12,14] compared the effects of perineural dexmedetomidine administration with saline, and one study[13] compared the effects of perineural dexmedetomidine administration with those of dexamethasone. The characteristics of the included studies are summarized in Table 1.

Quality of the included studies

Nine studies[12,13,15-19,22,24] used a random allocation method. Four studies [13-15,17]described the allocation concealment in detail. Four studies[12,16-18] concretely explained their blinding methods. The risk of the random allocation method was high in one study[20] and was unclear in the other three studies[14,21,23]. The risk of allocation concealment was unclear and the risk of blinding was high in the other studies. The risk of free of selective reporting was low in eight studies[12,14,17-20,22,23], unclear in one study[16] and high in other studies. For incomplete outcome data and free of other bias, most trials were judged as having a low risk of bias. The quality of the included trials is summarized in Table 2, Fig 2 and supplementary file 2.

Risk of bias across studies

A funnel plot was applied to assess the publication bias of the studies in this meta-analysis in supplementary file 3. Due to the small number of studies, most of the publication bias of outcomes was unclear.

The overall quality of evidence based on the GRADE system was judged as moderate (the need for postoperative rescue analgesics, respiratory adverse events, and cardiovascular adverse events), or low (EA and PONV) (Table 3).

Emergence agitation

Eight trials[15,18-24] including 684 patients reported the incidence of EA. EA was evaluated by the Ramsay score, behaviour score, Pediatric Anesthesia Emergence Delirium scale, or Aonos four-point scale. Dexmedetomidine administration (including intravenous and intranasal administration) showed significant evidence of reduced EA when compared with saline[15,18,19,21-24] (RR, 0.19; 95% CI, 0.10 to 0.38; P<0.00001; I^2 = 62%) and all control groups[15,18-24] (RR, 0.19; 95% CI, 0.10 to 0.36; P<0.00001; I^2 =56%). We found that different administration methods of dexmedetomidine increased the clinical heterogeneity. Excluding the 2016 study by Yun[22] (intranasal administration), intravenous dexmedetomidine administration showed a significant evidence of reduced EA when compared with saline[15,18,19,21,23,24] (RR,0.24;95% CI, 0.13 to 0.44; P<0.00001; I^2 =40%), and when compared with all control groups [15,18-21,23,24] (RR, 0.24;95% CI, 0.14 to 0.41; P<0.00001; I^2 =29%). However, subgroup analysis showed no difference when dexmedetomidine was compared with intravenous fentanyl[18] (RR, 0.14; 95% CI, 0.01 to 2.58; P=0.19) and intravenous ketamine[20] (RR, 0.14; 95% CI, 0.01 to 2.58; P=0.19). (Fig 3).

The need for postoperative rescue analgesics

Five studies[12,14,17,18,23] including 293 paediatric patients reported that dexmedetomidine had a greater analgesic effect than saline postoperatively (RR, 0.27; 95% CI, 0.10 to 0.73; P=0.01; I^2=84%). In contrast to the two studies that used perineural adminsitration[12,14], intravenous

dexmedetomidine administration[17,18,23] showed a significant analgesic effect when compared with saline (RR, 0.26; 95% CI, 0.16 to 0.44; P<0.00001; I^2=0%). Subgroup analysis showed that there was no difference when perineural dexmedetomidine [12,14] was compared with saline in the incidence of need for rescue analgesics at postoperative 24 h (RR, 0.16; 95% CI, 0.00 to 33.36; P=0.50).

Respiratory adverse events

Eight studies[15-21,23] including 794 paediatric patients reported the number of respiratory adverse events. We found that intravenous dexmedetomidine administration showed a significantly lower incidence of respiratory adverse events than saline administration (RR, 0.49; 95% CI, 0.31 to 0.78; P=0.003; I^2=0%). Only one study[19] (n=60) reported that dexmedetomidine showed a significantly lower incidence of cough than saline (RR, 0.45; 95% CI, 0.25 to 0.82; P=0.009). There were no differences when dexmedetomidine was compared with saline in the incidence of breath holding[18,19,21] (RR, 1.35; 95% CI, 0.31 to 5.92; P=0.69; I^2=0%), desaturation[16,17,19-21,23] (RR, 0.47; 95% CI, 0.17 to 1.29; P=0.14; I^2=0%) or airway spasm[15,19,21] (RR, 0.33; 95% CI, 0.07 to 1.54; P=0.16; I^2=0%).

Cardiovascular adverse events

Three studies[17,18,24] including 880 paediatric patients reported the number of cardiovascular adverse events. We found that no differences when dexmedetomidine was compared with saline in the incidence of hypotension[17,24] (RR, 1.18; 95% CI, 0.61 to 2.28; P=0.62), bradycardia[17,24] (RR, 0.78; 95% CI, 0.30 to 2.07; P=0.62) or postoperative bleeding[18,24] (RR, 0.45; 95% CI, 0.17 to 1.15; P=0.09; I^2=0%).

Postoperative Nausea and vomiting

Eight trials[13-15,17-20,23] including 524 patients reported the incidence of PONV. Patients who received dexmedetomidine administration experienced

no statistically significant increase in PONV when compared with saline [14,15,17-19,23] (RR, 0.95; 95% CI, 0.41 to 2.19; P=0.91; I^2=0%), and when compared with all control groups[13-15,17-20,23] (RR, 0.96; 95% CI, 0.48 to 1.90; P=0.90; I^2=0%). Subgroup analysis showed that there was also no difference when perineural dexmedetomidine was compared with control groups[13,14].Additionally, another subgroup analysis showed no difference when intravenous dexmedetomidine was compared with fentanyl[20] (RR, 0.50; 95% CI, 0.06 to 4.15; P=0.52) and ketamine [20] (RR, 0.50; 95% CI, 0.06 to 4.15; P=0.52) , or when perineural dexmedetomidine was compared with dexamethasone[13] (RR, 1.33; 95% CI, 0.31 to 5.65; P=0.70).

DISCUSSION

Main findings

This meta-analysis revealed that perioperative administration of dexmedetomidine reduced the incidence of EA in children undergoing CLP repair. Paediatric patients receiving dexmedetomidine had a lower need for rescue analgesics postoperatively and a lower incidence of respiratory adverse events. However, there were no significant differences in the risk of PONV and cardiovascular adverse events.

Although dexmedetomidine is not approved by U.S. Food and Drug Administration (FDA) for administration in children, it has been an authorized drug in Europe since September 2011.[25] It is increasingly used in the pediatric setting for various indications such as premedication, adjunct, sedative, intraoperative analgesia, and adjuvant therapy[8], but the efficacy is still controversial.

Our results found that both the incidence of EA and the need for rescue analgesics postoperatively were significantly decreased in the dexmedetomidine group as compared to the saline group. This was consistent with previous studies. [4,6,9,10] Two recent meta-analyses[26,27] found

that the effects of dexmedetomidine on reducing the risk of EA in children were superior to those of other drugs (including fentanyl, propofol, ketamine), which was inconsistent with our study. Numerous aetiological factors (such as pre-existing anxiety, pain, age, type of surgical procedures, rapid awakening and anaesthetic technique) were considered to cause EA.[28] All of the included studies used sevoflurane anaesthesia. It is widely believed that pain relief of decreases the incidence of EA associated with sevoflurane general anaesthesia.[9,28] Dexmedetomidine shows dose-dependent effects on pain control and sedation. Reliable analgesic, sedative and neuroprotective effects could be the main explanations for the effects of dexmedetomidine on EA.

Respiration is slightly affected by dexmedetomidine.[7-9] Our meta-analysis showed that dexmedetomidine did not influence the incidence of breath holding, desaturation or airway spasm. In contrast, the incidence of cough and total respiratory adverse events were decreased in the dexmedetomidine group. This was attributed to the residual sedation caused by the sedative effect of dexmedetomidine. Due to the rapid decrease in the concentration of sevoflurane during the recovery period, rapidly awakening paediatric patients were in a highly sensitive state. It has minimal respiratory changes from the residual sedation, even extubation during the infusion of dexmedetomidine, in contrast to other sedatives.[7] However, we should pay attention to the fact that the strength of residual sedation was related to the early phase of postanaesthesia recovery time in postoperative anaesthesia care unit.

As a selective α2-agonist, dexmedetomidine acts on the autonomic ganglia and exerts its cardiovascular effect by decreasing sympathetic outflow and augmenting vagal activity, thus low infusion rates could cause bradycardia and hypotension while high doses could cause hypertension and aggravate bradycardia.[7,8] In addition to the dose, rapid injection may result in excessive haemodynamic alterations, and it is recommended that dexmedetomidine be administered slowly. Only two of thirteen included studies reported the incidence of bradycardia and hypotension. One study

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administered dexmedetomidine as a loading dose over 10 min and followed by a maintenance infusion of 0.5 μg/kg/h until the last suture was applied, while the other study administrated dexmedetomidine as a maintenance infusion of 0.5 μg/kg/h intravenously after the induction of anaesthesia until 20 min before the surgery was finished. There was no significant difference in the dexmedetomidine group as compared to the placebo group. The haemodynamic stability was due to the method of low dose, slow injection and continuous infusion.

Few studies have focused on the effect of dexmedetomidine on PONV. Dexmedetomidine did not affect the incidence of PONV in our meta-analysis. This was consistent with a recent systematic review[29] in which dexmedetomidine intraoperative administration had no effect upon PONV during paediatric surgery, but it was inconsistent with a recent systematic review[30] in which dexmedetomidine was superior to placebo with a reduction in the need for an antiemetic in adults undergoing gynaecological surgery. Another study also showed that dexmedetomidine appeared to prevent postoperative vomiting after sevoflurane anaesthesia for paediatric strabismus surgery. In their opinion, it is difficult to estimate the true incidence of nausea in younger children.[31] This may be the explanation for the different effects of dexmedetomidine on PONV between children and adults.

Limitations

There were still some limitations in our meta-analysis. First, only one study was designed with a low risk of bias, and the others had a moderate risk of bias. Second, due to differences in the doses and timing of administration, we did not use subgroup analysis for the administration doses.

CONCLUSIONS

Our findings demonstrate that perioperative administration of dexmedetomidine in children undergoing CLP repair efficiently decreases pain, EA,

and respiratory adverse events. However, standardized usage and dosage need further investigation, and larger rigorous studies need to be included.

