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Efficaciousness 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, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP) and Wanfang (up to October 2020). Studies in languages other than English and Chinese were excluded.

Eligibility criteria for selecting studies Randomised 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% 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 with 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 higher-quality RCTs is needed.

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 cleft lip and palate 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.

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 randomised controlled trials (RCTs) 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 and the Cochrane Review Method was used.[11]

Search strategy and selection criteria

We searched the following databases from inception to 1 October 2020: PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (VIP) and Wanfang. The main keywords used were the following: dexmedetomidine, 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 online supplemental file 1).

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, randomised 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); and (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 V.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 V.5.1, https://training.cochrane.org/). We reported binary data as a risk ratio (RR) with a 95% CI. The X^2 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-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 1040 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 figure 1.

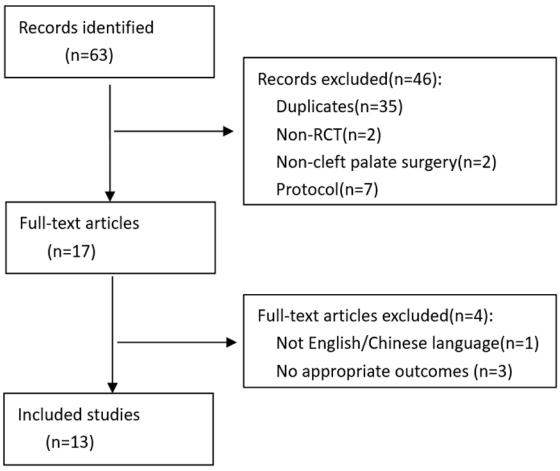

Figure 1 Flow diagram of the literature search strategy. RCT, randomised controlled trials.

Description of studies

The included studies were undertaken from 2012 to 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 summarised in table 1.

Risk of bias across studies

The risk of bias of included studies can be found in table 2, figure 2 and online supplemental 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 summarised in table 2, figure 2 and online supplemental 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 (online supplemental 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, Paediatric Anaesthesia Emergence Delirium Scale or Aono's 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[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) (figure 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 administration,[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 hours (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

