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Sedation for Pediatric Echocardiography in Congenital Heart Disease: Dexmedetomidine versus Chloral Hydrate

Jane Elvina Sentosa[1*], Ratna Farida Soenarto[1], Aries Perdana[1], Jefferson Hidayat[1], Aldy Heriwardito[1], Anas Alatas[1], Komang Ayu Ferdiana[1], Andy Omega[1], Azhraa Qinan Pranaya[1]

[1]Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Indonesia / Dr. Cipto Mangunkusumo National Central General Hospital, Jakarta, Indonesia
*Email: janesentosa41@gmail.com

Abstract

Background: Chloral hydrate is commonly used for paediatric transthoracic echocardiography (TTE) sedation, but safety concerns have prompted interest in alternatives. This meta-analysis compared intranasal dexmedetomidine with oral chloral hydrate for TTE sedation in children with known or suspected congenital heart disease (CHD). **Method:** This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement and was registered in PROSPERO [CRD420261376912]. PubMed/MEDLINE, Europe PMC, Cochrane CENTRAL, and ClinicalTrials.gov were searched to 30 September 2026. Risk of bias was assessed with Cochrane tools and certainty of evidence with the Grading of Recommendations Assessment, Development and Evaluation approach. Data were pooled using random-effects models, with Hartung–Knapp adjustment when ≥3 studies contributed. **Results:** Four studies (one randomised trial and three cohort studies; 1414 children, 1187 in the primary analysis) were included. Single-dose sedation success did not differ in the randomised trial (risk ratio [RR] 1.02; 95% confidence interval [CI] 0.96–1.09), in the pooled non-randomised studies (RR 1.11; 95% CI 0.71–1.73), or overall (RR 1.08; 95% CI 0.85–1.36; very low certainty). Onset time and hypoxia did not differ significantly (very low certainty); rescue dose requirement was not pooled because its definition was not comparable across studies. Recovery time was shorter with dexmedetomidine (mean difference −9.96 min; 95% CI −18.71 to −1.22; low certainty). Bradycardia was more frequent with dexmedetomidine (RR 2.32; 95% CI 1.09–4.95; very low certainty), although no study reported its treatment. **Conclusion:** In children with known or suspected CHD, the two agents showed no clear difference in TTE sedation success, whereas bradycardia was more frequent with dexmedetomidine. Given low-to-very-low certainty of evidence, neither agent can be considered superior; adequately powered randomised trials are needed.

Keywords: Chloral Hydrate, Child, Conscious Sedation, Dexmedetomidine, Echocardiography, Heart Defects, Congenital

Abstrak

Latar Belakang: *Kloral hidrat umum digunakan untuk sedasi ekokardiografi transtorakal (TTE) pada anak, tetapi kekhawatiran terkait keamanannya mendorong pencarian alternatif. Meta-analisis ini membandingkan deksmedetomidin intranasal dengan kloral hidrat oral untuk sedasi TTE pada anak dengan penyakit jantung bawaan (PJB) yang telah diketahui atau dicurigai.* ***Metode:*** *Telaah ini mengikuti pernyataan Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 dan telah diregistrasi di PROSPERO [CRD420261376912]. Pencarian dilakukan pada PubMed/MEDLINE, Europe PMC, Cochrane CENTRAL, dan ClinicalTrials.gov hingga 30 September 2026. Risiko bias dinilai menggunakan perangkat Cochrane, dan kepastian bukti dinilai dengan pendekatan Grading of Recommendations Assessment, Development and Evaluation. Data digabungkan menggunakan model efek acak, dengan penyesuaian Hartung–Knapp bila terdapat ≥3 studi.* ***Hasil:*** *Empat studi (satu uji acak terkontrol dan tiga studi kohort; 1414 anak, 1187 dalam analisis utama) diikutsertakan. Keberhasilan sedasi dosis tunggal tidak berbeda pada uji acak terkontrol (rasio risiko [RR] 1,02; interval kepercayaan [IK] 95% 0,96–1,09), pada gabungan studi nonacak (RR 1,11;*

IK 95% 0,71–1,73), maupun secara keseluruhan (RR 1,08; IK 95% 0,85–1,36; kepastian sangat rendah). Waktu awitan dan hipoksia tidak berbeda bermakna (kepastian sangat rendah); kebutuhan dosis penyelamatan tidak digabungkan karena definisinya tidak sebanding antarstudi. Waktu pemulihan lebih singkat dengan deksmedetomidin (perbedaan rerata −9,96 menit; IK 95% −18,71 hingga −1,22; kepastian rendah). Bradikardia lebih sering terjadi dengan deksmedetomidin (RR 2,32; IK 95% 1,09–4,95; kepastian sangat rendah), meskipun tidak ada studi yang melaporkan tata laksananya. ***Kesimpulan:*** *Pada anak dengan PJB yang telah diketahui atau dicurigai, kedua obat tidak menunjukkan perbedaan yang jelas dalam keberhasilan sedasi TTE, sedangkan bradikardia lebih sering terjadi dengan deksmedetomidin. Mengingat kepastian bukti yang rendah hingga sangat rendah, tidak ada obat yang dapat dianggap lebih unggul; diperlukan uji acak terkontrol dengan kekuatan statistik yang memadai.*

Kata kunci: *Anak, Deksmedetomidin, Ekokardiografi, Kloral Hidrat, Penyakit Jantung Bawaan, Sedasi Sadar*

I. INTRODUCTION

Congenital heart disease (CHD) is the most common congenital anomaly, with a reported birth prevalence of approximately 9 per 1,000 live births worldwide.[1] Children with CHD require lifelong surveillance with transthoracic echocardiography (TTE) to assess cardiac anatomy, ventricular function, pulmonary artery pressure, and post-intervention residual lesions, making TTE the primary imaging modality throughout the continuum of CHD care.[2]

Adequate TTE image quality depends on patient immobility. The 2024 American Society of Echocardiography guidelines note that procedural sedation is often needed in children younger than 3 years or with developmental challenges and recommend that centres have a sedation policy defining personnel, patient selection, contraindications, medication dosing and timing, monitoring, and documentation of sedation successes, failures, and adverse events.[2] Sedation of children with CHD also involves specific haemodynamic considerations.[3]

