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Review Article

REVIEW ARTICLE

Needle-free pharmacological sedation techniques in paediatric patients for imaging procedures: a systematic review and meta-analysis

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Abstract

Background: Sedation techniques and drugs are increasingly used in children undergoing imaging procedures. In this systematic review and meta-analysis, we present an overview of literature concerning sedation of children aged 0–8 yr for magnetic resonance imaging (MRI) procedures using needle-free pharmacological techniques.

Methods: Embase, MEDLINE, Web of Science, and Cochrane databases were systematically searched for studies on the use of needle-free pharmacological sedation techniques for MRI procedures in children aged 0–8 yr. Studies using i.v. or i.m. medication or advanced airway devices were excluded. We performed a meta-analysis on sedation success rate. Secondary outcomes were onset time, duration, recovery, and adverse events.

Results: Sixty-seven studies were included, with 22 380 participants. The pooled success rate for oral chloral hydrate was 94% (95% confidence interval [CI]: 0.91–0.96); for oral chloral hydrate and intranasal dexmedetomidine 95% (95% CI: 0.92–0.97); for rectal, oral, or intranasal midazolam 36% (95% CI: 0.14–0.65); for oral pentobarbital 99% (95% CI: 0.90–1.00); for rectal thiopental 92% (95% CI: 0.85–0.96); for oral melatonin 75% (95% CI: 0.54–0.89); for intranasal dexmedetomidine 62% (95% CI: 0.38–0.82); for intranasal dexmedetomidine and midazolam 94% (95% CI: 0.78–0.99); and for inhaled sevoflurane 98% (95% CI: 0.97–0.99).

Conclusions: We found a large variation in medication, dosage, and route of administration for needle-free sedation. Success rates for sedation techniques varied between 36% and 98%.

Keywords: buccal administration; conscious sedation; deep sedation; hypnotics; intranasal administration; MRI; oral administration; rectal administration

Editor's key points

- It is unclear which needle-free pharmacological sedation method is most effective and most suitable for paediatric MRI.
- Needle-free sedation can be successful in children 8 yr or younger who are scheduled for MRI as an alternative to i.v. or i.m. techniques.
- The presence of well-organised teams dedicated to paediatric sedation is likely to be more important than the use of a specific sedative regimen.
- Careful selection of appropriate patients for sedation is essential. General anaesthesia remains a safe alternative in those who fail the selection process.

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The use of advanced diagnostic imaging, particularly MRI, in the paediatric population continues to increase.[1] Magnetic resonance imaging (MRI) provides better imaging than computed tomography (CT) or ultrasound when scanning soft tissue, ligaments, or organs, and it has no risk of carcinogenesis.[2] To minimise artifacts, the patient must lie still during scanning, which varies between 30 and 90 min depending on the purpose of the examination. Lying still for such a long time is difficult for children younger than 8 yr; also, they are difficult to instruct or anxious of the procedure.[3] These young children, therefore, commonly receive general anaesthesia.[4] More than 20% of the non-surgical anaesthetic procedures in children are performed for MRI scanning.[5] Unfortunately, this is often accompanied with a controlled airway by an orotracheal tube or laryngeal mask, which is an invasive procedure exclusively performed by anaesthesiologists.

Sedation has been suggested as a less invasive alternative technique for general anaesthesia and is defined as a drug-induced state, which varies in depth and can also be provided by non-anaesthesiologists. The depth of sedation is a continuum from minimal sedation or anxiolysis whilst being responsive to verbal commands, to deep sedation whilst unresponsive to pain stimulation and maintaining spontaneous ventilation and cardiovascular function[6] and ending with general anaesthesia.[7] This continuum reflects the practical difficulty to distinguish deep sedation from general anaesthesia. Sedative drugs can be administered *via* multiple routes, such as oral, rectal, or intranasal route. Traditionally, tracheal intubation or use of a laryngeal mask insertion should not be necessary for sedation.[8]

The range of drugs and protocols described in current literature for sedation in paediatric MRI illustrates an uncertainty as to which agents should be utilised. Studies included a broad mix of diagnostic and therapeutic procedures, varying from EEG, dental procedures, gastroscopy, placement of a peripherally inserted central catheter, CT to MRI.[9–11] However, each indication for sedation has typical conditions and requirements, most importantly regarding procedure time, intensity of stimuli, and effect of movement. MRI is prone to motion artifacts, needs a relatively long time, and has an inconvenient loud noise factor. These affect the sedation success rate of a specific sedation protocol or drug.[12]

Sedation techniques using i.v. infusion have been shown to be suitable as well but are less desirable for children because the i.v. cannulation is an invasive procedure. The ideal sedation technique for MRI in children should be safe, effective, and needle-free with an easy route of administration, rapid onset, and recovery with minimal adverse events.

