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

Dengfeng Liu,1 Li Pan,1 Yin Gao,1 Jiefan Liu,1 Feng Li,1 Xiangwei Li,2 Jiale Quan,3,4 Congcong Huang,3,4 Chunwei Lian 3,4

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; I²=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; I²=84%) and a lower incidence of respiratory adverse events (RR, 0.49; 95% CI 0.31 to 0.78; p=0.003; I²=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.

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-adrenoceptor 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 study8 had demonstrated that dexmedetomidine was helpful as a valuable adjunct for multiple applications and was increasingly used in paediatric anaesthesia settings. A meta-analysis9 recently showed that perioperative administration of
dexametomidine can provide pain and agitation relief without side effects in children undergoing adenotonsillectomy. Another meta-analysis found that intranasal dexametomidine 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 dexametomidine in children undergoing CLP repair.

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

METHODS
We evaluated the efficacy and safety of dexametomidine 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.

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: dexametomidine, 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: dexametomidine 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 X² test (Mantel-Haenszel method) was used to assess the heterogeneity between studies. An I² \(>50\%\) 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. The flow diagram of the literature search strategy is shown in figure 1.
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 trials15 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 saline15 18 19 21–24 (RR, 0.19; 95% CI 0.10 to 0.38; p<0.00001; I²=62%) and all control groups15 18–24 (RR, 0.19; 95% CI 0.10 to 0.36; p<0.00001; I²=56%). We found that different administration methods of dexmedetomidine increased the clinical heterogeneity. Excluding the 2016 study by Yun22 (intranasal administration), intravenous dexmedetomidine administration showed a significant evidence of reduced EA when compared with saline15 18 19 21 23 24 (RR, 0.24; 95% CI 0.13 to 0.44; p<0.00001; I²=40%) and when compared with all control groups15 18–24 (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 fentanyl20 (RR, 0.14; 95% CI 0.01 to 2.58; p=0.19) and intravenous ketamine20 (RR, 0.14; 95% CI 0.01 to 2.58; p=0.19) (figure 3).

The need for postoperative rescue analgesics

Five studies12 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; I²=84%). In contrast to the two studies that used perineural administration12 14 intravenous dexmedetomidine administration17 18 23 showed a significant analgesic effect when compared with saline (RR, 0.26; 95% CI 0.16 to 0.44; p<0.00001; I²=0%). Subgroup analysis showed that there was no difference when perineural dexmedetomidine12 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 studies15–21 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

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Country</th>
<th>Language</th>
<th>Age (month/year)</th>
<th>Other anaesthetic agents</th>
<th>Administration method</th>
<th>Comparison</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mostafa et al (2020)</td>
<td>Egypt</td>
<td>English</td>
<td>1–5 years</td>
<td>Sevoflurane, fentanyl, propofol</td>
<td>Perineural</td>
<td>Dex (n=15): 0.5 μg/kg Control (n=15): saline</td>
<td>The incidence of need for rescue analgesia</td>
</tr>
<tr>
<td>El-Emam and El Motlib (2019)</td>
<td>Egypt</td>
<td>English</td>
<td>3–6 months</td>
<td>Sevoflurane, fentanyl, rocuronium</td>
<td>Perineural</td>
<td>Dex (n=50): 0.5 μg/kg Control (n=50): 0.1 mg/kg DA</td>
<td>The incidence of PONV</td>
</tr>
<tr>
<td>Obaya et al (2010)</td>
<td>Egypt</td>
<td>English</td>
<td>11.7±2.4 months</td>
<td>Sevoflurane, fentanyl, propofol</td>
<td>Perineural</td>
<td>Dex (n=15): 1 μg/kg Control (n=15): saline</td>
<td>The incidence of rescue analgesia, PONV, and desaturation</td>
</tr>
<tr>
<td>Peng and Zhang (2019)</td>
<td>China</td>
<td>English</td>
<td>3–24 months</td>
<td>Sevoflurane, fentanyl, rocuronium, propofol, cisatracurium, remifentanil</td>
<td>Intravenous</td>
<td>Dex (n=20): 0.8 μg/kg/min (continuous intravenous infusion after induction) Control (n=20): saline</td>
<td>The incidence of EA, PONV and airway spasm</td>
</tr>
<tr>
<td>Boku et al (2015)</td>
<td>Japan</td>
<td>English</td>
<td>10–14 months</td>
<td>Sevoflurane, fentanyl, rocuronium</td>
<td>Intravenous</td>
<td>Dex (n=35): 6 μg/kg/hour (10 min before the end of the surgery) +0.4 μg/kg/hour (continuous intravenous infusion until 5 min before extubate) Control (n=35): saline</td>
<td>The incidence of desaturation</td>
</tr>
<tr>
<td>Surana et al (2017)</td>
<td>India</td>
<td>English</td>
<td>6 months to 12 years</td>
<td>Sevoflurane, fentanyl, glycopyrrolate, vecuronium, isoflurane</td>
<td>Intravenous</td>
<td>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)</td>
<td>The incidence of need for rescue analgesia, PONV, desaturation, hypotension and bradycardia</td>
</tr>
<tr>
<td>Luo et al (2017)</td>
<td>China</td>
<td>English</td>
<td>1–5 years</td>
<td>Sevoflurane, remifentanil</td>
<td>Intravenous</td>
<td>Dex (n=50): 0.5 μg/kg (prior to induction of anaesthesia) Control (n=50): saline</td>
<td>The incidence of EA, need for rescue analgesia, PONV, breath-holding and postoperative bleeding</td>
</tr>
<tr>
<td>Mei et al (2014)</td>
<td>China</td>
<td>Chinese</td>
<td>8 months to 3 years</td>
<td>Sevoflurane, fentanyl, propofol, vecuronium</td>
<td>Intravenous</td>
<td>Dex (n=30): 0.5 μg/kg (30 min before surgery finish for 10 min) Control (n=30): saline</td>
<td>The incidence of EA, PONV, breath-holding, cough, desaturation and airway spasm</td>
</tr>
<tr>
<td>Xiao et al (2012)</td>
<td>China</td>
<td>Chinese</td>
<td>1.22±0.22 years</td>
<td>Sevoflurane, vecuronium, propofol,</td>
<td>Intravenous</td>
<td>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</td>
<td>The incidence of EA, PONV and desaturation</td>
</tr>
<tr>
<td>Xi et al (2012)</td>
<td>China</td>
<td>Chinese</td>
<td>1–3 years</td>
<td>Sevoflurane, midazolam propofol, vecuronium, fentanyl</td>
<td>Intravenous</td>
<td>Dex (n=15): 1 μg/kg (30 min before surgery finish for 10 min) Control (n=15): saline</td>
<td>The incidence of EA, breath-holding, desaturation and airway spasm</td>
</tr>
<tr>
<td>Yun et al (2016)</td>
<td>China</td>
<td>Chinese</td>
<td>6 months to 3 years</td>
<td>Sevoflurane, propofol, suxamethonium</td>
<td>Intranasal</td>
<td>Dex (n=60): 2 μg/kg (30 min before surgery finish) Control (n=60): saline</td>
<td>The incidence of EA</td>
</tr>
<tr>
<td>Ju et al (2013)</td>
<td>China</td>
<td>Chinese</td>
<td>4 months to 3 years</td>
<td>Propofol, vecuronium, fentanyl, succinylcholine</td>
<td>Intravenous</td>
<td>Dex (n=40): 0.5 μg/kg (10 min before surgery start for 10 min) Control (n=40): saline</td>
<td>The incidence of EA, need for rescue analgesia, PONV and desaturation</td>
</tr>
<tr>
<td>Jun et al (2018)</td>
<td>China</td>
<td>Chinese</td>
<td>1.71±0.61 years</td>
<td>Sevoflurane, fentanyl, propofol, rocuronium, sufentanil</td>
<td>Intravenous</td>
<td>Dex (n=110): 0.5 μg/kg/hour (20 min before surgery finished) Control (n=110): saline</td>
<td>The incidence of EA, hypotension, bradycardia and postoperative bleeding</td>
</tr>
</tbody>
</table>