Oral chloral hydrate (CH) has been the most widely used sedative for non-painful paediatric diagnostic procedures for over a century, favoured for its oral route, familiarity, and low cost. However, its sedation failure rate has been reported to reach 21.8%, with congenital heart disease and oxygen dependency identified as risk factors for sedation-related complications.[4]

Dexmedetomidine (DEX), a selective alpha-2 adrenergic agonist, produces arousable sedation resembling physiological non-rapid eye movement sleep without significant respiratory depression. Intranasal dexmedetomidine is rapidly absorbed in children and is needle-free, odourless, and non-irritating to the nasal mucosa — advantages that are particularly relevant in CHD patients, who often have difficult venous access.[5]

Intranasal DEX has therefore been proposed as an alternative to CH.[6] However, existing evidence comparing intranasal DEX with oral CH has largely come from heterogeneous paediatric populations undergoing computed tomography, magnetic resonance imaging, or electroencephalography, without a dedicated analysis of children with CHD undergoing TTE. [7,8] Children with CHD may respond differently to sedatives because of labile pulmonary vascular resistance and altered vascular reactivity, so findings from the general paediatric population may not be directly applicable. Anaesthesiologists are frequently asked to provide or supervise sedation for children with CHD outside the operating room, including in the echocardiography laboratory, where the choice of agent determines not only the likelihood of a completed examination but also the monitoring and rescue plan that must be in place.[3,4] We therefore conducted a systematic review and meta-analysis to compare sedation success and safety outcomes of intranasal dexmedetomidine versus oral chloral hydrate specifically in children with known or suspected CHD undergoing TTE.

II. METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines[9] and was prospectively registered in PROSPERO [CRD420261376912]. The PROSPERO record was amended on 25 September 2026. All deviations from the originally registered protocol, with reasons, are summarised in Supplementary Table S4. The final literature search was conducted on 30 September

2026. The review was conducted from July to September 2026.

Eligibility criteria were defined using the PICO framework (Supplementary Tables S1 and S2).

We included randomised controlled trials and comparative cohort studies of children aged 0–18 years with known or suspected congenital heart disease (CHD) undergoing sedated transthoracic echocardiography (TTE) that compared intranasal dexmedetomidine as a single agent, administered by any intranasal delivery method, with oral chloral hydrate as a single agent. Studies using planned co-sedation were excluded; rescue or adjunct doses given after initial sedation failure were permitted. Studies were eligible if they reported at least one prespecified outcome.

PubMed/MEDLINE, Europe PMC, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov were searched from inception to 30 September 2026 without language restrictions. To maximise sensitivity, search strategies combined terms for dexmedetomidine and chloral hydrate only, without restriction by procedure or population; eligibility regarding TTE and CHD was assessed during screening. In PubMed, Medical Subject Headings (MeSH) were combined with free-text terms, including truncation and trade names, searched in the title and abstract fields; in Europe PMC and CENTRAL, equivalent free-text terms were searched in the title and abstract (and, in CENTRAL, keyword) fields; and ClinicalTrials.gov was searched by intervention for studies of all recruitment statuses. The complete strategy for each source is provided in Supplementary Table S5. PROSPERO was searched to identify ongoing or overlapping reviews.

Records were deduplicated and screened independently by two reviewers using a standardised, piloted Microsoft Excel form, first by title and abstract and then by full text. When more than one exclusion criterion applied, the most specific criterion was recorded. Disagreements were resolved by discussion or, if necessary, by a third reviewer. Full-text reports excluded, with reasons, are listed in Supplementary Table S6. The selection process is summarised in the PRISMA 2020 flow diagram (Fig. 1).

Two reviewers independently extracted data on study design, setting and period, population characteristics (age, weight, proportion with confirmed CHD, and proportion with cyanotic and complex CHD), intervention and comparator details (dose, delivery method, co-sedation, and rescue protocol), outcome definitions, and outcome data. Disagreements were resolved by discussion or by a third reviewer. For non-randomised studies, adjusted effect estimates (propensity-score weighted or matched) were extracted when available, and unadjusted data were extracted for sensitivity analyses. Trial registry records of included studies were reviewed. Study authors were not contacted, and data were extracted from published reports only. Because three included studies[10–12] were conducted at the same institution (Shanghai Children's Medical Center, Shanghai, China), their study periods and eligibility criteria were compared to exclude overlapping patient populations.

Risk of bias was assessed independently by two reviewers using the Cochrane Risk of Bias 2 (RoB 2) tool[13] for randomised trials, applied separately for each outcome, and the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool[14] for cohort studies. Disagreements were resolved by consensus or by a third reviewer.

Dichotomous outcomes were pooled as risk ratios (RR) and continuous outcomes as mean differences (MD), with 95% confidence intervals (CI). Given anticipated clinical and methodological heterogeneity, a random-effects model with restricted maximum-likelihood (REML) estimation of between-study variance and the Hartung–Knapp adjustment[15] was used as the primary analysis for all outcomes. Because only one randomised trial was identified, results were stratified by study design and the design-specific estimates were regarded as the principal findings; the overall estimate combining randomised and non-randomised evidence is presented for completeness and was interpreted with caution, given differences in design, adjustment for confounding, and sedation protocols. For analyses with only two studies, Hartung–Knapp adjustment was not used because of the unstable degrees-of-freedom estimation with k=2, these estimates were therefore interpreted cautiously.

Adjusted estimates from non-randomised studies were pooled as log RR with standard errors using the generic inverse-variance method. Because the propensity-weighted pseudo-population in Hu et al. was twice the original sample size, the weighted proportions were applied to the original group sizes to avoid overstating precision. Weighted proportions rather than weighted counts were used, because the weighted counts in the original report were rounded. For Saudek et al., single-dose success with chloral hydrate was defined as neither receiving a second medication nor failing sedation, because more children failed sedation (1.1%) than received a second medication (0.3%). For bradycardia and hypoxia, Hu et al. reported data only for children assessed at the completion of TTE (71 and 72 given dexmedetomidine, 62 given chloral hydrate); these denominators were used, although the missing data were unbalanced (13 children with chloral hydrate vs 2 to 3 with dexmedetomidine). When an outcome was reported at several time points, the time point closest to the procedure (completion of TTE) was used. The two dexmedetomidine arms of the three-arm trial by Miller et al. were combined into a single group to avoid a unit-of-analysis error. Medians and interquartile ranges were converted to means and standard deviations using the method of Wan et al.[16] A continuity correction of 0.5 was applied to all cells of studies with zero events in one arm; studies with zero events in both arms were not included in the pooled RR.