Author Contributions

LP, YG and XL helped read and screen abstracts and titles of potentially relevant studies. JL, FL and XL helped read the retained papers and were responsible for extracting data and assessing their quality independently. DL helped design the study, conduct the study, analyse the data, and write the manuscript. JQ helped revise the paper with language. CH and CL helped design the study, conduct the study, analyse the data, and revise the manuscript. All authors contributed to conceptualize ideas, interpret findings and reviewed drafts of the manuscript.

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

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Figure captions:

Figure 1: Flow diagram of the literature search strategy

Figure 2: Risk of bias of the included studies.

Figure 3: Perioperative dexmedetomidine versus control groups for emergence agitation (EA). CI: confidence interval; RR: risk ratio.

Table1 Characteristics of the included randomized-controlled trials.

Study (year)	Country	Language	Age (month/year)	Other anesthetic agents	Administration method	Comparison	Outcomes
Mostafa 2020[12]	Egypt	English	1-5y	Sevoflurane, fentanyl, propofol	perineural	Dex(n=15)0.5ug/kg Control(n=15): saline	the incidence of need for rescue analgesia
El-Emam 2019[13]	Egypt	English	3-6m	Sevoflurane, fentanyl, rocuronium	perineural	Dex(n=50)0.5ug/kg Control(n=50): 0.1mg/kg DA	the incidence of PONV
Obayah 2010[14]	Egypt	English	11.7±2.4m 12±2.7m	Sevoflurane	perineural	Dex(n=15)1ug/kg Control(n=15): saline	the incidence of PONV, need for rescue analgesia
Peng 2015[15]	China	English	3-24m	Sevoflurane, fentanyl, propofol, cisatracurium, remifentanil	intravenous	Dex(n=20)0.8ug/kg/min (continuous intravenous infusion after induction) Control(n=20): saline	the incidence of EA, PONV, airway spasm
Boku 2015[16]	Japan	English	10-14m	Sevoflurane, fentanyl, rocuronium	intravenous	Dex(n=35)6ug/kg/h (10 min before the end of the surgery for 10 min) +0.4ug/kg/h (continuous intravenous infusion until 5min before	the incidence of desaturation

						extubate) Control(n=35): saline	
Surana 2017[17]	India	English	6m-12y	Sevoflurane, fentanyl, glycopyrrolate, vecuronium, isoflurane	intravenous	Dex(n=30):1ug/kg+0.5ug/kg/h(continuous intravenous infusion) Control(n=30): 0.05 mg/kg midazolam+saline(continuous intravenous infusion)	the incidence of need for rescue analgesia, PONV, desaturation, hypotension, bradycardia
Luo 2017[18]	China	English	1-5y	Sevoflurane, remifentanil	intravenous	Dex(n=50):0.5ug/kg (prior to induction of anesthesia) Control(n=50): saline	the incidence of EA, need for rescue analgesia, PONV, breath-holding, postoperative bleeding
Mei 2014[19]	China	Chinese	8m-3y	Sevoflurane, morphine	intravenous	Dex(n=30):0.5ug/kg (30min before surgery finish for 10min) Control(n=30): saline	the incidence of EA, PONV, breath-holding, cough, desaturation, airway spasm
Xiao 2012[20]	China	Chinese	1.22±0.22y 1.26±0.24y 1.25±0.23y	Sevoflurane, vecuronium, propofol,	intravenous	Dex(n=18):2ug/kg (during induction) +0.5ug/kg/h	the incidence of EA, PONV, desaturation

						(continuous intravenous infusion after intubation) Control 1(n=18):2mg/kg (during induction) +0.5mg/kg/h (continuous intravenous infusion after intubation) ketamine Control 2(n=18):3ug/kg (during induction) + 1ug/kg (intermittent administration twice) fentanyl	
Xi 2012[21]	China	Chinese	1-3y	Sevoflurane, midazolam propofol, cisatracurium, fentanyl	intravenous	Dex(n=15):1ug/kg (30min before surgery finish for10min) Control(n=15): saline	the incidence of EA, breath-holding, desaturation, airway spasm
Yun 2016[22]	China	Chinese	6m-3y	Sevoflurane, propofol, succinylcholine	intranasal	Dex(n=60):2ug/kg (30min before surgery finish) Control(n=60): saline	the incidence of EA
Ju 2013[23]	China	Chinese	4m-3y	Propofol, cisatracurium, fentanyl	intravenous	Dex(n=40):0.5ug/kg (10min before surgery start for 10min)	the incidence of EA, need for rescue

				sevoflurane, remifentanil		Control(n=40): saline	analgesia, PONV, Desaturation
Jun 2018[24]	China	Chinese	1.71±0.61y 1.74±0.62y	Sevoflurane, propofol, rocuronium, sufentanil	intravenous	Dex(n=110):0.5ug/kg/h (20min before surgery finished) Control(n=110): saline	the incidence of EA, hypotension, Bradycardia, postoperative bleeding

dexmedetDA dexamethasoneagitation; PONV: postoperative nausea and vomiting.

Table 2 Individual Randomized Controlled Trial Methodological Quality.

Study (year)	Adequate sequence generation	Allocation concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Mostafa2020[12]	yes	?	yes	yes	yes	yes	yes
El-Emam2019[13]	yes	yes	No	yes	yes	No	yes
Obayah2010[14]	?	yes	No	No	yes	yes	yes
Peng2015[15]	yes	yes	No	No	No	No	yes
Boku2015[16]	yes	?	yes	yes	yes	?	yes
Surana2017[17]	yes	yes	yes	yes	yes	yes	yes
Luo2017[18]	yes	?	yes	yes	yes	yes	No
Mei2014[19]	yes	?	No	No	yes	yes	yes
Xiao2012[20]	No	?	No	No	yes	yes	yes
Xi2012[21]	?	?	No	No	yes	No	yes
Yun2016[22]	yes	?	yes	No	yes	yes	yes
Ju2013[23]	?	?	No	No	yes	yes	yes
Jun2018[24]	yes	?	No	No	yes	No	yes

Yes=low risk of bias; No=high risk of bias; ?=unclear risk of bias.

Table 3 Summary of findings for the main outcomes

Dexmedetomidine for cleft lip and palate repair						
Patient or population: patients with cleft lip and palate repair **Settings:** surgery **Intervention:** Dexmedetomidine						
Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **Control**	Corresponding risk **Dexmedetomidine**	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Emergence agitation	**Study population**		**RR 0.19** (0.10 to 0.36)	684 (8 studies)	⊕⊕⊖⊖ **low**[1,2,3,4,5]	
	458 per 1000	**87 per 1000** (46 to 165)				
Respiratory adverse events	**Study population**		**RR 0.49** (0.31 to 0.78)	794 (8 studies)	⊕⊕⊕⊖ **moderate**[1,6]	
	103 per 1000	**50 per 1000** (32 to 80)				
The need for postoperative rescue analgesics	**Study population**		**RR 0.27** (0.1 to 0.73)	293 (5 studies)	⊕⊕⊕⊖ **moderate**[1,2,6]	
	592 per 1000	**160 per 1000** (59 to 432)				
Cardiovascular adverse events	**Study population**		**RR 0.83** (0.52 to 1.31)	880 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
	105 per 1000	**87 per 1000** (55 to 138)				

Postoperative Nausea and vomiting	**Study population**		**RR 0.92**	524	⊕⊕⊖⊖
	63 per 1000	**58 per 1000** (30 to 113)	(0.47 to 1.80)	(8 studies)	**low**[1]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Allocation concealment and/or blinding of outcome assessors unclear/inadequate in 50% or more of the included studies

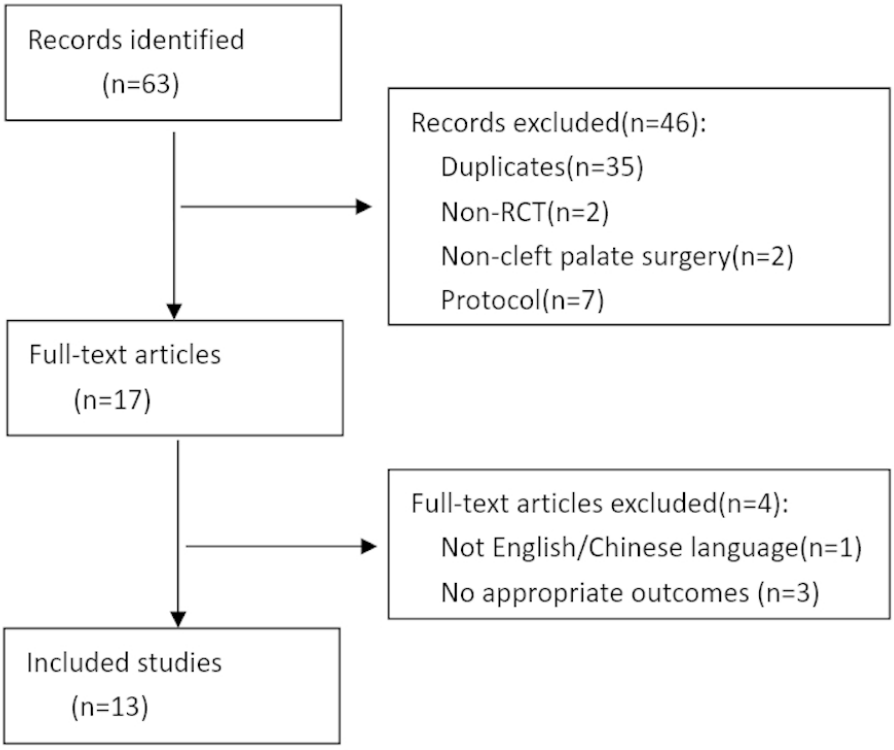
[2] Significant heterogeneity (I 2 > 50%) is partially explained by different administration method ,dose and comparators.

[3] Use of several different scoring criterias to evaluate emergence agitation.