From the currently available studies, it is unclear which needle-free pharmacological sedation method is most effective and suitable for paediatric MRI. Therefore, we conducted a systematic review and meta-analysis to present an overview of the current literature concerning needle-free pharmacological sedation techniques for MRI procedures in children aged 0–8 yr.

Methods

We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (International Prospective Register of Systematic Reviews registered under registration number 233926) on the success rate of the use of needle-free pharmacological techniques without the use of i.v. or i.m. medication or need for an advanced airway (e.g. laryngeal mask airway) for adequate and safe sedation of children aged 0–8 yr undergoing MRI imaging.[13]

Literature search strategy

With the help of a medical librarian (WMB), we performed a systematic search of Embase.com, Ovid MEDLINE, Web of Science Core Collection, and Cochrane CENTRAL register of trials. The search combined terms on magnetic resonance imaging and sedation or sedatives, with terms on child or paediatrics. See Supplementary Appendix 1 for the full search strategies in all databases. After deduplication of the studies yielded by the search, two researchers (IdR and JW) independently screened the titles and abstracts of the remaining studies on relevance for the review. All studies considered relevant by one of the reviewers were considered eligible. Next, the findings of both were merged, and all selected studies were read in full text. After a consensus was reached on the inclusion of studies, a final selection was formed. If the two reviewers failed to reach a consensus, a third researcher (JCdG) was consulted. The reference lists of the selected studies were scanned to identify relevant studies that had been missed upon which the search string was adapted.

Study selection

Studies meeting all of the following criteria were eligible for inclusion in this systematic review:

(i) Children aged 0–8 yr receiving sedation before undergoing MRI examination.
(ii) Children receiving needle-free administered medication (e.g. *via* the oral, rectal, intranasal, or buccal route).
(iii) Outcome measures, including sedation success rate.

This means that we excluded studies in which children were sedated using i.v. or i.m. medication, or with an invasive advanced artificial airway (e.g. laryngeal mask airway), unless these medications or methods were used only as rescue treatment when the planned needle-free sedation method failed. Our reasoning was that these techniques are invasive and potentially uncomfortable or painful.

Studies using only non-pharmacological techniques, such as sleep deprivation and feed and wrap methods, or instructions, including simulator practice, were excluded. Also, studies without any data about the sedation success rate or written in languages other than English, Dutch, German, or French; case studies; and studies without a full text available were excluded. Reviews were considered irrelevant for data extraction, but we scanned applicable reviews for relevant references using the method of snowballing sampling.

Data extraction and outcomes

The following study information was extracted by the two reviewers independently in a previously self-designed data extraction form: first author, country, date, study type, study period, population, administration of medication used, doses, sedation tool used, and primary and secondary outcomes.

The primary outcome, sedation success rate, was defined as the success rate of adequate sedation using needle-free pharmacological techniques allowing to perform a successful MRI scan. Needle-free is defined as a minimally invasive way of administrating sedative medication, without the introduction of objects, such as needles, into the bodies of children. For

determining the success rate of a sedation technique, we considered the use of invasive rescue medications as failure. Secondary outcomes were (i) onset time, defined as time between administration of sedative(s) until time of adequate sedation level; (ii) sedation duration, defined as time between adequate sedation level until patient was fully awake and alert; (iii) recovery time, defined as time between fully awake and alert and discharge; and (iv) adverse events.

Quality assessment

The methodological quality of the included studies was rated using the Methodological Index for Non-Randomized Studies.[14] This tool lists 12 items, partly for non-comparative studies and partly for comparative studies. A score of 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate) for each item resulted in a maximum score of 24 points for comparative studies and a total of 16 points for non-comparative studies. Methodological quality was classified as poor (0–6/8 points), moderate (6–11/9–16 points), or good (12–16/17–24 points). Qualitatively poor studies were excluded from the meta-analysis. If the two independent reviewers could not agree on the quality of a study, the third reviewer was consulted.

Data synthesis

The primary outcome, sedation success rate, is expressed in percentages (%). The secondary outcomes onset time, duration, and recovery time are expressed as mean differences. Adverse events are described in numbers and text. The literature is compared in text when only one or two studies were published on the same medication. A meta-analysis was performed when three or more studies concerning the same medication were published.