Heterogeneity was assessed using the I^2 statistic, τ^2, and Cochran's Q test; I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively.[17] Ninety-five per cent prediction intervals were calculated using the Higgins–Thompson–Spiegelhalter method (t distribution with $k - 2$ degrees of freedom) when at least four studies contributed.

Sensitivity analyses comprised (1) use of unadjusted instead of adjusted estimates for non-randomised studies, (2) exclusion of the

study using historical controls,[18] (3) a common-effect model, (4) separate analysis of the two dexmedetomidine doses in the trial by Miller et al., with the shared chloral hydrate group split evenly between the two comparisons, (5) inclusion of the study excluded for planned co-sedation,[19] (6) restriction to studies at low risk of bias, where feasible, and (7) exclusion of Hu et al. from the analysis of onset time, because its medians were identical in both groups but its distributions were markedly skewed, so that conversion to means may be unreliable. Analyses (3) and (6) were specified in the original protocol; analyses (1) and (2) were added in the protocol amendment, and analyses (4), (5), and (7) were not specified in either version. Results are presented stratified by study design. Subgroup analysis by cyanotic versus acyanotic CHD was not feasible because sedation outcomes were not reported separately by CHD type; vital-sign data reported for the cyanotic subgroup by Saudek et al. are described narratively. Meta-regression and assessment of publication bias were not performed because fewer than ten studies contributed to each outcome. Outcomes that could not be pooled (rescue dose requirement, nausea and vomiting, hypotension, and parental and sonographer satisfaction) were synthesised narratively. Rescue dose requirement was not pooled because single-dose success was derived from the same rescue data in two studies and because, in Hu et al., not all children with initial sedation failure received rescue medication; the outcome was therefore not comparable across studies. Analyses were performed in R using the meta and metafor packages.

Certainty of evidence for each outcome was assessed using the GRADE approach. Evidence from randomised trials, and from non-randomised studies assessed with ROBINS-I, started at high certainty, in line with current GRADE guidance.[20] Evidence was downgraded for risk of bias, inconsistency, indirectness, imprecision, and publication bias.

III. RESULTS

The literature search identified 232 records (PubMed/MEDLINE, n = 88; Europe PMC, n = 82; CENTRAL, n = 51; ClinicalTrials.gov, n = 11). After removal of 107 duplicates, 125 records were screened, of which 116 were excluded on title and abstract. Of the nine reports assessed in full, four were excluded (Supplementary Table S6): two because of planned co-sedation, one because sedation was for magnetic resonance imaging, and one because it was an ongoing trial without extractable data. Four studies, described in five reports (four articles and the trial registration of Miller et al.), were included (Fig. 1).

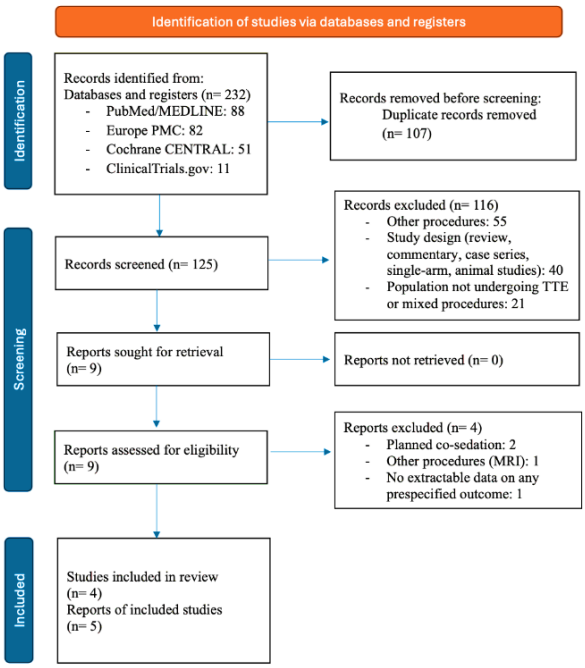


FIG. 1. PRISMA FLOW CHART

Three studies were conducted at Shanghai Children's Medical Center. Overlap of study populations was excluded based on

eligibility criteria and study periods. Miller et al. excluded children with trisomy 21, Hu et al. enrolled only children with Down syndrome, and the study period of Lv and Jin (2023–2024) did not overlap with those of the other two studies.

In total, 1414 participants were included, of whom 853 received intranasal dexmedetomidine and 561 received oral chloral hydrate (Table I; Supplementary Table S3).

TABLE 1. STUDY CHARACTERISTICS: DESIGN AND POPULATION

Characteristic	Miller et al. 2016	Hu et al. 2025	Lv and Jin 2026	Saudek et al. 2022
Country and centre	China; Shanghai Children's Medical Center (collaboration with Cincinnati Children's Hospital Medical Center, USA)	China; Shanghai Children's Medical Center; single centre	China; Shanghai Children's Medical Center; single centre	USA; Children's Hospital of Wisconsin, Milwaukee; single centre
Design	Randomised controlled trial, three arms; double-dummy placebo; observer blinded to allocation	Retrospective cohort	Retrospective cohort	Retrospective cohort with historical controls (chloral hydrate until September 2018; dexmedetomidine from October 2018)
Study period (registration)	September–October 2014 (NCT02523144)	June 2014–September 2021	January 2023–January 2024	September 2017–October 2019
Participants analysed	DEX: 100 (2 μg/kg: 50, 3 μg/kg: 50) CH: 50	DEX: 74 CH: 75	DEX: 303 CH: 80	DEX: 376 CH: 356
Adjustment for confounding	Randomisation	IPTW (age, sex, weight, CHD type, fasting time) Weighted pseudo-population: DEX 148, CH 150	1:1 PSM (age, sex, weight, fasting time, CHD type) Matched sample: DEX 78, CH 78	None
Population	Children aged 3–36 months with known or suspected CHD scheduled for sedated TTE	Outpatients with Down syndrome and a heart murmur or known CHD undergoing sedated TTE	Infants aged <3 months with CHD undergoing outpatient sedated TTE	Children sedated for echocardiography in the echocardiography laboratory (routinely aged 1 month to 2 years)
Main exclusions	ASA IV–V; trisomy 21; severe coarctation of the aorta; recent digoxin or beta-blockers; second-degree heart block	Incomplete data; second- or third-degree AV block; recent digoxin or beta-blockers	Incomplete data; lost to follow-up	Sedation with other agents only; sedation outside the echocardiography laboratory, including all patients with shunt-dependent pulmonary blood flow
Age	Mean ± SD, months DEX 2 μg/kg: 13.7 ± 8.6 DEX 3 μg/kg: 15.4 ± 8.5 CH: 13.6 ± 7.6	Median [IQR], months DEX: 16.5 [9–24] CH: 11 [7–22]	Median (Q1, Q3), days, before matching DEX: 43 (34, 51.5) CH: 40 (30, 51.25)	Mean ± SD, months DEX: 10.1 ± 8.3 CH: 9.4 ± 6.6