Table 1 Characteristics of the included randomised-controlled trials

Study (year)	Country	Language	Age (month/year)	Other anaesthetic agents	Administration method	Comparison	Outcomes
Mostafa *et al* (2020)[12]	Egypt	English	1–5 years	Sevoflurane, fentanyl, propofol	Perineural	Dex (n=15): 0.5 µg/kg Control (n=15): saline	The incidence of need for rescue analgesia
El-Emam and El Motlb (2019)[13]	Egypt	English	3–6 months	Sevoflurane, fentanyl, rocuronium	Perineural	Dex (n=50): 0.5 µg/kg Control (n=50): 0.1 mg/kg DA	The incidence of PONV
Obayah *et al* (2010)[14]	Egypt	English	11.7±2.4 months 12±2.7 months	Sevoflurane	Perineural	Dex (n=15): 1 µg/kg Control (n=15): saline	The incidence of PONV and need for rescue analgesia
Peng and Zhang (2015)[15]	China	English	3–24 months	Sevoflurane, fentanyl, propofol, cisatracurium, remifentanil	Intravenous	Dex (n=20): 0.8 µg/kg/min (continuous intravenous infusion after induction) Control (n=20): saline	The incidence of EA, PONV and airway spasm
Boku *et al* (2015)[16]	Japan	English	10–14 months	Sevoflurane, fentanyl, rocuronium	Intravenous	Dex (n=35): 6 µg/kg/hour (10 min before the end of the surgery for 10 min)+0.4 µg/kg/hour (continuous intravenous infusion until 5 min before extubate) Control (n=35): saline	The incidence of desaturation
Surana *et al* (2017)[17]	India	English	6 months to 12 years	Sevoflurane, fentanyl, glycopyrrolate, vecuronium, isoflurane	Intravenous	Dex (n=30): 1 µg/kg+0.5 µg/kg/hour (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 and bradycardia
Luo *et al* (2017)[18]	China	English	1–5 years	Sevoflurane, remifentanil	Intravenous	Dex (n=50): 0.5 µg/kg (prior to induction of anaesthesia) Control (n=50): saline	The incidence of EA, need for rescue analgesia, PONV, breath-holding and postoperative bleeding
Mei *et al* (2014)[19]	China	Chinese	8 months to 3 years	Sevoflurane, morphine	Intravenous	Dex (n=30): 0.5 µg/kg (30 min before surgery finish for 10 min) Control (n=30): saline	The incidence of EA, PONV, breath-holding, cough, desaturation and airway spasm
Xiao *et al* (2012)[20]	China	Chinese	1.22±0.22 years 1.26±0.24 years 1.25±0.23 years	Sevoflurane, vecuronium, propofol,	Intravenous	Dex (n=18): 2 µg/kg (during induction)+0.5 µg/kg/hour (continuous intravenous infusion after intubation) Control 1 (n=18): 2 mg/kg (during induction)+0.5 mg/kg/hour (continuous intravenous infusion after intubation) ketamine Control 2 (n=18): 3 µg/kg (during induction)+1 µg/kg (intermittent administration twice) fentanyl	The incidence of EA, PONV and desaturation
Xi *et al* (2012)[21]	China	Chinese	1–3 years	Sevoflurane, midazolam propofol, cisatracurium, fentanyl	Intravenous	Dex (n=15): 1 µg/kg (30 min before surgery finish for 10 min) Control (n=15): saline	The incidence of EA, breath-holding, desaturation and airway spasm
Yun *et al* (2016)[22]	China	Chinese	6 months to 3 years	Sevoflurane, propofol, succinylcholine	Intranasal	Dex (n=60): 2 µg/kg (30 min before surgery finish) Control (n=60): saline	The incidence of EA
Ju *et al* (2013)[23]	China	Chinese	4 months to 3 years	Propofol, cisatracurium, fentanyl sevoflurane, remifentanil	Intravenous	Dex (n=40): 0.5 µg/kg (10 min before surgery start for 10 min) Control (n=40): saline	The incidence of EA, need for rescue analgesia, PONV and desaturation
Jun *et al* (2018)[24]	China	Chinese	1.71±0.61 years 1.74±0.62 years	Sevoflurane, propofol, rocuronium, sufentanil	Intravenous	Dex (n=110): 0.5 µg/kg/hour (20 min before surgery finished) Control (n=110): saline	The incidence of EA, hypotension, bradycardia and postoperative bleeding

DA, dexamethasone; Dex, dexmedetomidine; EA, emergence agitation; PONV, postoperative nausea and vomiting.

Table 2 Individual randomised 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
Mostafa *et al* (2020)[12]	Yes	?	Yes	Yes	Yes	Yes	Yes
El-Emam and El Motlb (2019)[13]	Yes	Yes	No	Yes	Yes	No	Yes
Obayah *et al* (2010)[14]	?	Yes	No	No	Yes	Yes	Yes
Peng *et al* (2015)[15]	Yes	Yes	No	No	No	No	Yes
Boku *et al* (2015)[16]	Yes	?	Yes	Yes	Yes	?	Yes
Surana *et al* (2017)[17]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Luo *et al* (2017)[18]	Yes	?	Yes	Yes	Yes	Yes	No
Mei *et al* (2014)[19]	Yes	?	No	No	Yes	Yes	Yes
Xiao *et al* (2012)[20]	No	?	No	No	Yes	Yes	Yes
Xi *et al* (2012)[21]	?	?	No	No	Yes	No	Yes
Yun *et al* (2016)[22]	Yes	?	Yes	No	Yes	Yes	Yes
Ju *et al* (2013)[23]	?	?	No	No	Yes	Yes	Yes
Jun *et al* (2018)[24]	Yes	?	No	No	Yes	No	Yes

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

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 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