[4] a dose response gradient was present

[5] RR >5 or <0.2

[6] RR >2 or <0.5



Flow diagram of the literature search strategy

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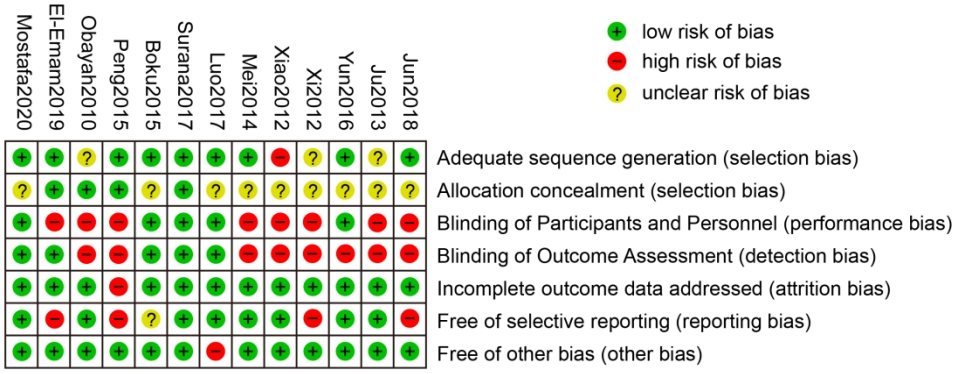

Risk of bias of the included studies.

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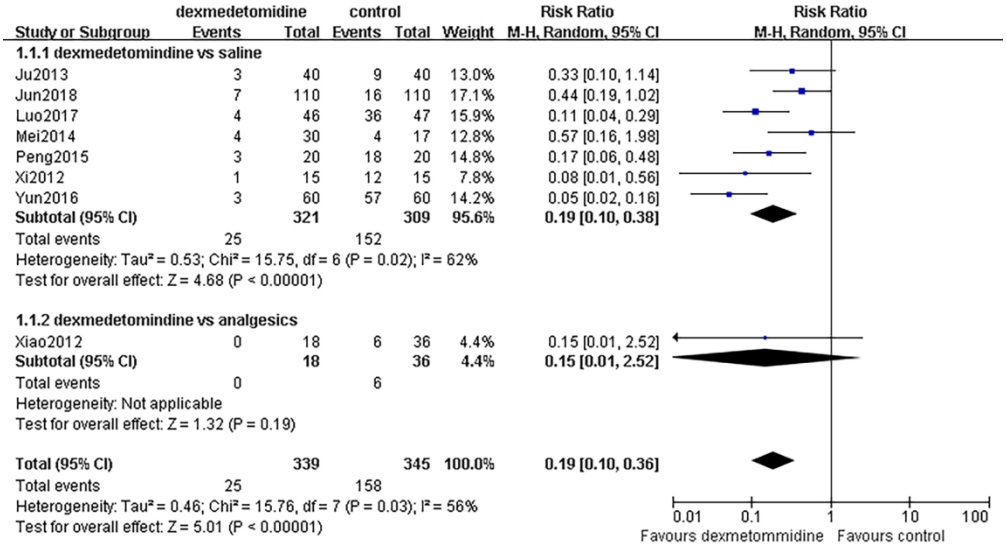

Perioperative dexmedetomidine versus control groups for emergence agitation (EA). CI: confidence interval; RR: risk ratio.

205x114mm (300 x 300 DPI)

#1 dexmedetomidine [MeSH Terms]

#2 "cleft palate"[All Fields] OR "lip palate"[All Fields] OR "cleft palate and lip"[All Fields]

#3 infant or children or pediatric patient [All Fields]

#4 randomized controlled trial [All Fields]

#5 #1 and #2 and #3 and #4

Risk of bias

Mostafa2020[12] (ClinicalTrials.gov ID: NCT03412474).

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated program of random numbers
Allocation concealment (selection bias)	unclear	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the doctors (investigators) nor the patients' guardians or even the children themselves were aware of the group al- location and the drug received. One anesthesiologist not involved in the block implementation or the data collection, prepared all the study solutions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	While a third, blinded to the previous protocol, was responsible only for data collection.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 80 patients
Other bias	Low risk	Groups well balanced

El-Emam2019[13] Clinical Trials.gov (NCT03480607)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated randomization numbers
Allocation concealment (selection bias)	Low risk	a closed-seal envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	The principal investigator prepared the drug and performed the block
Blinding of outcome assessment (detection bias) All outcomes	Low risk	the person observing and recording the parameters was blinded to the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	The primary outcome was to compare both groups regarding time to first rescue analgesic, while the primary outcomes in the pre-registration site were postoperative FLACC scale and postoperative sedation score.
Other bias	Low risk	Groups well balanced

Obayah2010[14]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated", no details
Allocation concealment (selection bias)	Low risk	The randomization was achieved by the opening of a sealed envelope by the attending physician
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 30 patients
Other bias	Low risk	Groups well balanced

Peng2015[15] Chinese Clinical Trial Register (ChiCTR-TRC-13003865).

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly divided with a computer-generated sequence of numbers
Allocation concealment (selection bias)	Low risk	a sealed envelop
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	The actual sample was 40 while the planned sample in the pre-registration site was 60.
Selective reporting (reporting bias)	High risk	The primary outcome was to compare both groups regarding emergence agitation and time about recovery parameters while the primary outcomes in the pre-registration site were heart rate and blood pressure.
Other bias	Low risk	Groups well balanced

Boku2015[16] (UMIN 000009869) http://upload.umin.ac.jp.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The patient' s parents and the attending anesthesiologist were blinded to the group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data for each patient were obtained by the blinded anesthesiologist.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Do not get the protocol
Other bias	Low risk	Groups well balanced

Surana2017[17]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a computer-generated randomized chart
Allocation concealment (selection bias)	Low risk	The random group assignments were enclosed in a sealed opaque envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	the surgeons, the patients, and the anesthesiologist in the post-anesthesia care unit (PACU) were all blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data was recorded by a blinded observer.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 60 patients
Other bias	Low risk	Groups well balanced

Luo2017[18]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a computer-generated table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All pharmacological agents used in the present study were prepared and administrated by the anesthesiologists who were blinded to the details of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pediatric Anesthesia Emergence Delirium and CHIPPS scores were documented by a well-trained PACU nurse who was blinded to the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 patients from group DS and 3 patients from group SF were excluded from the analysis
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 93 patients
Other bias	High risk	Groups well balanced. Not in intention-to-treat: Of the 100 patients admitted to the study, 7 were later excluded by the authors for the reasons listed in table II, leaving data from 93 patients for consideration

Mei2014[19]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a table of random numbers, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 60 patients
Other bias	Low risk	Groups well balanced.

Xiao2012[20]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	randomized according to the operation time sequence
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 54 patients
Other bias	Low risk	Groups well balanced.

Xi2012[21]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random mentioned, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	High risk	Lack of complications, such as postoperative hoarseness, nausea and vomiting
Other bias	Low risk	Groups well balanced.

Yun2016[22]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a table of random numbers, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A blinded anesthesia nurse prepared and administrated drugs
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 120 patients
Other bias	Low risk	Groups well balanced.

Ju2013[23]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentioned random, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 80 patients
Other bias	Low risk	Groups well balanced.

Jun2018[24]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Compute randomized
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	High risk	The secondary outcomes were to compare both groups regarding extubation time and incision bleeding which were not mentioned in method.
Other bias	Low risk	Groups well balanced.

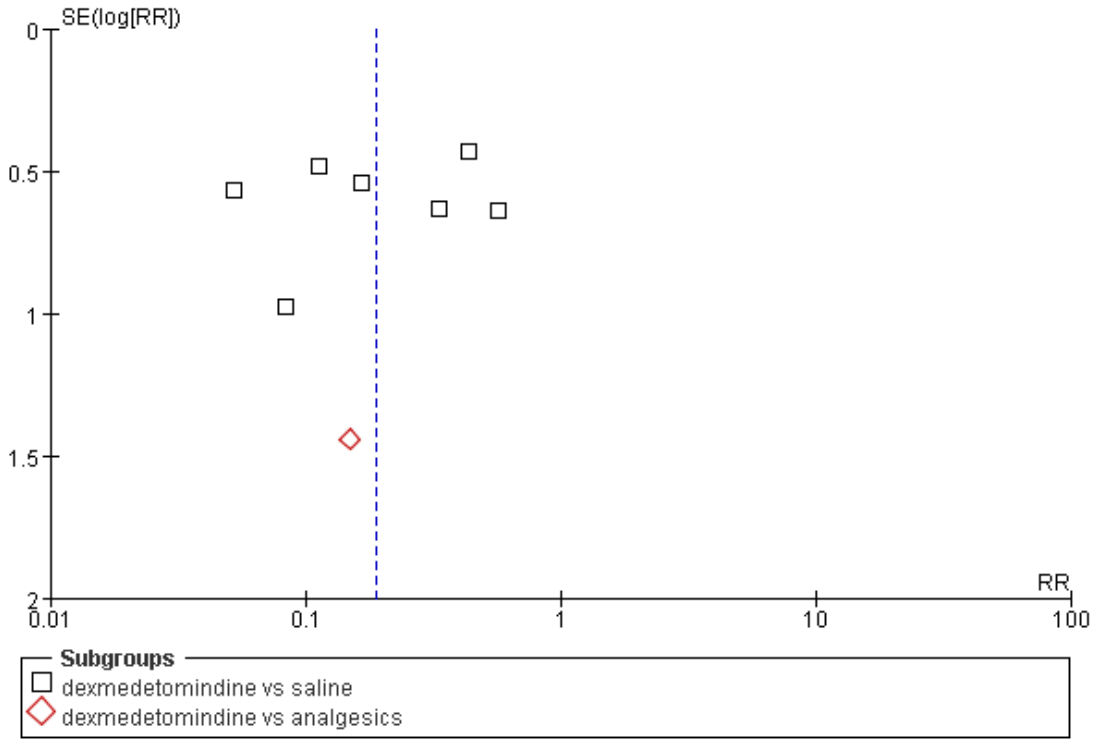

Figure1 Funnel plot of comparison: dexmedetomidine vs control, outcome: 1.1 emergence agitation.