DA, dexamethasone; Dex, dexmedetomidine; EA, emergence agitation; PONV, postoperative nausea and vomiting.
adverse events than saline administration (RR, 0.49; 95% CI 0.31 to 0.78; p=0.003; I²=0%). Only one study (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 hypotension (RR, 1.18; 95% CI 0.61 to 2.28; p=0.62), bradycardia (RR, 0.78; 95% CI 0.30 to 2.07; p=0.62) or postoperative bleeding (RR, 0.45; 95% CI 0.17 to 1.15; p=0.09; I²=0%).

Postoperative nausea and vomiting
Eight trials including 524 patients reported the incidence of PONV. Patients who received dexmedetomidine administration experienced no statistically significant increase in PONV when compared with saline (RR, 1.18; 95% CI 0.61 to 2.28; p=0.62) or any other control group (RR, 0.95; 95% CI 0.41 to 2.19; p=0.91; I²=0%) and when compared with all control groups (RR, 0.96; 95% CI 0.48 to 1.90; p=0.90; I²=0%). Subgroup analysis showed that there was also no difference when perineural

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Adequate sequence generation</th>
<th>Allocation concealment</th>
<th>Blinding of participants and personnel</th>
<th>Blinding of outcome assessment</th>
<th>Incomplete outcome data addressed</th>
<th>Free of selective reporting</th>
<th>Free of other bias</th>
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<tr>
<td>Mostafa et al (2020)</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<td>El-Emam and El Motib (2019)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<td>Obayah et al (2010)</td>
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<td>No</td>
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<td>No</td>
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<td>Boku et al (2015)</td>
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<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Xiao et al (2012)</td>
<td>No</td>
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<td>Xi et al (2012)</td>
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<td>No</td>
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<td>Yun et al (2016)</td>
<td>Yes</td>
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<td>Ju et al (2013)</td>
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<td>No</td>
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<td>Yes</td>
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<tr>
<td>Jun et al (2018)</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>No</td>
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</table>

?, unclear risk of bias; No, high risk of bias; Yes, low risk of bias.
Table 3  Summary of findings for the main outcomes

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

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 (I² >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. Additionally, another subgroup analysis showed no difference when intravenous dexmedetomidine was compared with fentanyl (RR, 0.50; 95% CI 0.06 to 4.15; p=0.52) and ketamine (RR, 0.50; 95% CI 0.06 to 4.15; p=0.52) or when perineural dexmedetomidine was compared with dexamethasone (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. It is increasingly used in the paediatric setting for various indications such as premedication, adjunct, sedative, intraoperative analgesia and adjuvant therapy, 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 with the saline group. This was consistent with previous studies.4 6 9 10 Two recent meta-analyses26 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, 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 review29 in which dexmedetomidine intraoperative administration had no effect PONV during paediatric surgery, but it was inconsistent with a recent systematic review30 in which dexmedetomidine was superior to placebo with a reduction in the need
for an antemate 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. 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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