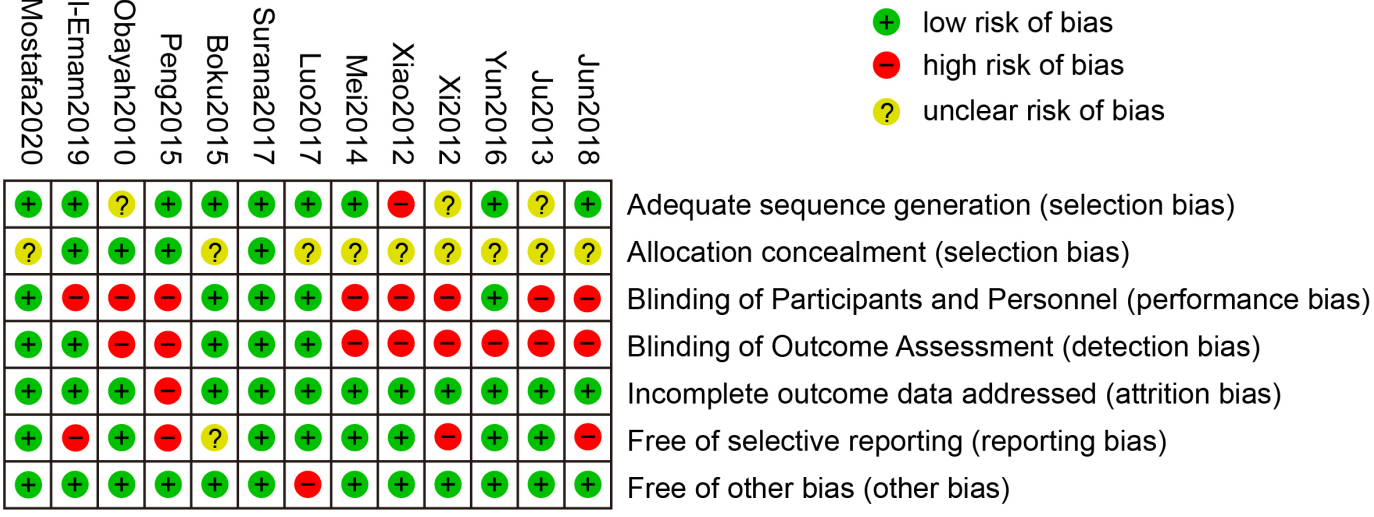

Figure 2 Risk of bias of the included studies.

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						
	Illustrative comparative risks* (95% CI)					
	Assumed risk	**Corresponding risk**				
Outcomes	**Control**	**Dexmedetomidine**	**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
Emergence agitation	Study population 458 per 1000	87 per 1000 (46 to 165)	RR 0.19 (0.10 to 0.36)	684 (eight studies)	⊕⊕⊖⊖ Low†‡§¶**	
Respiratory adverse events	Study population 103 per 1000	50 per 1000 (32 to 80)	RR 0.49 (0.31 to 0.78)	794 (eight studies)	⊕⊕⊕⊖ Moderate†††	
The need for postoperative rescue analgesics	Study population 592 per 1000	160 per 1000 (59 to 432)	RR 0.27 (0.1 to 0.73)	293 (five studies)	⊕⊕⊕⊖ Moderate†‡††	
Cardiovascular adverse events	Study population 105 per 1000	87 per 1000 (55 to 138)	RR 0.83 (0.52 to 1.31)	880 (three studies)	⊕⊕⊕⊖ Moderate†	
Postoperative nausea and vomiting	Study population 63 per 1000	58 per 1000 (30 to 113)	RR 0.92 (0.47 to 1.80)	524 (eight studies)	⊕⊕⊖⊖ Low†	

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.
*The basis for the assumed risk (eg, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
†Allocation concealment and/or blinding of outcome assessors unclear/inadequate in 50% or more of the included studies.
‡Significant heterogeneity (I^2 >50%) is partially explained by different administration method, dose and comparators.
§Use of several different scoring criteria to evaluate emergence agitation.
¶A dose–response gradient was present.
**RR >5 or <0.2.
††RR >2 or <0.5.
GRADE, Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio.