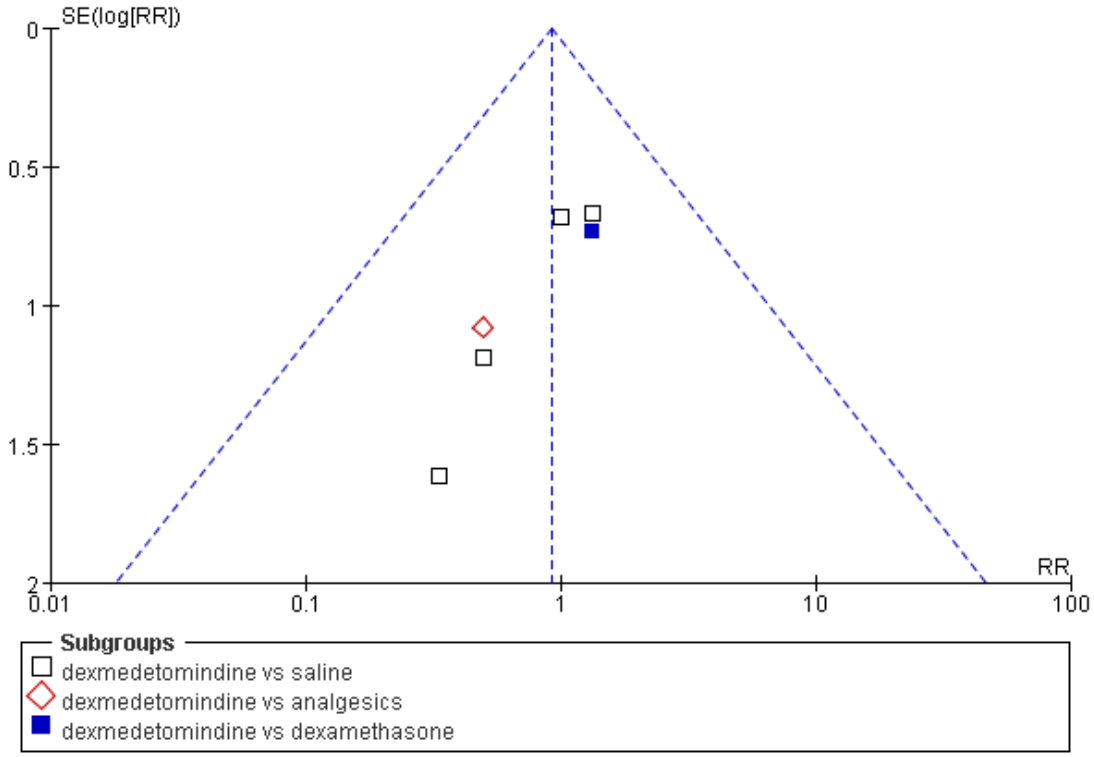

Figure 2 Funnel plot of comparison: dexmedetomidine vs control, outcome: 1.2 postoperative nausea and vomiting.

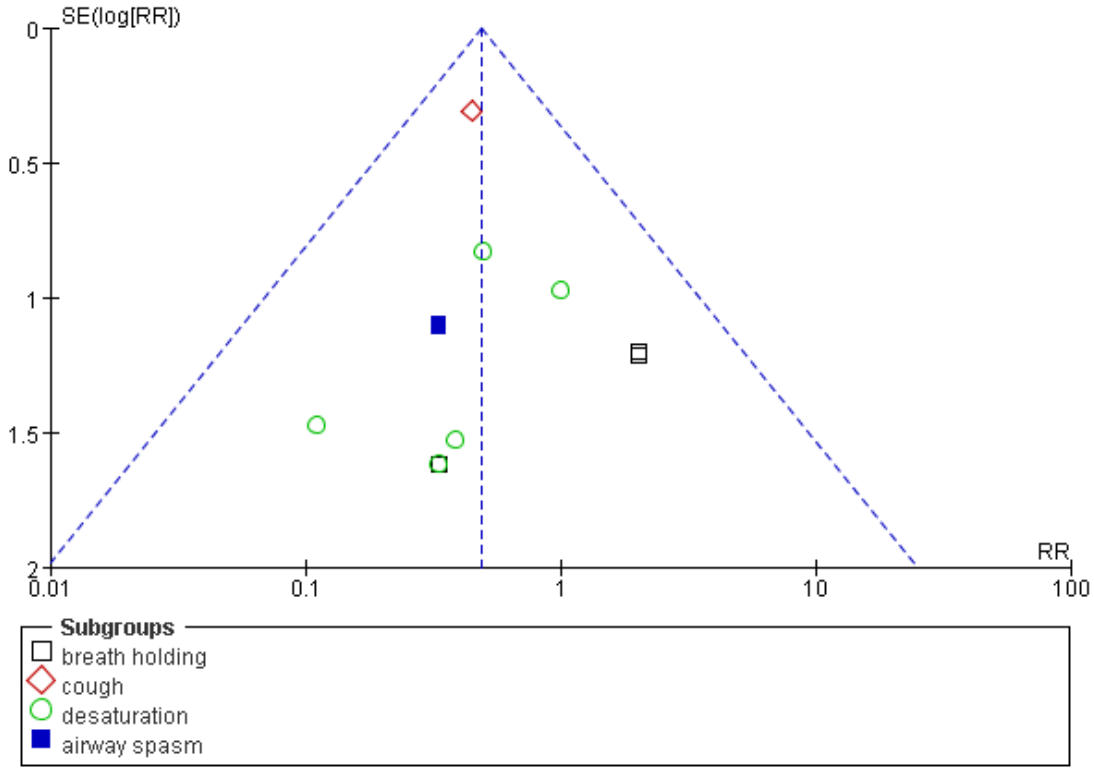

Figure 3 Funnel plot of comparison: dexmedetomidine vs control, outcome: 1.3 complication in respiration.

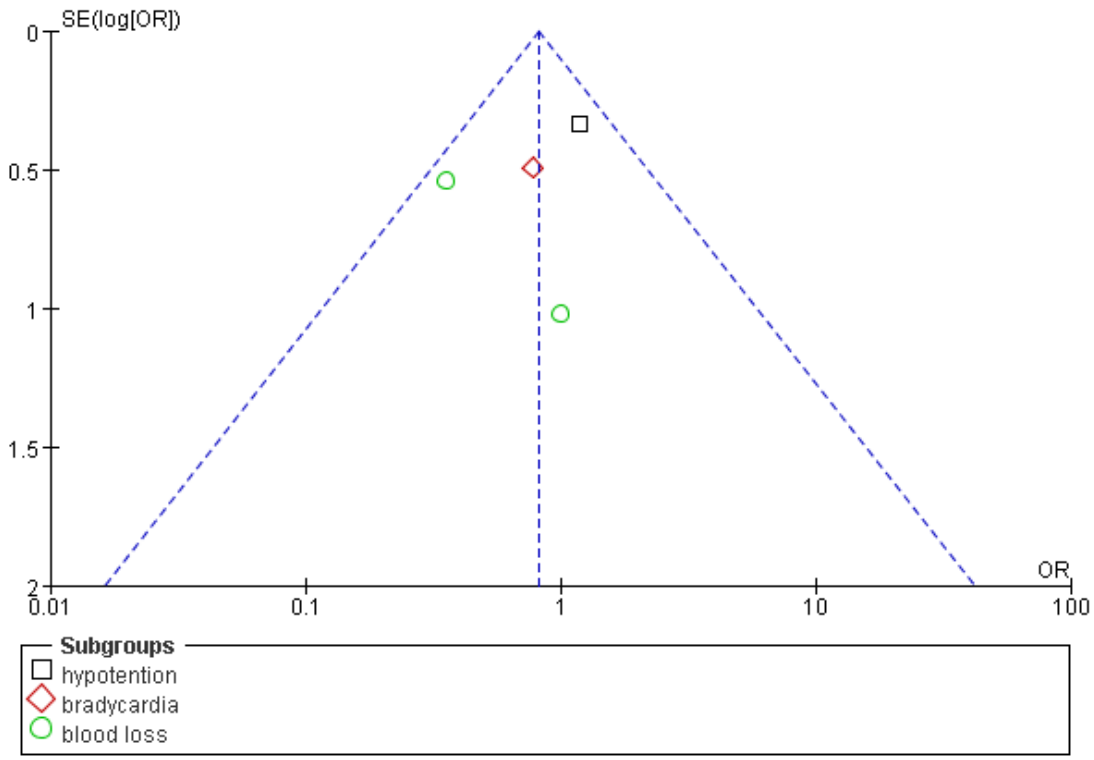

Figure 4 Funnel plot of comparison: dexmedetomidine vs control, outcome: 1.4 complication in circulation.

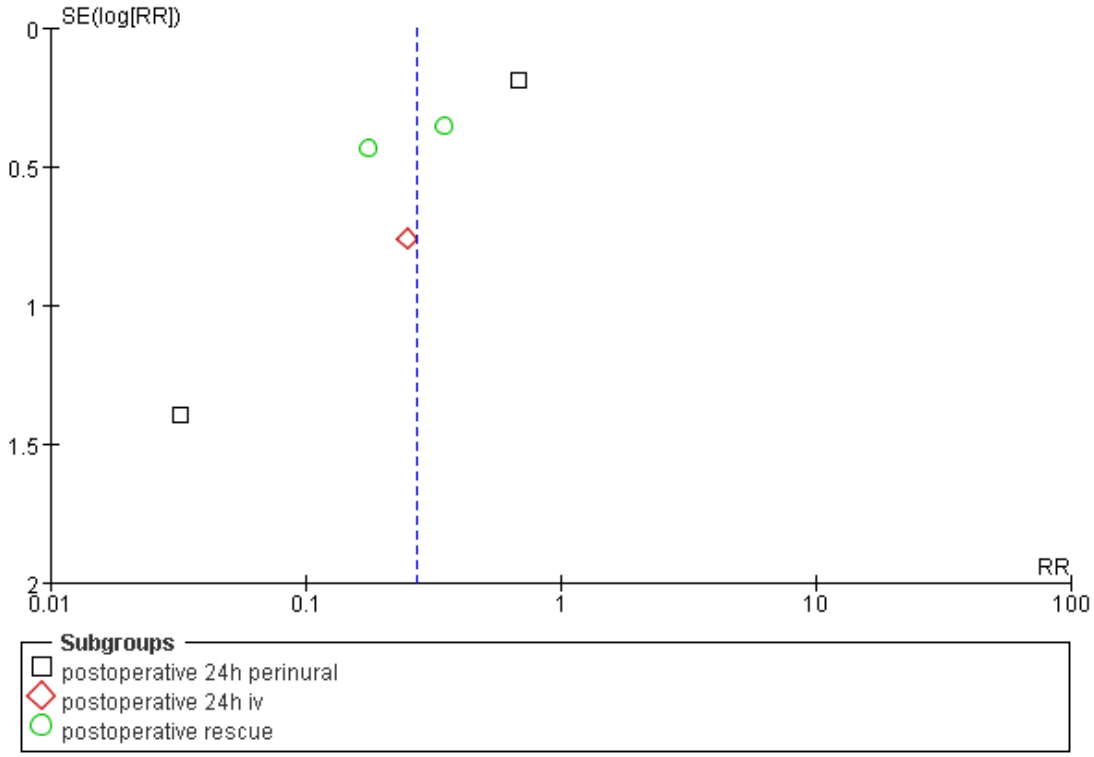

Figure 5 Funnel plot of comparison: dexmedetomidine vs control, outcome:1.5 postoperative analgesia rescue.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1-2
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			3-4
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			5
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			6-8
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	--
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	--
RESULTS			8-12,21-27
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9,21-24
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,25
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9,10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10,26-27
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	--
DISCUSSION			12-15
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14,15
FUNDING			15
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Efficacious of dexmedetomidine in children undergoing cleft lip and palate repair: a systematic review and meta-analysis