Statistical analysis

Continuous data are presented as medians and inter-quartile ranges, and categorical data are presented as numbers and proportions. The results were processed in IBM SPSS Statistics 25 (IBM Corp., Armonk, NY, USA) and Microsoft Excel 2016 (Microsoft Corp., Redmond, WA, USA). Pooled estimates of the sedation success rate and the study population were calculated using a random effects model together with a 95% confidence interval (CI) and prediction interval. Between-study heterogeneity was assessed using I^2 statistics. I^2 above 50% was considered significant heterogeneity. A funnel plot to assess publication bias was constructed when more than 10 studies were included per sedative and dispersed the logit transformed proportion of successful sedation. The meta-analysis and funnel plot were made using R version 3.2.3 (R Project for Statistical Computing; R Foundation for Statistical Computing, Vienna, Austria) using the packages meta and metaphor.[15] A P-value < 0.05 was considered statistically significant.[16]

Results

Search and study characteristics

The search strategy was last performed on the October 29, 2021 and identified 1351 studies. Three additional relevant studies were identified through scanning of the references of relevant reviews but were excluded after full-text screening. After deduplication, titles and abstracts of 645 studies were screened. After this first screening, 316 of the 645 studies were assessed for eligibility by reading the full text (Fig. 1). Of the 67 studies that eventually were included in the qualitative synthesis, 52 were included in the meta-analysis (Table 1; stratified per sedation method).

Results of sedative techniques

The following sedatives or combinations of sedatives for use as sedation for MRI were reported: chloral hydrate (33 studies), chloral hydrate and hydroxyzine (one study), chloral hydrate and midazolam (one study), chloral hydrate and thioridazine (one study), chloral hydrate and melatonin (one study), chloral hydrate and dexmedetomidine (two studies), midazolam (four studies), midazolam and diphenhydramine (one study), pentobarbital (five studies), thiopental (seven studies), melatonin (three studies), dexmedetomidine (six studies), dexmedetomidine and midazolam (five studies), dexmedetomidine and ketamine (one study), dexmedetomidine and sevoflurane (one study), sevoflurane (three studies), glucose (one study), chlorprothixene (one study), diazepam (one study), trimeprazine and droperidol (one study), and temazepam and droperidol (one study) (Table 1). The primary outcome in pooled estimate and the secondary outcomes in range per sedative are shown in Table 2.

Quality and risk of bias of included studies

None of the included studies were comparative studies. Therefore, a total of 16 points could be scored on methodological quality. Twelve studies were scored as good quality, and 53 studies were scored as moderate quality. Two studies were of poor quality and were therefore excluded from the meta-analysis (Supplementary Appendix 2).[80,81]

Chloral hydrate

A total of 33 studies (2883 patients; Table 1) reported the use of oral chloral hydrate 30–105 mg kg^{-1} as a sedative technique for paediatric MRI.[17–45,48,49,82,83] The sedation success rate ranged from 37.4% to 100%. The onset sedation time varied from 15 to 45 min, and the sedation duration lasted from 48 to 165 min. The recovery time varied from 22 to 278 min. The most common and most serious adverse events were respiratory arrest in 0.06%,[83] need for resuscitation in 0.3%,[38] unplanned admission in 0.3–0.6%,[38,42] agitation in 0.5–29%,[34,35,43,83] gastrointestinal effects in 28–37%,[34,35] motor imbalance in 31–66%,[34,35] restlessness in 14–29%,[34,35] (next-day) drowsiness in 27–35%,[39,44] and prolonged sedation in 0.18–30%.[18,40,42,43,48,83]

The meta-analysis of studies on chloral hydrate shows a pooled proportion of success of 0.94 (95% CI: 0.91–0.96; P<0.01; I^2=98%) (Fig 2a). The funnel plot shows the standard error by logit transformed proportion of success of chloral hydrate at 2.7 (Fig 2b).

Oral chloral hydrate 40 mg kg^{-1} was combined with oral hydroxyzine 2 mg kg^{-1} in one study,[46] which reported a success rate of 78%, onset time of 19 (standard deviation; sd 8) min, sedation duration of 34 (sd 12) min, recovery of 69 (sd 22) min, and vomiting in 3.3% of the patients. In that study, oral chloral hydrate 40 mg kg^{-1} was also combined with oral midazolam 0.5 mg kg^{-1},[46] with a success rate of 74%, onset time of 22 (sd 9) min, sedation duration of 39 (sd 11) min, recovery time of 82 (sd 23) min, vomiting in 3.3%, and agitation in