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 the US Food and Drug Administration for administration in children, it has been an authorised drug in Europe since September 2011.[25] It is increasingly used in the paediatric 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

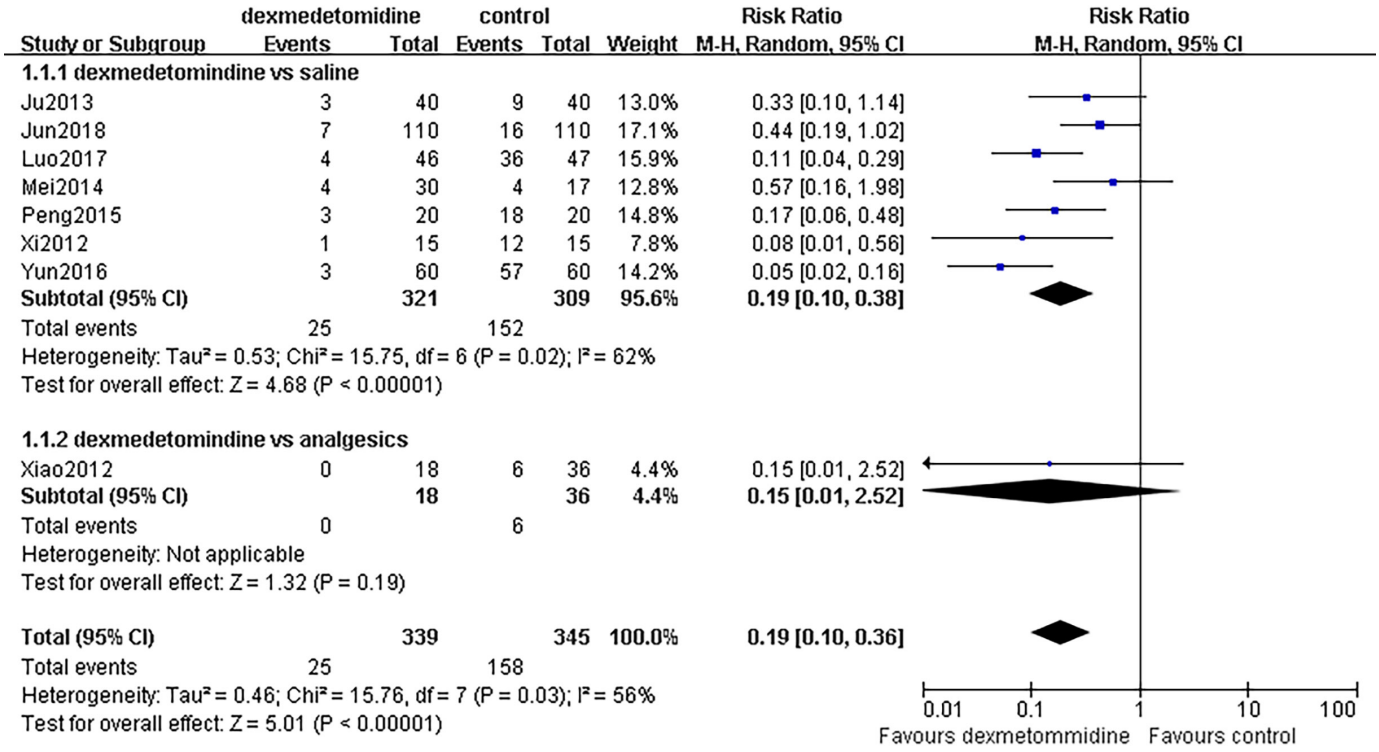

Figure 3 Perioperative dexmedetomidine versus control groups for emergence agitation.

compared with 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 and 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 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 administered dexmedetomidine as a loading dose over 10 min and followed by a maintenance infusion of 0.5 µg/kg/hour until the last suture was applied, while the other study administrated dexmedetomidine as a maintenance infusion of 0.5 µg/kg/hour 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 with 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 because 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, standardised usage and dosage need further investigation, and larger rigorous studies need to be included.

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Contributors 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 conceptualise ideas, interpret findings and reviewed drafts of the manuscript.

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#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)