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Anaesthesia, Paediatrics, Dentistry and oral medicine
Keywords:	ORAL & MAXILLOFACIAL SURGERY, Paediatric anaesthesia < ANAESTHETICS, Pain management < ANAESTHETICS

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Efficacious of dexmedetomidine in children undergoing cleft lip and palate repair: a systematic review and meta-analysis

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ABSTRACT

Objective To systematically assess the efficacy and safety of dexmedetomidine as an anaesthesia adjuvant for cleft lip and palate (CLP) repair in children.

Design Systematic review and meta-analysis.

Data sources PubMed, Embase, Cochrane, CNKI, VIP, and Wanfang (up to Oct 2020). Studies in languages other than English and Chinese were excluded.

Eligibility criteria for selecting studies Randomized controlled trials (RCTs) evaluating the impact of dexmedetomidine on emergence agitation (EA), the need for postoperative rescue analgesics, postoperative nausea and vomiting (PONV), and other adverse events in paediatric patients during CLP repair.

Data extraction and synthesis The quality of evidence was assessed by using the Cochrane Review Methods and the Grading of Recommendations Assessment, Development, and Evaluation approach. Data were screened, extracted and assessed by two independent authors. Outcomes were reported as a risk ratio (RR) with a 95% confidence interval (CI). A random effect model was used when heterogeneity was detected.

Results Thirteen studies including 1040 children met the inclusion criteria. The incidence of EA was significantly decreased in the dexmedetomidine group (RR, 0.19; 95% CI, 0.10 to 0.36; P<0.00001; I^2=56%) as compared to the control group. Paediatric patients receiving dexmedetomidine had lower postoperative analgesic requirements (RR, 0.27; 95% CI, 0.10 to 0.73; P=0.0 I^2=84%) and a lower incidence of respiratory adverse events (RR, 0.49; 95% CI, 0.31 to 0.78; P=0.003; I^2=0%). There were no significant differences in the risk of PONV and

cardiovascular adverse events.

Conclusions There was a lack of high-quality studies in this field. Perioperative administration of dexmedetomidine reduced the need for postoperative rescue analgesics and the incidence of EA in children without side effects undergoing CLP repair. However, further verification with larger samples and higher quality RCTs are needed.

Keywords children, dexmedetomidine, cleft lip and palate repair, pain, emergence agitation

ARTICLE SUMMARY

Strengths and limitations of this study

Studies in both English language and Chinese language were included.

This is a comprehensive systematic review that identified the benefits of dexmedetomidine in children undergoing CLP repair.

Heterogeneity was observed in the doses, the timing of administration and evaluation methods for the outcomes across studies.

For some comparisons, the numbers of trials included and the outcomes reported were small.

The low quality of the included studies impedes us from drawing firm conclusions.

Word account: 4226

INTRODUCTION

Cleft lip and palate (CLP) are widespread congenital disfigurements requiring surgical correction early in life.[1] Early surgery is important to alleviate feeding difficulty, reduce airway complications and improve phonation problems.[2] However, cleft palate repair is needed to dissect the soft and hard palates and may result in significant postoperative oropharyngeal pain and bleeding. High-dose opioids with sevoflurane anaesthesia are commonly used to block the autonomic response,[3] while many paediatric patients suffer from high risks of respiratory depression, postoperative emergence agitation (EA), postoperative nausea and vomiting (PONV), prolonged hospital stay and increased hospital costs.[4-6]

Dexmedetomidine is a potent α2 adrenoreceptor agonist with sedative, anxiolytic, sympatholytic and analgesic properties. It alleviated the autonomic response to surgery and ensured a stable haemodynamic state without significant respiratory depression.[7] One previous study[8] had demonstrated that dexmedetomidine was helpful as a valuable adjunct for multiple applications and was increasingly used in paediatric anaesthesia settings. A meta-analysis[9] recently showed that perioperative administration of dexmedetomidine can provide pain and agitation relief without side effects in children undergoing adenotonsillectomy. Another meta-analysis[10] found that intranasal dexmedetomidine provided more satisfactory sedation at parent separation and reduced the need for postoperative rescue analgesics in paediatric patients. However, evidences in the existing literature were still insufficient to fully support the effective and safe use of dexmedetomidine in children undergoing CLP repair.

Therefore, our study aimed to identify the efficacy and safety of dexmedetomidine in children during CLP repair. We performed a meta-analysis of randomized controlled trials comparing dexmedetomidine with controls.

METHODS

We evaluated the efficacy and safety of dexmedetomidine administration during CLP repair in children. A systematic review approach based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and the Cochrane Review Method was used. [11]

Search strategy and selection criteria

We searched the following databases from inception to October 1, 2020: PubMed, Embase, Cochrane Library, CNKI, VIP, and Wanfang. The main keywords used were: dexmedetomidine, randomized controlled trial (RCT), cleft palate, cleft lip, infant and children. The reference lists of identified studies were searched for additional eligible studies. (search strategy of PubMed as supplementary file1)

Inclusion and exclusion criteria

Two authors (LP and YG) systematically and independently identified all the studies using predefined selection criteria. A third author (XL) resolved disagreements when conflicting selections occurred. Studies were included in this meta-analysis if they met the following criteria: 1) Literature type: prospective, randomized controlled studies; 2) Language: both English and Chinese; 3) Subjects: children undergoing CLP repair; 4) Interventions: dexmedetomidine by any route of administration compared with any controls(including saline and other drugs); 5) Outcomes: the primary outcome was the incidence of EA, the secondary outcome was the need for postoperative rescue analgesia, and the third outcomes were the incidence of adverse effects: PONV, respiratory adverse effects (breath-holding, cough, desaturation and airway spasm), and cardiovascular adverse effects (hypotension, bradycardia and postoperative bleeding).

Data collection

Two authors (JL and FL) independently extracted all the relevant information with a prespecified data abstraction form. The following variables were collected: the name of the first author, publication year, country, publication language, other anaesthetic agents, number of patients, protocol for administration method and dose, and outcomes. If the variables were not reported, we emailed the original authors to ask for the data.

Risk of bias across studies

Two authors (JL and FL) independently assessed the risk of bias based on the Cochrane risk of bias tool, which considers the following aspects: adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding of the outcome assessor, incomplete reporting of outcome data, free of selective reporting, and free of other bias. We assessed the risk of bias based on the information presented in the studies, with no assumptions: low risk of bias, high risk of bias or unclear risk of bias. In case of conflicting evaluations, a third author (XL) was consulted to resolve disagreements.

Quality of the evidence

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation approach (GRADE)**.** We used GRADE profiler software version 3.2 to create the ‘‘Summary of findings’’ table, which includes the following outcomes: 1) EA; 2) respiratory adverse events; 3) the need for postoperative rescue analgesics; 4) cardiovascular adverse events; and 5) PONV.

Publication bias across studies

Publication bias was assessed by using a funnel plot or Begg's test.

Statistical analysis

The meta-analysis was performed using Cochrane Collaboration Review Manager Software (RevMan version 5.1, https://training.cochrane.org/). We reported binary data as a risk ratio (RR) with a 95% confidence interval (CI). The chi-square test (Mantel Haenszel method) was used to assess the heterogeneity between studies. An I^2 >50% and a P-value <0.10 were considered to indicate statistical heterogeneity. Subgroup analysis or sensitivity analysis was performed to analyze reasons for heterogeneity. A random effect model (DerSimonian and Laird method) was used when significant statistical or clinical heterogeneity was detected. P≤0.05 was considered to indicate a statistically significant difference for testing values of the overall effect.

Patient and public involvement

There was no patient or public involvement in this study.

RESULTS

Study selection

A total of 63 potentially relevant studies were identified. After excluding 50 studies, 13 studies including 1041 children aged 3 months to 12 years

were finally included in this analysis.[12-24] The flow diagram of the literature search strategy is shown in Fig 1.

Description of studies

The included studies were undertaken from 2012-2020 in four different countries: Egypt (three)[12-14], Japan (one)[16], India (one)[17], and China (eight)[15,18-24]. Seven studies[12-18] were published in English, and the other six studies[19-24] were published in Chinese. In all of the included studies, dexmedetomidine was administered via intravenous[15-21,23,24], intranasal[22], and perineural[12-14] administration.

Eleven studies[12,14-19,21-24] compared the effects of intravenous dexmedetomidine with saline, and one study[20] compared the effects of intravenous dexmedetomidine with those of ketamine and fentanyl. One study[22] compared the effects of intranasal dexmedetomidine with saline. Two studies[12,14] compared the effects of perineural dexmedetomidine administration with saline, and one study[13] compared the effects of perineural dexmedetomidine administration with those of dexamethasone. The characteristics of the included studies are summarized in Table 1.

Risk of bias across studies

The risk of bias of included studies can be found in Table 2, Fig 2 and Supplementary file 2. Nine studies[12,13,15-19,22,24] used a random allocation method. Four studies [13-15,17]described the allocation concealment in detail. Four studies[12,16-18] concretely explained their blinding methods. The risk of the random allocation method was high in one study[20] and was unclear in the other three studies[14,21,23]. The risk of allocation concealment was unclear and the risk of blinding was high in the other studies. The risk of free of selective reporting was low in eight studies[12,14,17-20,22,23], unclear in one study[16] and high in other studies. For incomplete outcome data and free of other bias, most trials were judged as having a low risk of bias. The quality of the included trials is summarized in Table 2, Fig 2 and supplementary file 2.