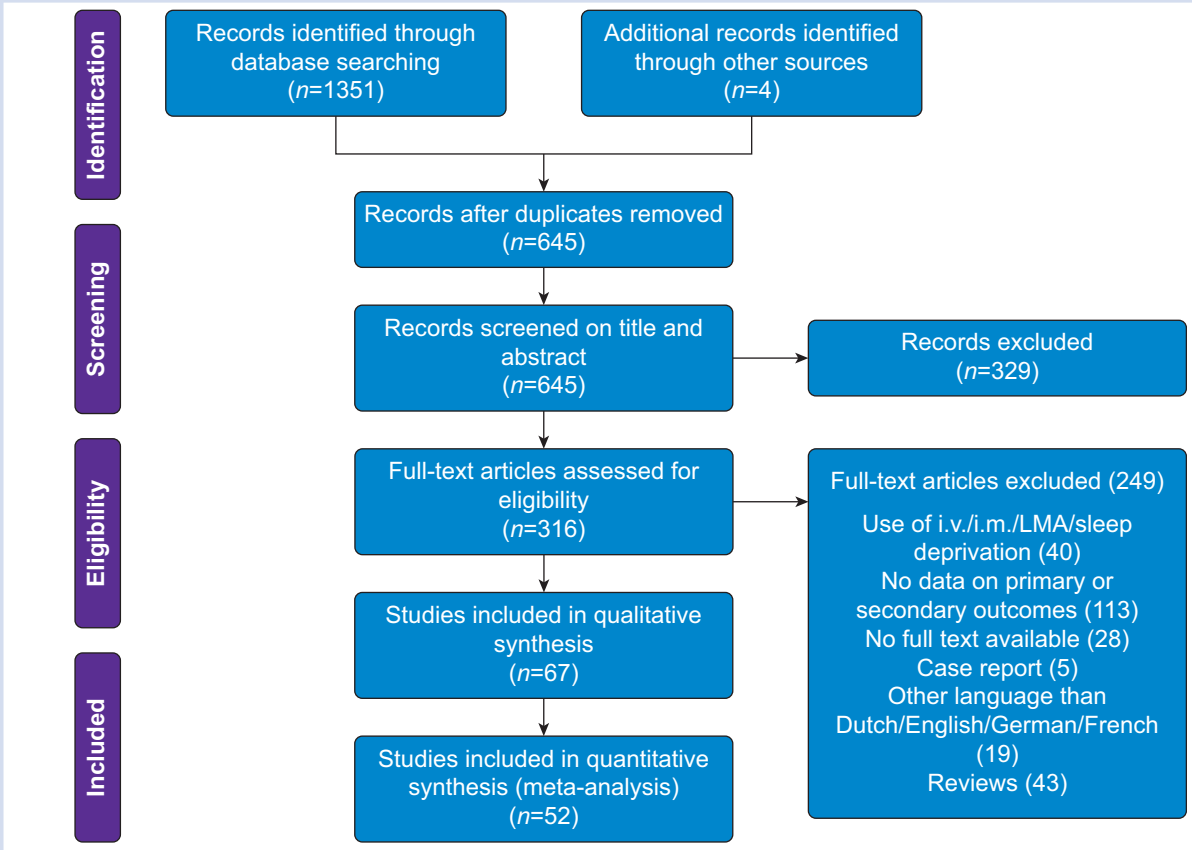


Fig 1. Flow diagram of search and included studies. LMA, laryngeal mask airway.

6.6% of the patients. In another study, oral chloral hydrate 50–100 mg kg^{-1} was combined with oral thioridazine 2–4 mg kg^{-1},[47] with a success rate of 89%, vomiting in 5.7%, oxygen desaturation in 4.6%, hyperactivity in 1.2%, tachycardia in 1.2%, and prolonged sedation in 1.3% of the patients. In yet another study, oral chloral hydrate 50–100 mg kg^{-1} was also combined with oral melatonin 3 mg kg^{-1},[50] with a success rate of 100%, onset time of 39 (sd 14) min, and procedure time of 32 min

Two studies described the combination of oral chloral hydrate 50 mg kg^{-1} with intranasal dexmedetomidine in three cohort groups: 0.4–1.0, 1 or 2 μg kg^{-1},[45,51] (Table 1), with a success rate of 95% when using dexmedetomidine 0.4–1.0 μg kg^{-1}, 94% when using dexmedetomidine 1 μg kg^{-1}, and 98% when using dexmedetomidine 2 μg kg^{-1}. Onset time varied from 13 to 17 min, procedure time was 21 min, and recovery time was 46–92 min.