Weight	Mean ± SD, kg DEX 2 µg/kg: 9.5 ± 2.3 DEX 3 µg/kg: 9.7 ± 2.3 CH: 8.9 ± 2.0	Median [IQR], kg DEX: 9 [7–11] CH: 7 [6–10]	Median (Q1, Q3), kg, before matching DEX: 4.5 (4.0, 5.0) CH: 4.4 (3.9, 5.0)	Mean (range), kg DEX: 8.2 (3.5–35) CH: 7.8 (3.2–16.8)
Confirmed CHD	126/150 (84%); 24 with structurally normal hearts	Not reported; patients without CHD were grouped with simple lesions	Not reported separately; 19/383 (5%) referred for murmur screening; ASD and PFO reported together (126/383)	Not reported
Complex CHD	Overall (not reported by group): 41/150 (27%) complex two-ventricle defects (35 repaired, 6 unrepaired); no single-ventricle lesions	DEX: 33/74 (44.6%) CH: 32/75 (42.7%)	Before matching DEX: 80/303 (26.4%) CH: 26/80 (32.5%)	Diagnosis expected to require surgery in the first year of life DEX: 32% CH: 35%
Cyanotic CHD	Overall (not reported by group): 1/150 (unrepaired tetralogy of Fallot)	Not reported	Not reported	Pre-sedation SpO_2 <90% DEX: 7% CH: 8%
Baseline SpO_2	Mean ± SD, % DEX 2 µg/kg: 98 ± 2 DEX 3 µg/kg: 98 ± 2 CH: 97 ± 2	Mean ± SD, %, before weighting DEX: 93.4 ± 6.2 CH: 93.8 ± 4.9	Not reported	Mean ± SD, % DEX: 97.7 ± 4.9 CH: 97.4 ± 5.1

ASA, American Society of Anesthesiologists physical status; ASD, atrial septal defect; AV, atrioventricular; CH, chloral hydrate; CHD, congenital heart disease; DEX, dexmedetomidine; IPTW, inverse probability of treatment weighting; IQR, interquartile range; PFO, patent foramen ovale; PSM, propensity score matching; SD, standard deviation; SpO_2, peripheral oxygen saturation; TTE, transthoracic echocardiography.

Outcome-specific analyses used the populations available for each outcome; for single-dose sedation success, the analysis included 1187 participants because the propensity-score-matched population from Lv and Jin (78 per group) was used. One study was a randomised controlled trial (Miller et al.) and three were retrospective cohort studies. Of the cohort studies, Hu et al. adjusted for confounding with inverse probability of treatment weighting, Lv and Jin with 1:1 propensity score matching, and Saudek et al. compared consecutive periods before and after a change in sedation protocol without adjustment.

The randomised trial was judged to have some concerns for all outcomes (Fig. 2A), as details of allocation concealment were not available in the published report and the trial was registered after enrolment; outcome assessment was blinded within a double-dummy design.

The three cohort studies were judged to be at serious risk of bias, reflecting the potential for residual confounding inherent to retrospective designs (Fig. 2B). As no study was at low risk of bias overall, the sensitivity analysis restricted to such studies could not be performed.