Quality of the included studies

The overall quality of evidence based on the GRADE system was judged as moderate (the need for postoperative rescue analgesics, respiratory adverse events, and cardiovascular adverse events), or low (EA and PONV) (Table 3).

Publication bias across studies

Test for funnel plot asymmetry was inappropriate to assess risk of publication bias. Since no significant asymmetry patterns were identified in Begg's test (supplementary file 3), we concluded no significant publication bias. Due to the small number of studies, the power is still low.

Emergence agitation

Eight trials[15,18-24] including 684 patients reported the incidence of EA. EA was evaluated by the Ramsay score, behaviour score, Pediatric Anesthesia Emergence Delirium scale, or Aonos four-point scale. Dexmedetomidine administration (including intravenous and intranasal administration) showed significant evidence of reduced EA when compared with saline[15,18,19,21-24] (RR, 0.19; 95% CI, 0.10 to 0.38; P<0.00001; I^2 = 62%) and all control groups[15,18-24] (RR, 0.19; 95% CI, 0.10 to 0.36; P<0.00001; I^2 =56%). We found that different administration methods of dexmedetomidine increased the clinical heterogeneity. Excluding the 2016 study by Yun[22] (intranasal administration), intravenous dexmedetomidine administration showed a significant evidence of reduced EA when compared with saline[15,18,19,21,23,24] (RR,0.24;95% CI, 0.13 to 0.44; P<0.00001; I^2 =40%), and when compared with all control groups [15,18-21,23,24] (RR, 0.24;95% CI, 0.14 to 0.41; P<0.00001; I^2 =29%). However, subgroup analysis showed no difference when dexmedetomidine was compared with intravenous fentanyl[19] (RR, 0.14; 95% CI, 0.01 to 2.58; P=0.19) and intravenous ketamine[20] (RR, 0.14; 95% CI, 0.01 to 2.58; P=0.19). (Fig 3).

The need for postoperative rescue analgesics

Five studies[12,14,17,18,23] including 293 paediatric patients reported that dexmedetomidine had a greater analgesic effect than saline postoperatively (RR, 0.27; 95% CI, 0.10 to 0.73; P=0.01; I^2=84%). In contrast to the two studies that used perineural adminsitration[12,14], intravenous dexmedetomidine administration[17,18,23] showed a significant analgesic effect when compared with saline (RR, 0.26; 95% CI, 0.16 to 0.44; P<0.00001; I^2=0%). Subgroup analysis showed that there was no difference when perineural dexmedetomidine [12,14] was compared with saline in the incidence of need for rescue analgesics at postoperative 24 h (RR, 0.16; 95% CI, 0.00 to 33.36; P=0.50).

Respiratory adverse events

Eight studies[15-21,23] including 794 paediatric patients reported the number of respiratory adverse events. We found that intravenous dexmedetomidine administration showed a significantly lower incidence of respiratory adverse events than saline administration (RR, 0.49; 95% CI, 0.31 to 0.78; P=0.003; I^2=0%). Only one study[19] (n=60) reported that dexmedetomidine showed a significantly lower incidence of cough than saline (RR, 0.45; 95% CI, 0.25 to 0.82; P=0.009). There were no differences when dexmedetomidine was compared with saline in the incidence of breath holding[18,19,21] (RR, 1.35; 95% CI, 0.31 to 5.92; P=0.69; I^2=0%), desaturation[16,17,19-21,23] (RR, 0.47; 95% CI, 0.17 to 1.29; P=0.14; I^2=0%) or airway spasm[15,19,21] (RR, 0.33; 95% CI, 0.07 to 1.54; P=0.16; I^2=0%).

Cardiovascular adverse events

Three studies[17,18,24] including 880 paediatric patients reported the number of cardiovascular adverse events. We found that no differences when dexmedetomidine was compared with saline in the incidence of hypotension[17,24] (RR, 1.18; 95% CI, 0.61 to 2.28; P=0.62), bradycardia[17,24] (RR,

0.78; 95% CI, 0.30 to 2.07; P=0.62) or postoperative bleeding[18,24] (RR, 0.45; 95% CI, 0.17 to 1.15; P=0.09; I^2=0%).

Postoperative Nausea and vomiting

Eight trials[13-15,17-20,23] including 524 patients reported the incidence of PONV. Patients who received dexmedetomidine administration experienced no statistically significant increase in PONV when compared with saline [14,15,17-19,23] (RR, 0.95; 95% CI, 0.4 to 2.19; P=0.91; I^2=0%), and when compared with all control groups[13-15,17-20,23] (RR, 0.96; 95% CI, 0.48 to 1.90; P=0.90; I^2=0%). Subgroup analysis showed that there was also no difference when perineural dexmedetomidine was compared with control groups[13,14].Additionally, another subgroup analysis showed no difference when intravenous dexmedetomidine was compared with fentanyl[20] (RR, 0.50; 95% CI, 0.06 to 4.15; P=0.52) and ketamine [20] (RR, 0.50; 95% CI, 0.06 to 4.15; P=0.52) , or when perineural dexmedetomidine was compared with dexamethasone [13] (RR, 1.33; 95% CI, 0.31 to 5.65; P=0.70).

DISCUSSION

Main findings

This meta-analysis revealed that perioperative administration of dexmedetomidine reduced the incidence of EA in children undergoing CLP repair. Paediatric patients receiving dexmedetomidine had a lower need for rescue analgesics postoperatively and a lower incidence of respiratory adverse events. However, there were no significant differences in the risk of PONV and cardiovascular adverse events.

Although dexmedetomidine is not approved by U.S. Food and Drug Administration (FDA) for administration in children, it has been an authorized drug in Europe since September 2011.[25] It is increasingly used in the pediatric setting for various indications such as premedication,

adjunct, sedative, intraoperative analgesia, and adjuvant therapy[8], but the efficacy is still controversial.

Our results found that both the incidence of EA and the need for rescue analgesics postoperatively were significantly decreased in the dexmedetomidine group as compared to the saline group. This was consistent with previous studies. [4,6,9,10] Two recent meta-analyses[26,27] found that the effects of dexmedetomidine on reducing the risk of EA in children were superior to those of other drugs (including fentanyl, propofol, ketamine), which was inconsistent with our study. Numerous aetiological factors (such as pre-existing anxiety, pain, age, type of surgical procedures, rapid awakening and anaesthetic technique) were considered to cause EA.[28] All of the included studies used sevoflurane anaesthesia. It is widely believed that pain relief of decreases the incidence of EA associated with sevoflurane general anaesthesia. [9,28] Dexmedetomidine shows dose-dependent effects on pain control and sedation. Reliable analgesic, sedative and neuroprotective effect could be the main explanations for the effects of dexmedetomidine on EA.

Respiration is slightly affected by dexmedetomidine.[7-9] Our meta-analysis showed that dexmedetomidine did not influence the incidence of breath-holding, desaturation or airway spasm. In contrast, the incidence of cough and total respiratory adverse events were decreased in the dexmedetomidine group. This was attributed to the residual sedation caused by the sedative effect of dexmedetomidine. Due to the rapid decrease in the concentration of sevoflurane during the recovery period, rapidly awakening paediatric patients were in a highly sensitive state. It has minimal respiratory changes from the residual sedation, even extubation during the infusion of dexmedetomidine, in contrast to other sedatives.[7] However, we should pay attention to the fact that the strength of residual sedation was related to the early phase of postanaesthesia recovery time in postoperative anaesthesia care unit.

As a selective α2-agonist, dexmedetomidine acts on the autonomic ganglia and exerts its cardiovascular effect by decreasing sympathetic outflow

and augmenting vagal activity, thus low infusion rates could cause bradycardia and hypotension while high doses could cause hypertension and aggravate bradycardia.[7,8] In addition to the dose, rapid injection may result in excessive haemodynamic alterations, and it is recommended that dexmedetomidine be administered slowly. Only two of thirteen included studies reported the incidence of bradycardia and hypotension. One study administered dexmedetomidine as a loading dose over 10 min and followed by a maintenance infusion of 0.5 μg/kg/h until the last suture was applied, while the other study administrated dexmedetomidine as a maintenance infusion of 0.5 μg/kg/h intravenously after the induction of anaesthesia until 20 min before the surgery was finished. There was no significant difference in the dexmedetomidine group as compared to the placebo group. The haemodynamic stability was due to the method of low dose, slow injection and continuous infusion.

Few studies have focused on the effect of dexmedetomidine on PONV. Dexmedetomidine did not affect the incidence of PONV in our meta-analysis. This was consistent with a recent systematic review[29] in which dexmedetomidine intraoperative administration had no effect PONV during paediatric surgery, but it was inconsistent with a recent systematic review[30] in which dexmedetomidine was superior to placebo with a reduction in the need for an antiemetic in adults undergoing gynaecological surgery. Another study also showed that dexmedetomidine appeared to prevent postoperative vomiting after sevoflurane anaesthesia for paediatric strabismus surgery. In their opinion, it is difficult to estimate the true incidence of nausea in younger children.[31] This may be the explanation for the different effects of dexmedetomidine on PONV between children and adults.

Limitations

There were some limitations in methodology. First, most of the studies were focused on developing countries, which might be relevant with that CLP disease was common in developing countries. But only one study was designed with a low risk of bias, and the others had a moderate risk of

bias. There are some possibilities of selective bias, detection bias, performance bias and so on. Second, due to differences in the doses and timing of administration, we did not use subgroup analysis for the administration doses. To a certain extent, it affected the strength of the system review.

CONCLUSIONS

Our findings demonstrate that perioperative administration of dexmedetomidine in children undergoing CLP repair efficiently decreases pain, EA, and respiratory adverse events. However, standardized usage and dosage need further investigation, and larger rigorous studies need to be included.