The meta-analysis of chloral hydrate and dexmedetomidine (n=3) shows a pooled proportion of success of 0.95 (95% CI: 0.92–0.97; P<0.01; I^2=0%) (Fig 2c).

Midazolam and combinations

The use of oral, rectal, or intranasal midazolam 0.5–0.87 mg kg^{-1} as a sedative technique in MRI procedures was described in five studies (298 patients; Table 1).[24,28,48,52,53] The success rate varied between 14% and 62%. The mean onset time was 53 (41) min,[28] and sedation lasted 59–76 min.[24,28] Recovery time was reported as 113 (sd 48) min.[28] Decreases in saturation >10% below baseline and agitation were reported for 6.3% of the patients.[28] Rectal midazolam 1 mg kg^{-1} was applied in four patients, with a success rate of 0% and a recovery time of 60–100 min without any adverse events.[52] Intranasal midazolam 0.2–0.6 mg kg^{-1} was reported in 98 patients, with a success rate of 35%, an onset time of 9 min, and 2% of the patients experienced bradycardia and 7% oxygen desaturation.[53]

The meta-analysis of the five studies using midazolam shows a pooled proportion of success of 0.36 (95% CI: 0.14–0.65; P<0.01; I^2=76%) (Fig 2d).

In one study, midazolam was also used as an oral combination with diphenhydramine (n=96).[54] Diphenhydramine 1.25 mg kg^{-1} with midazolam 0.5 mg kg^{-1} resulted in an 82% sedation success rate with an onset time of 20 (sd 6) min, sedation duration of 31 (9) min, and a recovery time of 28 (8) min. In addition, 6% of the patients experienced nausea and vomiting during the procedure.

Pentobarbital

Five studies (n=2724; Table 1) described the use of oral pentobarbital in doses of 4–8 mg kg^{-1}.[22,38,42,55,56] The success sedation rate was 67–99.7%, the onset time was 18–30 min, the sedation duration was 47–85 min, and the recovery time was 61–108 min. One study reported different success rates per age category. The success rate in children aged <12

Table 1 Basic characteristics of included studies. MABP, mean arterial blood pressure, MOAA/S, Modified Observer's Assessment of Alertness/Sedation; N-PASS, Neonatal Pain, Agitation and Sedation Scale; SpO_2, oxygen saturation; UMSS, University of Michigan Sedation Scale.

Authors; country location; year of publication	Study type; no. of patients; age	Medication	Sedation tool used	Success rate (%)	Onset time (min)	Sedation duration (min)	Recovery time	Adverse events
Chloral hydrate								
Akhtar and colleagues[17]; Pakistan; 2013	Retrospective; 324; 5 months to 10 yr	Oral chloral hydrate 90 mg kg^{-1}	—	93	—	—	—	Respiratory depressions (0.3%)
Bailey and colleagues[18]; UK; 2016	Retrospective; 105; 5 months to 11 yr	Oral chloral hydrate 100 mg kg^{-1}	—	100	40–45	—	—	Prolonged sedation (11%)
Beebe and colleagues[19]; USA; 2000	Clinical; 130; 0–18 months	Oral chloral hydrate 80–100 mg kg^{-1}	—	98	—	69 (32)	61 (53) min	Emesis
Bluemke and Breiter[20]; USA; 2000	Retrospective; 2081; 0–3 yr	Oral chloral hydrate 80–100 mg kg^{-1}	—	95	—	—	—	Bronchospasm (0.04%); congestion and coughing (0.04%); oxygen desaturation (0.2%); seizure (0.04%); vomiting (0.04%)
Bracken and colleagues[21]; Australia; 2012	Retrospective; 653; 1 month to 3 yr and 10 months	Oral chloral hydrate 50–100 mg kg^{-1}	—	97	32	—	—	Oxygen desaturation (0.2%); vomiting (0.2%)
Chung and colleagues[22]; USA; 2000	Prospective; 16; 2–12 months	Oral chloral hydrate 50 mg kg^{-1}	—	100	19 (13)	83 (31)	102 (33) min	None
Cortellazzi and colleagues[23]; Italy; 2007	Retrospective; 888; 28 (18) months	Oral chloral hydrate 50–100 mg kg^{-1}	Skeie scale	80	39.1 (20.5)	164.5 (85.9)	29.6 (20.8) min	Vomiting (0.2%); respiratory obstruction (2.8%); <90% SpO_2 (4.2%); nausea and vomiting (post-procedure; 1.5%); ataxia (post-procedure; 1.2%); sweating and dizziness (post-procedure; 0.4%); respiratory obstruction (post-procedure; 4.6%)
D'Agostino and Terndrup[24]; USA; 2000	RCT; 11; 30 (25) months	Oral chloral hydrate 50–100 mg kg^{-1}	—	100	—	95 (26)	—	—
Finnemore and colleagues[25]; UK; 2014	Retrospective; 411; 42 weeks gestational age	Oral chloral hydrate 30–50 mg kg^{-1}	—	—	—	—	3.05 h	Decreases in arterial SpO_2 (5%); episode of colour change