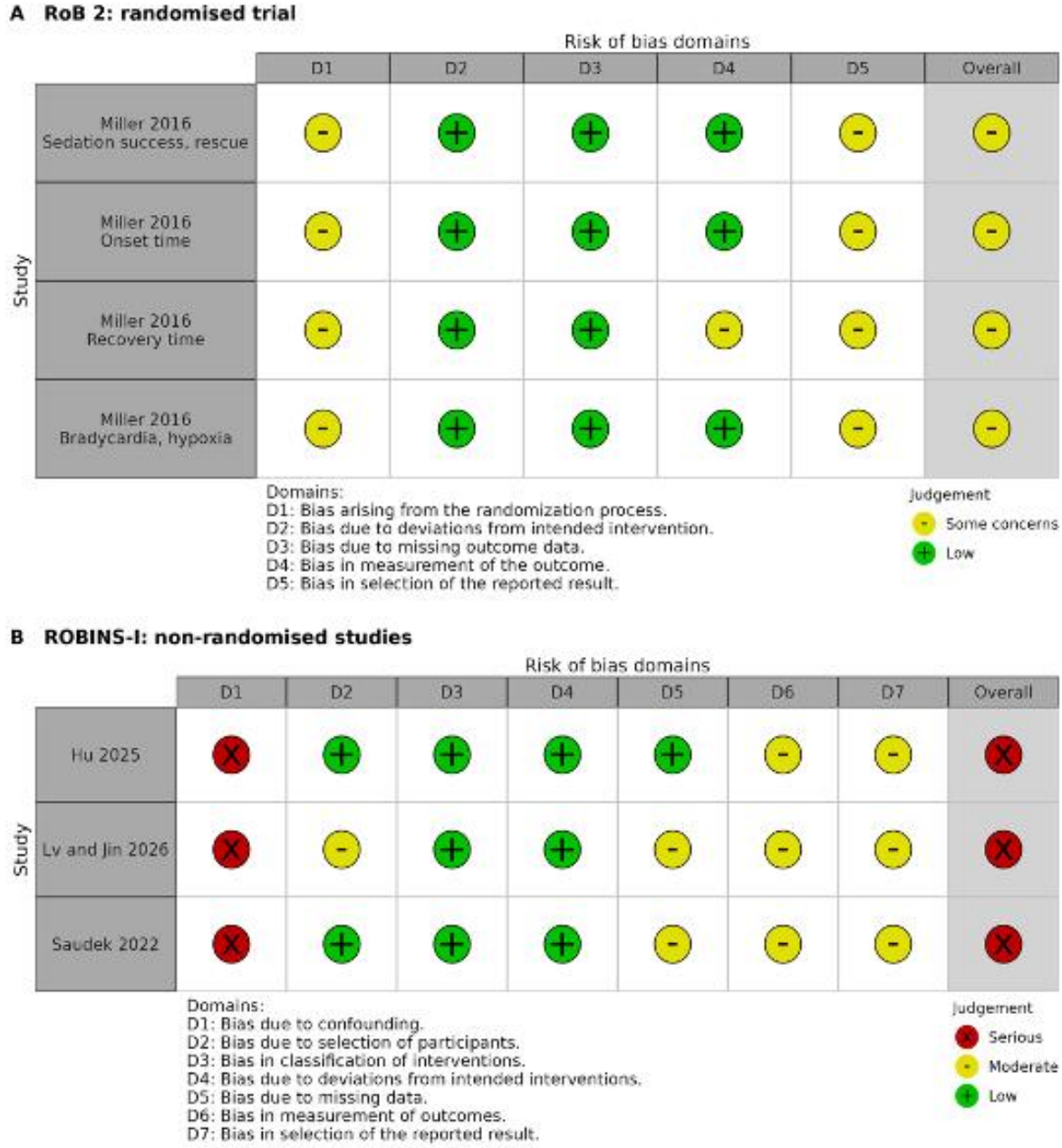


FIG. 2. RISK OF BIAS OF INCLUDED STUDIES. (A) RANDOMISED TRIAL ASSESSED WITH ROB 2, BY OUTCOME. (B) NON-RANDOMISED STUDIES ASSESSED WITH ROBINS-I, FOR SINGLE-DOSE SEDATION SUCCESS; FOR BRADYCARDIA AND HYPOXIA, D5 WAS RATED MODERATE AND D6 LOW IN HU ET AL., AND D6 WAS RATED LOW IN SAUDEK ET AL.

Four studies (1187 participants) contributed to the analysis of single-dose sedation success. Results varied across studies, but there was no clear difference between dexmedetomidine and chloral hydrate (RR 1.08, 95% CI 0.85 to 1.36; p = 0.39; very low certainty) (Fig. 3A).

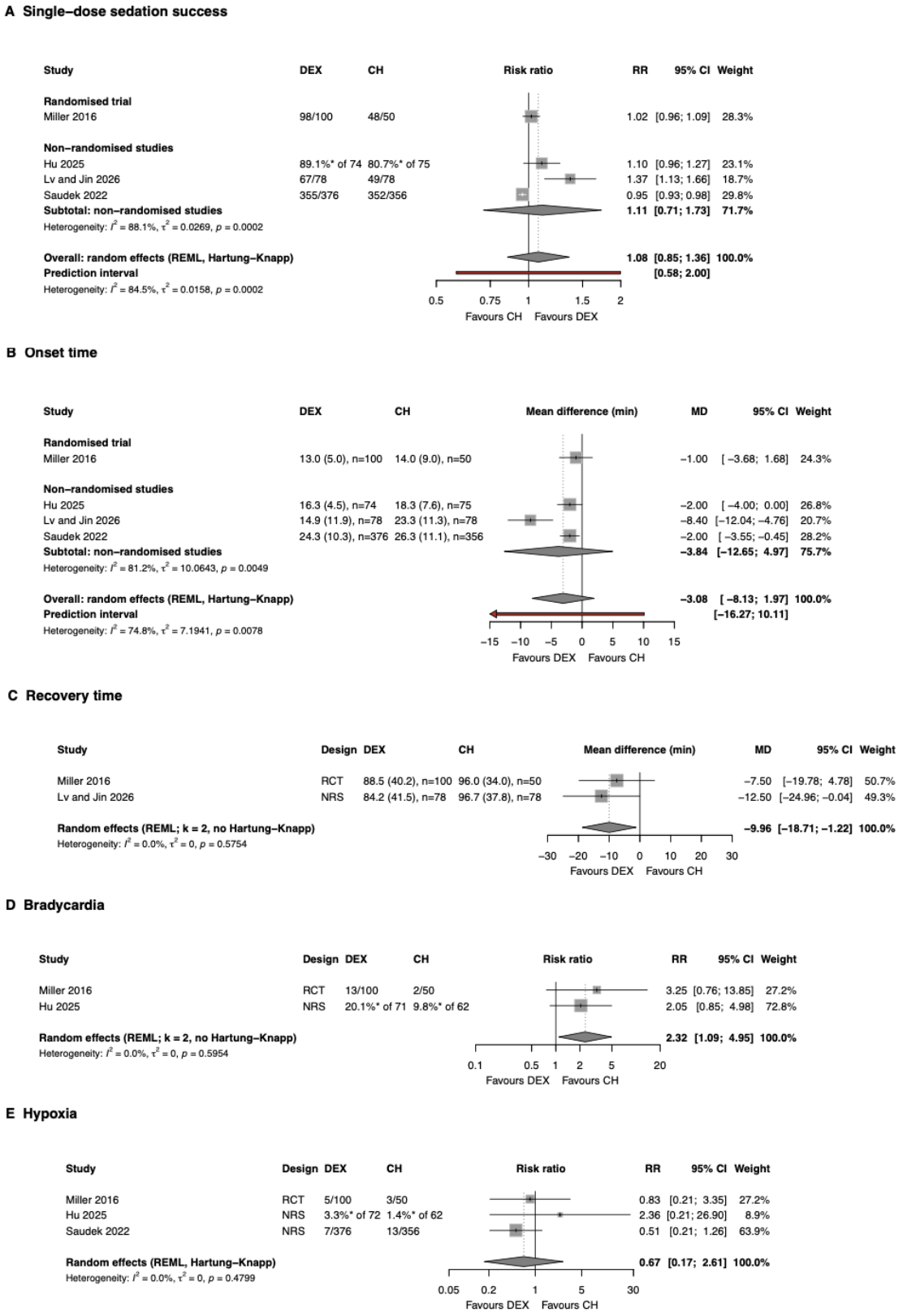


FIG. 3. FOREST PLOTS COMPARING INTRANASAL DEXMEDETOMIDINE (DEX) WITH ORAL CHLORAL HYDRATE (CH): (A) SINGLE-DOSE SEDATION SUCCESS; (B) ONSET TIME; (C) RECOVERY TIME; (D) BRADYCARDIA; (E) HYPOXIA.