Author Contributions

LP, YG and XL helped read and screen abstracts and titles of potentially relevant studies. JL, FL and XL helped read the retained papers and were responsible for extracting data and assessing their quality independently. DL helped design the study, conduct the study, analyse the data, and write the manuscript. JQ helped revise the paper with language. CH and CL helped design the study, conduct the study, analyse the data, and revise the manuscript. All authors contributed to conceptualize ideas, interpret findings and reviewed drafts of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval

Ethics approval to collect the patients' data was not required by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University.

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

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Figure captions:

Figure 1: Flow diagram of the literature search strategy

Figure 2: Risk of bias of the included studies.

Figure 3: Perioperative dexmedetomidine versus control groups for emergence agitation (EA). CI: confidence interval; RR: risk ratio.

Table1 Characteristics of the included randomized-controlled trials.

Study (year)	Country	Language	Age (month/year)	Other anesthetic agents	Administration method	Comparison	Outcomes
Mostafa 2020[12]	Egypt	English	1-5y	Sevoflurane, fentanyl, propofol	perineural	Dex(n=15): 0.5ug/kg Control(n=15): saline	the incidence of need for rescue analgesia
El-Emam 2019[13]	Egypt	English	3-6m	Sevoflurane, fentanyl, rocuronium	perineural	Dex(n=50): 0.5ug/kg Control(n=50): 0.1mg/kg DA	the incidence of PONV
Obayah 2010[14]	Egypt	English	11.7±2.4m 12±2.7m	Sevoflurane	perineural	Dex(n=15): 1ug/kg Control(n=15): saline	the incidence of PONV, need for rescue analgesia
Peng 2015[15]	China	English	3-24m	Sevoflurane, fentanyl, propofol, cisatracurium, remifentanil	intravenous	Dex(n=20): 0.8ug/kg/min (continuous intravenous infusion after induction) Control(n=20): saline	the incidence of EA, PONV, airway spasm
Boku	Japan	English	10-14m	Sevoflurane,	intravenous	Dex(n=35): 6ug/kg/h (10	the incidence of

2015[16]				fentanyl, rocuronium		min before the end of the surgery for 10 min) +0.4ug/kg/h (continuous intravenous infusion until 5min before extubate) Control(n=35): saline	desaturation
Surana 2017[17]	India	English	6m-12y	Sevoflurane, fentanyl, glycopyrrolate, vecuronium, isoflurane	intravenous	Dex(n=30):1ug/kg+0.5ug/kg/h(continuous intravenous infusion) Control(n=30): 0.05 mg/kg midazolam+saline(continuous intravenous infusion)	the incidence of need for rescue analgesia, PONV, desaturation, hypotension, bradycardia
Luo 2017[18]	China	English	1-5y	Sevoflurane, remifentanil	intravenous	Dex(n=50):0.5ug/kg (prior to induction of anesthesia) Control(n=50): saline	the incidence of EA, need for rescue analgesia, PONV, breath-holding, postoperative bleeding
Mei 2014[19]	China	Chinese	8m-3y	Sevoflurane, morphine	intravenous	Dex(n=30):0.5ug/kg (30min before surgery finish for	the incidence of EA, PONV, breath-holding,

						10min) Control(n=30): saline	cough, desaturation, airway spasm
Xiao 2012[20]	China	Chinese	1.22±0.22y 1.26±0.24y 1.25±0.23y	Sevoflurane, vecuronium, propofol,	intravenous	Dex(n=18):2ug/kg (during induction) +0.5ug/kg/h (continuous intravenous infusion after intubation) Control 1(n=18):2mg/kg (during induction) +0.5mg/kg/h (continuous intravenous infusion after intubation) ketamine Control 2(n=18):3ug/kg (during induction) + 1ug/kg (intermittent administration twice) fentanyl	the incidence of EA, PONV, desaturation
Xi 2012[21]	China	Chinese	1-3y	Sevoflurane, midazolam propofol, cisatracurium, fentanyl	intravenous	Dex(n=15):1ug/kg (30min before surgery finish for10min) Control(n=15): saline	the incidence of EA, breath-holding, desaturation, airway spasm

Yun 2016[22]	China	Chinese	6m-3y	Sevoflurane, propofol, succinylcholine	intranasal	Dex(n=60):2ug/kg (30min before surgery finish) Control(n=60): saline	the incidence of EA
Ju 2013[23]	China	Chinese	4m-3y	Propofol, cisatracurium, fentanyl sevoflurane, remifentanil	intravenous	Dex(n=40):0.5ug/kg (10min before surgery start for 10min) Control(n=40): saline	the incidence of EA, need for rescue analgesia, PONV, Desaturation
Jun 2018[24]	China	Chinese	1.71±0.61y 1.74±0.62y	Sevoflurane, propofol, rocuronium, sufentanil	intravenous	Dex(n=110):0.5ug/kg/h (20min before surgery finished) Control(n=110): saline	the incidence of EA, hypotension, Bradycardia, postoperative bleeding

dexmedetDA dexamethasoneagitation; PONV: postoperative nausea and vomiting.

Table 2 Individual Randomized Controlled Trial Methodological Quality.

Study (year)	Adequate sequence generation	Allocation concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Mostafa2020[12]	yes	?	yes	yes	yes	yes	yes
El-Emam2019[13]	yes	yes	No	yes	yes	No	yes
Obayah2010[14]	?	yes	No	No	yes	yes	yes
Peng2015[15]	yes	yes	No	No	No	No	yes
Boku2015[16]	yes	?	yes	yes	yes	?	yes
Surana2017[17]	yes	yes	yes	yes	yes	yes	yes
Luo2017[18]	yes	?	yes	yes	yes	yes	No
Mei2014[19]	yes	?	No	No	yes	yes	yes
Xiao2012[20]	No	?	No	No	yes	yes	yes
Xi2012[21]	?	?	No	No	yes	No	yes
Yun2016[22]	yes	?	yes	No	yes	yes	yes
Ju2013[23]	?	?	No	No	yes	yes	yes
Jun2018[24]	yes	?	No	No	yes	No	yes

Yes=low risk of bias; No=high risk of bias; ?=unclear risk of bias.

Table 3 Summary of findings for the main outcomes

Dexmedetomidine for cleft lip and palate repair						
Patient or population: patients with cleft lip and palate repair **Settings:** surgery **Intervention:** Dexmedetomidine						
Outcomes	**Illustrative comparative risks* (95% CI)** Assumed risk **Control**	 Corresponding risk **Dexmedetomidine**	**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Emergence agitation	**Study population**		**RR 0.19**	684	⊕⊕⊖⊖	
	458 per 1000	**87 per 1000** (46 to 165)	(0.10 to 0.36)	(8 studies)	**low**[1,2,3,4,5]	
Respiratory adverse events	**Study population**		**RR 0.49**	794	⊕⊕⊕⊖	
	103 per 1000	**50 per 1000** (32 to 80)	(0.31 to 0.78)	(8 studies)	**moderate**[1,6]	
The need for postoperative rescue analgesics	**Study population**		**RR 0.27**	293	⊕⊕⊕⊖	

	592 per 1000	**160 per 1000** (59 to 432)	(0.1 to 0.73)	(5 studies)	**moderate**[1,2,6]
Cardiovascular adverse events	**Study population**		**RR 0.83** (0.52 to 1.31)	880 (3 studies)	⊕⊕⊕⊖ **moderate**[1]
	105 per 1000	**87 per 1000** (55 to 138)			
Postoperative Nausea and vomiting	**Study population**		**RR 0.92** (0.47 to 1.80)	524 (8 studies)	⊕⊕⊖⊖ **low**[1]
	63 per 1000	**58 per 1000** (30 to 113)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] Allocation concealment and/or blinding of outcome assessors unclear/inadequate in 50% or more of the included studies

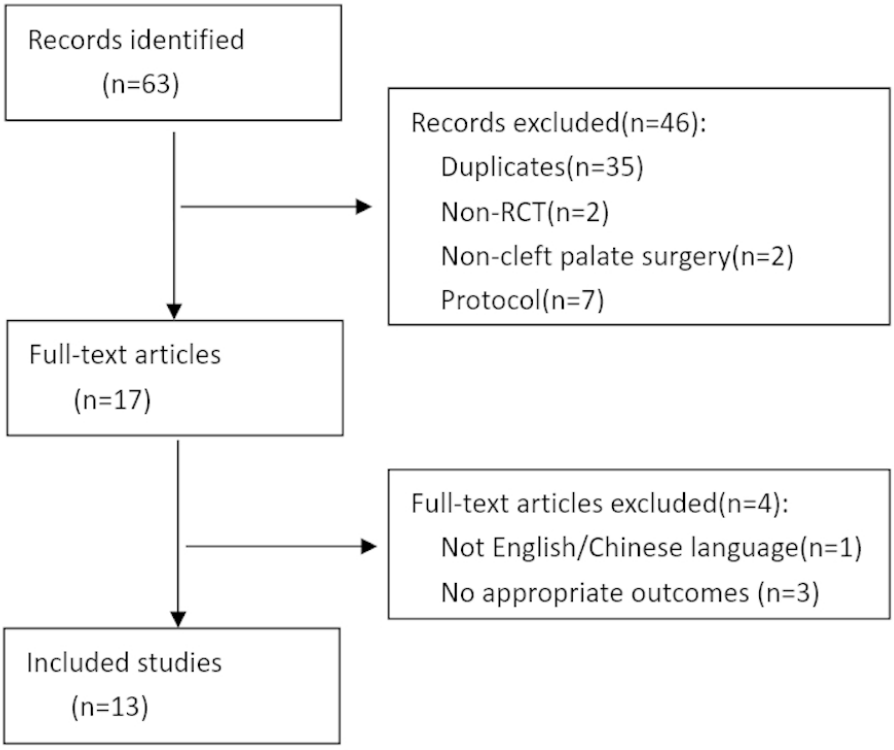
[2] Significant heterogeneity (I 2 > 50%) is partially explained by different administration method ,dose and comparators.

[3] Use of several different scoring criterias to evaluate emergence agitation.