Continued

Table 1 Continued

Authors; country location; year of publication	Study type; no. of patients; age	Medication	Sedation tool used	Success rate (%)	Onset time (min)	Sedation duration (min)	Recovery time	Adverse events
								and reduced responsiveness (0.2%)
Goo and colleagues[26]; Korea; 2011	Prospective; 54; 1–8 yr	Oral chloral hydrate 60–75 mg kg^{-1}	—	95	31 min	—	—	—
Greenberg and colleagues[27]; USA; 1993	Prospective; 300; 1 month to 11 yr	Oral chloral hydrate 100 mg kg^{-1}	—	96 (<48 months); 81 (4–11 yr)	30 min	51	—	Vomiting (4%); respiratory depression (4%); hyperactivity (6%)
Hijazi and colleagues[28]; Saudi Arabia; 2014	RCT; 144; 26.5 (19.8) months	Oral chloral hydrate 75–105 mg kg^{-1}	Ramsay sedation score	94	24 (17)	76 (38)	99 (40) min	5.6% decrease in SpO_2 >10% below baseline and decrease in MABP >25%
Hubbard and colleagues[29]; USA; 1992	Retrospective; 259; <7 yr	Oral chloral hydrate 60–75 mg kg^{-1}	—	98	20–30	—	—	—
Keengwe and colleagues[30]; UK; 1999	Retrospective; 677; 5 months to 19 yr	Oral chloral hydrate 90 mg kg^{-1}	—	37	30	—	—	Respiratory depressions (0.3%)
Kimiya and colleagues[31]; Japan; 2017	Prospective and retrospective; 116; 0–3 yr	Oral triclofos sodium 60 mg kg^{-1}	—	95	—	60	278 min	Oxygen desaturation (3%); vomiting (0.8%)
Lee and colleagues[32]; Korea; 2012	Retrospective; 399; 0–6 yr	Oral chloral hydrate 50 mg kg^{-1}	—	91.2	44	—	—	Vomiting (6.7%)
Litman and colleagues[33]; USA; 2010	Retrospective; 1373; 147 (106) days	Oral chloral hydrate 63 mg kg^{-1}	—	95	—	53.9 (29.4)	34.7 (27.8) min	Bradycardia (0.7%)
Malviya and colleagues[34]; USA; 2000	Retrospective; 302; 3.8 yr	Oral chloral hydrate 64 mg kg^{-1}	—	87	—	—	—	Respiratory events (1.7%); agitation (19%); gastrointestinal effects (28%); motor imbalance (31%); restlessness (14%)
Malviya and colleagues[35]; USA; 2004	RCT; 35; 2–12 yr	Oral chloral hydrate 75 mg kg^{-1}	UMSS	63	28 (14)	Procedure time 45 (23)	31 (19) min; return to baseline activity 11 (10) h	Nausea and vomiting (11%); oxygen desaturation (11%); major motion artifact (4%); restlessness (29%); agitation (29%); gastrointestinal effects (37%);