*Weighted proportion applied to the original group size (sedation success) or to the number of children with data at completion of TTE (bradycardia and hypoxia) (Hu et al.). RCT, randomised controlled trial; NRS, non-randomised study. Pooled estimates by study design are shown only when a design group included at least three studies.

Heterogeneity was high (I^2 = 85%, τ^2 = 0.016), and the 95% prediction interval was 0.58 to 2.00. Individual studies differed in the direction of effect: Lv and Jin favoured dexmedetomidine (RR 1.37, 1.13 to 1.66), Saudek et al. favoured chloral hydrate (RR 0.95, 0.93 to 0.98), and the randomised trial showed no difference (RR 1.02, 0.96 to 1.09). The pooled estimate for the non-randomised studies was similar (RR 1.11, 0.71 to 1.73; I^2 = 88%).

Rescue dose requirement was reported by three studies (1031 participants) and was not pooled (very low certainty). Saudek et al. reported more adjunct doses with dexmedetomidine (21/376 vs 1/356; RR 19.88, 2.69 to 147.04), whereas Miller et al. (RR 0.50, 0.07 to 3.45) and Hu et al. (RR 0.88, 0.36 to 2.13) showed no clear difference. Lv and Jin did not report rescue requirement separately from initial sedation failure. In Hu et al., not all children with initial sedation failure received rescue medication (unweighted: 14 failures and 9 rescues with chloral hydrate; 8 and 8 with dexmedetomidine), which the authors attributed to refusal of further oral medication after chloral hydrate.

Four studies (1187 participants) reported onset time. There was no clear difference in onset time (MD −3.08 min, −8.13 to 1.97; p = 0.15; very low certainty) (Fig. 3B), with high heterogeneity (I^2 = 75%) and a prediction interval of −16.27 to 10.11 min. The largest difference was reported by Lv and Jin (MD −8.40 min, −12.04 to −4.76), who used a deeper sedation target.

Two studies (306 participants) reported time from administration to discharge. Recovery was shorter with dexmedetomidine (MD −9.96 min, 95% CI −18.71 to −1.22; p = 0.026; I^2 = 0%; low certainty) (Fig. 3C). Because only two studies contributed, the Hartung–Knapp adjustment was not applied. Hu et al. reported time from the end of TTE to discharge (weighted median 20 vs 28 min; p = 0.42), and Saudek et al. reported duration of sedation (71.2 vs 74.2 min; p = 0.18); neither difference was significant.

Two studies (283 participants) reported bradycardia as an incidence. Bradycardia was more frequent with dexmedetomidine (RR 2.32, 1.09 to 4.95; p = 0.029; very low certainty; Fig. 3D). Hu et al., a cohort of children with Down syndrome, contributed 73% of the weight. The other two included studies reported heart rate measures but did not report bradycardia as a dichotomous outcome. After matching, Lv and Jin found a larger decrease in heart rate with dexmedetomidine (median 30 vs 19 beats/min; p = 0.034), and Saudek et al. found lower mean (110.9 vs 124.1 beats/min) and minimum (96.9 vs 109.2 beats/min) heart rates during sedation (both p < 0.001). No study reported administration of specific treatment for bradycardia.

Three studies (1016 participants) contributed to the analysis of hypoxia. There was no clear difference in hypoxia (RR 0.67, 0.17 to 2.61; p = 0.33; I^2 = 0%; very low certainty) (Fig. 3E). Saudek et al. defined hypoxia as a fall in SpO_2 of more than 10%, whereas the other studies used SpO_2 below 92% or more than 5% below baseline. In Lv and Jin, SpO_2 fell by more than 5% in nine infants given dexmedetomidine, all of whom remained above 93%; data for the chloral hydrate group were not reported. In Hu et al., desaturation at completion of TTE was slightly more frequent with dexmedetomidine (3.3% vs 1.4%), whereas desaturation in the post-anaesthesia care unit was more frequent with chloral hydrate (4.7% vs 1.4%). No study reported the use of airway adjuncts or assisted ventilation; desaturation was managed with supplemental oxygen in Hu et al. and resolved with physical stimulation or neck extension in Lv and Jin.

Hypotension was reported only by Saudek et al. (2/376 with dexmedetomidine vs 1/356

with chloral hydrate; fall in blood pressure of more than 30%), and all episodes resolved without intervention, although the authors did not classify these episodes as adverse events. In the cyanotic subgroup of this study (pre-sedation SpO_2 <90%; 28 per group), findings were similar to those of the overall cohort: dexmedetomidine was associated with lower average (102 vs 122 beats/min) and minimum (88 vs 108 beats/min) heart rates, whereas oxygen saturation during sedation did not differ significantly. Parental and sonographer satisfaction were reported only by Miller et al.: median parental satisfaction was 10 of 10 in all groups, and sonographers reported some dissatisfaction with scanning conditions in 2% of children given chloral hydrate and in 10% and 8% of those given 2 and 3 µg/kg dexmedetomidine, although the between-group difference was not statistically significant. No study reported nausea and vomiting by group.

In the sensitivity analyses, for single-dose sedation success, all random-effects sensitivity analyses gave results similar to the main analysis, with no clear difference between groups. The common-effect model yielded an estimate favouring chloral hydrate (RR 0.97, 95% CI 0.95 to 1.00; p = 0.03), reflecting the large weight of Saudek et al. This contrast illustrates the extent of heterogeneity.