[4] a dose response gradient was present

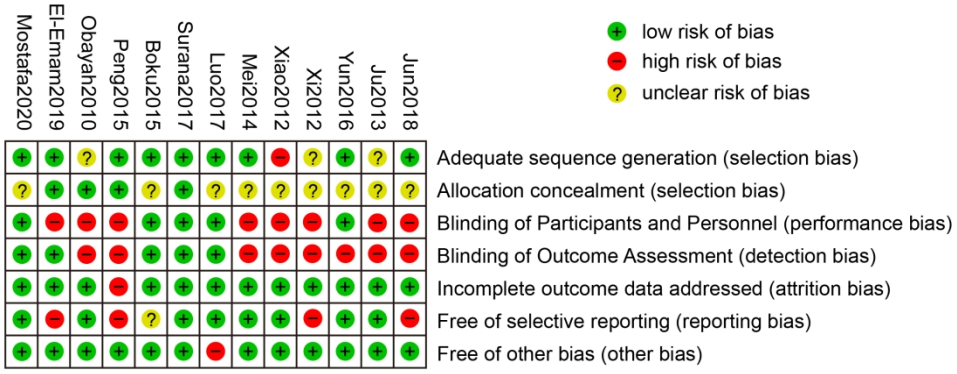
[5] RR >5 or <0.2

[6] RR >2 or <0.5



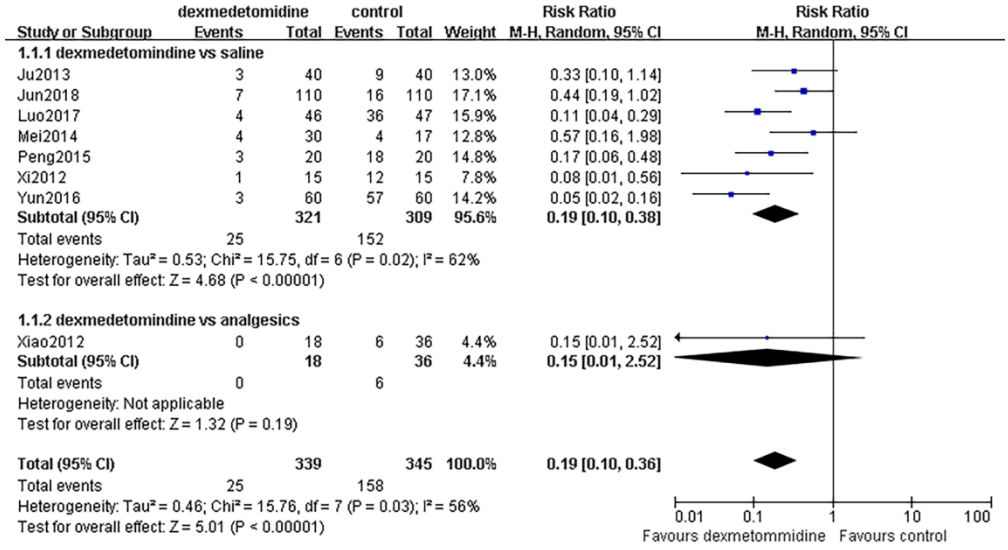
Flow diagram of the literature search strategy

82x73mm (300 x 300 DPI)



Risk of bias of the included studies.

210x86mm (300 x 300 DPI)



Perioperative dexmedetomidine versus control groups for emergence agitation (EA). CI: confidence interval; RR: risk ratio.

205x114mm (300 x 300 DPI)

#1 dexmedetomidine [MeSH Terms]

#2 "cleft palate"[All Fields] OR "lip palate"[All Fields] OR "cleft palate and lip"[All Fields]

#3 infant or children or pediatric patient [All Fields]

#4 randomized controlled trial [All Fields]

#5 #1 and #2 and #3 and #4

Risk of bias

Mostafa2020[12] (ClinicalTrials.gov ID: NCT03412474).

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated program of random numbers
Allocation concealment (selection bias)	unclear	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the doctors (investigators) nor the patients' guardians or even the children themselves were aware of the group al- location and the drug received. One anesthesiologist not involved in the block implementation or the data collection, prepared all the study solutions.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	While a third, blinded to the previous protocol, was responsible only for data collection.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 80 patients
Other bias	Low risk	Groups well balanced

El-Emam2019[13] Clinical Trials.gov (NCT03480607)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	computer-generated randomization numbers
Allocation concealment (selection bias)	Low risk	a closed-seal envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	The principal investigator prepared the drug and performed the block
Blinding of outcome assessment (detection bias) All outcomes	Low risk	the person observing and recording the parameters was blinded to the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	High risk	The primary outcome was to compare both groups regarding time to first rescue analgesic, while the primary outcomes in the pre-registration site were postoperative FLACC scale and postoperative sedation score.
Other bias	Low risk	Groups well balanced

Obayah2010[14]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly allocated", no details
Allocation concealment (selection bias)	Low risk	The randomization was achieved by the opening of a sealed envelope by the attending physician
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 30 patients
Other bias	Low risk	Groups well balanced

Peng2015[15] Chinese Clinical Trial Register (ChiCTR-TRC-13003865).

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly divided with a computer-generated sequence of numbers
Allocation concealment (selection bias)	Low risk	a sealed envelop
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	High risk	The actual sample was 40 while the planned sample in the pre-registration site was 60.
Selective reporting (reporting bias)	High risk	The primary outcome was to compare both groups regarding emergence agitation and time about recovery parameters while the primary outcomes in the pre-registration site were heart rate and blood pressure.
Other bias	Low risk	Groups well balanced

Boku2015[16] (UMIN 000009869) http://upload.umin.ac.jp.

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated random number table
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The patient' s parents and the attending anesthesiologist were blinded to the group allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data for each patient were obtained by the blinded anesthesiologist.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Do not get the protocol
Other bias	Low risk	Groups well balanced

Surana2017[17]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a computer-generated randomized chart
Allocation concealment (selection bias)	Low risk	The random group assignments were enclosed in a sealed opaque envelope
Blinding of participants and personnel (performance bias) All outcomes	Low risk	the surgeons, the patients, and the anesthesiologist in the post-anesthesia care unit (PACU) were all blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data was recorded by a blinded observer.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 60 patients
Other bias	Low risk	Groups well balanced

Luo2017[18]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a computer-generated table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All pharmacological agents used in the present study were prepared and administrated by the anesthesiologists who were blinded to the details of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pediatric Anesthesia Emergence Delirium and CHIPPS scores were documented by a well-trained PACU nurse who was blinded to the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 patients from group DS and 3 patients from group SF were excluded from the analysis
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 93 patients
Other bias	High risk	Groups well balanced. Not in intention-to-treat: Of the 100 patients admitted to the study, 7 were later excluded by the authors for the reasons listed in table II, leaving data from 93 patients for consideration

Mei2014[19]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a table of random numbers, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 60 patients
Other bias	Low risk	Groups well balanced.

Xiao2012[20]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	randomized according to the operation time sequence
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 54 patients
Other bias	Low risk	Groups well balanced.

Xi2012[21]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random mentioned, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	High risk	Lack of complications, such as postoperative hoarseness, nausea and vomiting
Other bias	Low risk	Groups well balanced.

Yun2016[22]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	a table of random numbers, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A blinded anesthesia nurse prepared and administrated drugs
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 120 patients
Other bias	Low risk	Groups well balanced.

Ju2013[23]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentioned random, no detail
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	Low risk	The authors provided results for all measurements for 80 patients
Other bias	Low risk	Groups well balanced.

Jun2018[24]

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Compute randomized
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not mentioned.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not mentioned.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up.
Selective reporting (reporting bias)	High risk	The secondary outcomes were to compare both groups regarding extubation time and incision bleeding which were not mentioned in method.
Other bias	Low risk	Groups well balanced.

outcomes	study	Begg's Test
EA	**7**	**0.086**
PONV	**8**	**0.060**
Respiratory adverse events	**8**	**0.230**
Cardiovascular adverse events	**2**	–
The need for postoperative rescue analgesics	**5**	**0.462**

EA:

	Dexmedetomidine group		Control group	
study	events	Total	events	total
Ju2013	0	40	0	40
Luo2017	4	50	4	50
Mei2014	0	30	1	30
Obayah2010	4	15	3	15
Peng2015	1	20	2	20
Surana2017	0	30	0	30
Xiao2012	1	18	2	18

Begg's test

adj. Kendall's Score (P-Q) = -8
Std. Dev. of Score = 4.08
Number of Studies = 5
z = -1.96
Pr > |z| = 0.050
z = 1.71 (continuity corrected)
Pr > |z| = 0.086 (continuity corrected)

PONV

	Dexmedetomidine group		Control group	
study	events	Total	events	Total
Ju2013	0	40	0	40
Luo2017	4	50	4	50
Mei2014	0	30	1	30
Obayah2010	4	15	3	15
Peng2015	1	20	2	20
Surana2017	0	30	0	30
Xiao2012	1	18	2	18
El-Emam 2019	4	50	3	50

Begg's test

adj. Kendall's Score (P-Q) = -11
Std. Dev. of Score = 5.32
Number of Studies = 6
z = -2.07
Pr > |z| = 0.039
z = 1.88 (continuity corrected)
Pr > |z| = 0.060 (continuity corrected)

Respiratory adverse events

	Dexmedetomidine group		Control group	
study	events	Total	study	events
Boku2015	2	35	2	35
Ju2013	0	40	4	40
Luo2017	2	30	4	30
Mei2014	13	50	25	50
Peng2015	1	20	3	20
Surana2017	0	30	0	30
Xiao2012	0	18	2	36
Xi2012	1	30	5	30

Begg's test

adj. Kendall's Score (P-Q) = -9
Std. Dev. of Score = 6.66
Number of Studies = 7
z = -1.35
Pr > |z| = 0.176
z = 1.20 (continuity corrected)
Pr > |z| = 0.230 (continuity corrected)

The need for postoperative rescue analgesics

	Dexmedetomidine group		Control group	
study	events	Total	study	events
Mostafa 2020	0	15	15	15
Obayah2010	10	15	15	15
Luo2017	5	46	29	47
Surana2017	7	30	20	30
Ju2013	2	40	8	40

Begg's test

adj. Kendall's Score (P-Q) = -4
Std. Dev. of Score = 4.08
Number of Studies = 5
z = -0.98
Pr > |z| = 0.327
z = 0.73 (continuity corrected)
Pr > |z| = 0.462 (continuity corrected)

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1-2
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			3-4
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			5
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			6-8
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	--
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-7

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	--
RESULTS			8-12,21-27
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8-9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9,21-24
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,25
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9,10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9-10,26-27
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	--
DISCUSSION			12-15
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14,15
FUNDING			15
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097