Continued

Table 1 Continued

Authors; country location; year of publication	Study type; no. of patients; age	Medication	Sedation tool used	Success rate (%)	Onset time (min)	Sedation duration (min)	Recovery time	Adverse events
								motor imbalance (66%)
Marchi and colleagues[36]; Italy; 2004	Retrospective; 52; 12.5 kg	Oral chloral hydrate 60–80 mg kg^{-1}	—	100	15–20	—	—	—
Marti-Bonmati and colleagues[37]; Spain; 1995	RCT; 50; 1.5–168 months	Oral chloral hydrate H 70 mg kg^{-1}	—	92	28 (2)	—	22 (6) min awakening after completion	Nausea and vomiting (16.5%); nervousness and unusual excitement (2%); stomach pain (1%)
Marti-Bonmati and colleagues[37]; Spain; 1995	RCT; 47; 1.5–168 months	Oral chloral hydrate 96 mg kg^{-1}	—	100	21 (1)	—	30 (5) min awakening after completion	Nausea and vomiting (16.5%); nervousness and unusual excitement (2%); stomach pain (1%)
Mason and colleagues[38]; USA; 2004	Retrospective; 374; 185 days	Oral chloral hydrate 50 mg kg^{-1}	—	99	17 (12)	86 (35)	103 (36) min	Decrease in SpO_2 (1.6%); vascular compromise (0.3%); vomiting (0.3%); need for resuscitation (0.3%); unplanned admission (0.3%); after discharge, hyperactivity (0.5%); irritability (0.5%)
Morriss and colleagues[39]; UK; 2007	Retrospective; 22; 6 months to 5 yr	Oral chloral hydrate 75 mg kg^{-1}	—	86	—	—	—	Excessive next-day drowsiness (27%)
Morriss and colleagues[39]; UK; 2007	Retrospective; 62; 6 months to 5 yr	Oral chloral hydrate 50–75 mg kg^{-1}	—	97	—	—	—	Minimal next-day drowsiness
Ronchera and colleagues[40]; Spain; 1992	Prospective; 172; 42 (26) months	Oral chloral hydrate 70 mg kg^{-1}	—	94	30 (19)	62 (24)	—	Nausea and vomiting (3.5%); stomach pain (3.5%); dizziness (0.6%); skin rash (0.6%); residual sedation (30%)
Ronchera-Oms and colleagues[41]; Spain; 1994 (3 yr)	Prospective; 596; 41 (30) months	Oral chloral hydrate 70 mg kg^{-1}	—	94	26 (1)	—	38 (2) min awakening after completion	Nausea and vomiting (6.9%); nervousness and unusual excitement (1%);

Continued

Table 1 Continued

Authors; country location; year of publication	Study type; no. of patients; age	Medication	Sedation tool used	Success rate (%)	Onset time (min)	Sedation duration (min)	Recovery time	Adverse events
								mental confusion (0.7%); stomach pain (0.3%); skin rash (0.3%); trembling (0.2%); hiccup (0.2%)
Ronchera and colleagues[40]; Spain; 1992	Prospective; 172; 42 (26) months	Oral chloral hydrate 70 mg kg^{-1}	—	94	30 (19)	62 (24)	—	Nausea and vomiting (3.5%); stomach pain (3.5%); dizziness (0.6%); skin rash (0.6%); residual sedation (30%)
Ronchera-Oms and colleagues[41]; Spain; 1994 (3 yr)	Prospective; 596; 41 (30) months	Oral chloral hydrate 70 mg kg^{-1}	—	94	26 (1)	—	38 (2) min awakening after completion	Nausea and vomiting (6.9%); nervousness and unusual excitement (1%); mental confusion (0.7%); stomach pain (0.3%); skin rash (0.3%); trembling (0.2%); hiccup (0.2%)
Rooks and colleagues[42]; USA; 2003	Prospective; 358; 5.9 (3.3) months	Oral chloral hydrate 50 mg kg^{-1}	—	99.7	16 (11)	86 (36)	103 (36)	Decreased SpO_2 (1.7%); unplanned hospital admissions (0.6%); irritability, hyperactivity, vomiting
Vade and colleagues[43]; USA; 1995	Prospective; 58; <1 yr	Oral or rectal chloral hydrate 50 mg kg^{-1}	—	97	—	Procedure time 20–120 min	—	Prolonged sedation (3%); vomiting (4%); agitation (0.5%); hypoxia (10%)
Woodthorpe and colleagues[44]; UK; 2007	Retrospective; 455; 5–15 kg	Oral chloral hydrate 100 mg kg^{-1}	UMSS	90	20–40	—	—	Drowsy (35%); nausea and vomiting (4%)
Zhang and colleagues[45]; China; 2016	RCT; 40; 1–6 months	Oral chloral hydrate 50–75 mg kg^{-1}	MOAA/S	80	14.6	—	85.9 min	—
Fallah and colleagues[46]; Iran; 2014	RCT; 30; 1–7 yr	Oral chloral hydrate 40 mg kg^{-1}+hydroxyzine 2 mg kg^{-1}	Ramsay sedation score	77	18.91 (8.15)	33.95 (12.06)	69.1 (22.49) min	Vomiting (3.3%)
	RCT; 30; 1–7 yr			74	22.27 (9.22)	39.18 (11.21)	81.81 (23.24) min	