The common-effect model also showed a shorter onset time with dexmedetomidine (MD −2.39 min, −3.46 to −1.32), which was not seen in the random-effects analysis. Excluding Hu et al., whose median onset times were identical in both groups (15 min), gave an onset-time difference of MD −3.59 min (−13.27 to 6.09). The difference in recovery time was no longer significant when the two doses of Miller et al. were analysed separately (MD −10.02 min, −24.07 to 4.04) or when Fett et al. was included (MD −6.21 min, −22.32 to 9.90). The findings for bradycardia and hypoxia did not change materially in any sensitivity analysis.

The certainty of evidence was very low for single-dose sedation success, rescue dose requirement, onset time, bradycardia, hypoxia, and hypotension, and low for recovery time and satisfaction (Table II). The main reasons for downgrading were risk of bias due to confounding in the non-randomised studies, inconsistency, imprecision, and, for bradycardia and hypoxia, indirectness.

TABLE 2. SUMMARY OF FINDINGS

Outcome	Participants (studies)	Certainty of evidence (GRADE)	Relative effect (95% CI)	Risk with CH	Risk difference with DEX (95% CI)	Comments
Single-dose sedation success	1187 (4: 1 RCT, 3 NRS)	⨁◯◯◯ Very low[a,b,c]	RR 1.08 (0.85 to 1.36); PI 0.58 to 2.00	884 per 1000	67 more per 1000 (129 fewer to 116 more*)	The evidence is very uncertain about the effect of DEX on single-dose sedation success. Studies differed in direction of effect.
Rescue dose requirement	1031 (3: 1 RCT, 2 NRS)	⨁◯◯◯ Very low[a,b,d]	Not pooled	—	—	Not pooled because definitions differed across studies. The evidence is very uncertain. The largest study showed more

						adjunct doses with DEX (21/376 vs 1/356); the other two showed no clear difference.
Onset time (min)	1187 (4: 1 RCT, 3 NRS)	⨁◯◯◯ Very low[a,b,c]	—	Mean 14 to 26 min	MD 3.1 min shorter (8.1 shorter to 2.0 longer)	The evidence is very uncertain about the effect of DEX on onset time.
Recovery time, administration to discharge (min)	306 (2: 1 RCT, 1 NRS)	⨁⨁◯◯ Low[e,f]	—	Mean 96 to 97 min	MD 10.0 min shorter (18.7 to 1.2 shorter)	DEX may slightly shorten recovery time; the difference is unlikely to be clinically important.
Bradycardia	283 (2: 1 RCT, 1 NRS)	⨁◯◯◯ Very low[a,g,h]	RR 2.32 (1.09 to 4.95)	69 per 1000	91 more per 1000 (6 more to 273 more)	DEX may increase bradycardia, but the evidence is very uncertain. No study reported treatment for bradycardia.
Hypoxia	1016 (3: 1 RCT, 2 NRS)	⨁◯◯◯ Very low[a,d,i]	RR 0.67 (0.17 to 2.61)	37 per 1000	12 fewer per 1000 (31 fewer to 60 more)	The evidence is very uncertain. No study reported airway adjuncts or assisted ventilation.
Hypotension	732 (1 NRS)	⨁◯◯◯ Very low[j]	Not pooled	—	—	Saudek et al.: 2/376 with DEX vs 1/356 with CH (fall in blood pressure >30%), all resolved without intervention. Blood pressure was not routinely monitored in the other three studies.
Parental and sonographer satisfaction	150 (1 RCT)	⨁⨁◯◯ Low[k]	Not pooled	—	—	Miller et al.: median parental satisfaction 10/10 in all groups; sonographer dissatisfaction (score 5–9) in 2% with CH, 10% with DEX 2 µg/kg, and 8% with DEX 3 µg/kg.

The risk with DEX (and its 95% CI) is based on the median risk in the CH groups and the relative effect of the intervention. Evidence from randomised trials and from non-randomised studies assessed with ROBINS-I started at high certainty. Publication bias could not be assessed (fewer than ten studies).

*Upper confidence limit truncated at 1000 per 1000, because the calculated risk with DEX exceeded 100% (884 per 1000 × RR 1.36 for single-dose sedation success).

a. Downgraded two levels for risk of bias (mainly non-randomised studies at serious risk of confounding).
b. Downgraded one level for inconsistency ($I^2 \geq 75\%$; effects in opposite directions).
c. Downgraded one level for imprecision (95% CI includes no effect and important effects).
d. Downgraded two levels for imprecision (very wide 95% CI; few events).
e. Downgraded one level for risk of bias (half of the weight from a non-randomised study at serious risk).
f. Downgraded one level for imprecision (two studies; 306 participants).
g. Downgraded one level for indirectness (73% of weight from a Down syndrome cohort; differing heart rate thresholds).
h. Downgraded one level for imprecision (few events; wide 95% CI).
i. Downgraded one level for indirectness (differing definitions of hypoxia).
j. Single non-randomised study at serious risk of bias; few events.
k. Single randomised trial with some concerns; imprecision.

CH, chloral hydrate; CI, confidence interval; DEX, intranasal dexmedetomidine; MD, mean difference; NRS, non-randomised study; PI, prediction interval; RCT, randomised controlled trial; RR, risk ratio.

IV. DISCUSSION

This systematic review and meta-analysis, comprising one randomised trial and three cohort studies, found no clear difference in single-dose sedation success between intranasal dexmedetomidine and oral chloral hydrate for TTE in children with known or suspected CHD (Randomised trial: RR 1.02, 95% CI 0.96–1.09). Recovery time was modestly shorter and bradycardia more frequent with dexmedetomidine, whereas onset time and hypoxia did not differ significantly and rescue dose requirement could not be pooled. The certainty of evidence was low for recovery time and very low for sedation success, rescue dose requirement, onset time, bradycardia, and hypoxia. As no equivalence margin was prespecified and the confidence intervals were compatible with clinically important differences in either direction, these findings should not be interpreted as evidence of equivalence.

The principal feature of the evidence is its inconsistency. Estimates for sedation success ranged from a benefit of dexmedetomidine in infants younger than 3 months (Lv and Jin) to a small benefit of chloral hydrate in the largest cohort (Saudek et al.), and the prediction interval (0.58–2.00) indicates that the effect in a new setting could favour either agent. Several differences between studies may account for this. Sedation targets differed, with Lv and Jin requiring a Ramsay score of at least 5, a deeper level than that used in the other studies. Rescue protocols also differed: in Saudek et al., single-dose success was derived from the use of a second medication, which was protocolised at 25 min for dexmedetomidine but without a specified time point for chloral hydrate. The time at which initial success was assessed also differed (25 min for dexmedetomidine in Saudek et al., 30 min in Hu et al., and 45 min in Miller et al.). Doses, delivery methods, age ranges, and fasting practices varied as well. With only four studies, these explanations could not be examined formally and should be regarded as hypotheses.

Bradycardia was more frequent with dexmedetomidine (RR 2.32, 95% CI 1.09–4.95), and heart rate was lower with this agent in the two cohorts that reported it, whereas Miller et al. found a similar decline in heart rate across groups, consistent with its alpha-2 adrenergic action.[5] This finding is important in CHD. In infants, cardiac output depends mainly on heart rate, and children with ventricular dysfunction, outflow obstruction, pulmonary hypertension, or conduction disorders may tolerate bradycardia poorly.[3] No study reported treatment for bradycardia; in Lv and Jin, one infant had a heart rate decrease of more than 30%, which resolved without

atropine. However, this does not prove that dexmedetomidine is harmless. Most of the pooled data came from children with Down syndrome,[11] who are more prone to bradycardia with dexmedetomidine,[21] and three of the four studies did not routinely measure blood pressure, so the effect of bradycardia on circulation is unknown. In addition, children at highest risk, such as those with heart block, digoxin or beta-blocker use, severe coarctation of the aorta, or shunt-dependent pulmonary blood flow, were excluded from individual studies. The safety of dexmedetomidine in these children remains uncertain, and continuous heart rate monitoring is recommended when it is used in children with limited cardiovascular reserve.

Recovery time was approximately 10 min shorter with dexmedetomidine (MD −9.96 min, 95% CI −18.71 to −1.22), relative to a mean recovery time of 96–97 min with chloral hydrate. The direction of this finding is consistent with the shorter elimination half-life of dexmedetomidine compared with trichloroethanol, the active metabolite of chloral hydrate.[5,22] However, the estimate was derived from two studies and was not robust in sensitivity analyses, and a difference of this magnitude is unlikely to be clinically important.

In the only trial that reported satisfaction, lower parental satisfaction clustered in the 3 µg/kg dexmedetomidine group, which the investigators attributed to prolonged drowsiness after awakening, and the slightly more frequent sonographer dissatisfaction with dexmedetomidine was attributed to arousability during scanning, although all examinations were completed.[10] These single-trial findings may reflect dose or local practice rather than an effect of the drug itself.

The incidence of hypoxia was low with both agents and did not differ significantly between them (RR 0.67, 95% CI 0.17–2.61). All desaturation episodes were transient and managed conservatively, and in Lv and Jin, all infants with desaturation remained above 93%. Dexmedetomidine is known to have limited effects on respiratory drive,[5] but the present data cannot establish whether either agent is safer in this respect, as events were few, definitions of hypoxia differed, and cyanotic patients, in whom small decreases in SpO_2 may be more consequential, were underrepresented.

This review focused on children undergoing sedated TTE for known or suspected CHD, in whom cardiovascular physiology, including labile pulmonary vascular resistance, may modify the response to sedation.[3] Previous reviews comparing these agents have drawn largely on children undergoing other diagnostic procedures.[7,8] Nevertheless, only one included study reported the proportion of participants with confirmed CHD, and two studies enrolled specific subgroups, namely infants younger than 3 months and children with Down syndrome. The findings therefore apply to a heterogeneous population referred for sedated TTE rather than exclusively to children with confirmed CHD.

The strengths of this review include transparent reporting of all deviations from the registered protocol, an updated search that included a trial registry, the use of adjusted estimates for non-randomised studies, a random-effects model suited to a small number of studies, and assessment of certainty using GRADE. Several limitations should be considered. The evidence base was small, and all studies had some concerns or a serious risk of bias; three of the four studies were conducted at a single institution, which may limit generalisability. Definitions of sedation success, rescue, and adverse events differed across studies, and the method of dexmedetomidine delivery was not reported in two. Equipotent doses of intranasal dexmedetomidine and oral chloral hydrate have not been established, doses

differed between studies, and the two agents were given by different routes, so differences in onset and acceptability may partly reflect route and dose rather than the drug itself. Some estimates required derivation or approximation, including single-dose success in Saudek et al., weighted proportions in Hu et al., and conversion of medians to means. Nausea and vomiting, hypotension, and satisfaction were reported too inconsistently for quantitative synthesis. Publication bias could not be assessed, citation searching was not performed, and study authors were not contacted. Finally, the protocol was amended to include non-randomised studies and to revise the analytical approach; these changes are reported in Supplementary Table S4, and three sensitivity analyses were not prespecified.

Two aspects of these findings are likely to remain contested. The first is how much weight the carcinogenicity classification of chloral hydrate, which rests on animal and mechanistic data,[22] should carry against its long clinical record in single-dose procedural sedation; the second is whether a higher incidence of bradycardia without systematic blood pressure measurement is sufficient to regard dexmedetomidine as haemodynamically safe in children with CHD. Current evidence does not establish that either agent is superior for sedation during TTE in this population. The choice between them may reasonably be guided by drug availability, institutional experience, and patient characteristics, with continuous heart rate monitoring when dexmedetomidine is used, particularly in children with Down syndrome or limited cardiovascular reserve. Adequately powered randomised trials in children with confirmed CHD are needed, with standardised definitions of sedation success, rescue, and adverse events, routine blood pressure monitoring, and prespecified analyses by CHD phenotype and dose. Comparisons with other non-invasive regimens, such as intranasal midazolam, would further inform clinical practice.

V. CONCLUSION

In children with known or suspected congenital heart disease undergoing transthoracic echocardiography, intranasal dexmedetomidine and oral chloral hydrate showed no clear difference in single-dose sedation success, whereas bradycardia was more frequent with dexmedetomidine, although no study reported treatment for bradycardia and most of the bradycardia data came from children with Down syndrome. Given the low to very-low certainty of evidence, neither agent can be considered superior. The choice may be guided by availability and clinical context, with heart rate monitoring when dexmedetomidine is used, pending adequately powered randomised trials.

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