Continued

Table 1 Continued

Authors; country location; year of publication	Study type; no. of patients; age	Medication	Sedation tool used	Success rate (%)	Onset time (min)	Sedation duration (min)	Recovery time	Adverse events
Fallah and colleagues[46]; Iran; 2014		Oral chloral hydrate 40 mg kg^{-1}+mida 0.5 mg kg^{-1}	Ramsay sedation score					Vomiting (3.3%); agitation (6.6%)
Greenberg and colleagues[47]; USA; 1994	Prospective; 87; 4 months to 17 yr	Oral chloral hydrate 50–100 mg kg^{-1}+thioridazine 2–4 mg kg^{-1}	—	89	CH 30 min thioridazine 2 h	—	—	Vomiting (5.7%); decrease in SpO_2 (4.6%); hyperactivity (1.2%): tachycardia (1.2%); prolonged sedation (1.3%)
Schmalfuss[48]; USA; 2005	Retrospective; 310; 19 (13) months	Oral chloral hydrate 65.2 mg kg^{-1}	—	94	—	—	—	Vomiting (3.6%); prolonged sedation (3.6%); decrease in SpO_2 (0.3%)
Sury and colleagues[49]; UK; 1999	Prospective; 205; 0–10 kg	Oral chloral hydrate 50–100 mg kg^{-1}	—	91	—	—	—	—
Sury and Fairweather[50]; UK; 2006	RCT; 25; 5–15 kg	Oral chloral hydrate 50–100 mg kg^{-1}; melatonin 3 mg kg^{-1}	UMSS	100	39 (14)	Procedure time 32 min	—	—
Chloral hydrate and dexmedetomidine								
Zhang and colleagues[51]; China; 2016	Prospective; 120; 1–36 months	Oral chloral hydrate 50 mg kg^{-1}; intranasal dexmedetomidine 0.4–1.0 μg kg^{-1}	MOAA/S	95	13–17	Procedure time 21 min	46–56 min	—
Zhang and colleagues[45]; China; 2016	RCT; 48; 1–6 months	Oral chloral hydrate 50 mg kg^{-1}; intranasal dexmedetomidine 1 μg kg^{-1}	MOAA/S	94	15.1	—	61.8 min	—
Zhang and colleagues[45]; China; 2016	RCT; 46; 1–6 months	Oral chloral hydrate 50 mg kg^{-1}; intranasal dexmedetomidine 2 μg kg^{-1}	MOAA/S	98	14.1	—	91.5 min	—
Midazolam and combinations								
Alp and colleagues[52]; Turkey; 2002	Clinical; 20; 2–78 months	Rectal midazolam 1 mg kg^{-1}	Five-grade scale according to Karl and colleagues[99]	0	—	—	60–100 min	None
D'Agostino and Terndrup[24]; USA; 2000	RCT; 22; 30 (25) months	Oral midazolam 0.5 mg kg^{-1}	—	50	—	76 (39) min	—	—
Hijazi and colleagues[28]; Saudi Arabia; 2014	RCT; 142; 26.2 (22.6) months	Oral midazolam 0.5–0.75 mg kg^{-1}	Ramsay sedation score	62	53 [41]	59 (35)	113 (48) min	Decrease in SpO_2 >10% below baseline and agitation (6.3%)
			N-PASS score	35	9	—	—	

Continued

Table 1 Continued

Authors; country location; year of publication	Study type; no. of patients; age	Medication	Sedation tool used	Success rate (%)	Onset time (min)	Sedation duration (min)	Recovery time	Adverse events
Inserra and colleagues[53]; Italy; 2022	Prospective; 98; 37.7–39.7 weeks	Intranasal midazolam 0.2–0.6 mg kg^{-1}						Bradycardia (2%); oxygen desaturation (7%)
Schmalfuss[48]; USA; 2005	Retrospective; 16; 19 (14) months	Oral midazolam 0.8 mg kg^{-1}	—	56	—	—	—	None
Cengiz and colleagues[54]; Turkey; 2006	RCT; 96; 1–7 yr	Oral diphenhydramine 1.25 mg kg^{-1}; midazolam 0.5 mg kg^{-1}	UMSS	82	20 (6)	Procedure time 31 (9)	28 (8) min	Nausea and vomiting (6%)
Pentobarbital								
Chung and colleagues[22]; USA; 2000	Prospective; 38; 0–12 months	Oral pentobarbital 4–6 mg kg^{-1}	—	97.4	21 (14)	67 (23)	88 (27) min	None
Mason and colleagues[38]; USA; 2004	Retrospective; 1024; 212 days	Oral pentobarbital 4 mg kg^{-1}	—	99.5	18 (11)	85 (34)	102 (34) min	Decrease in SpO_2 (0.2%); vomiting (0.2%); prolonged sedation (0.1%); After discharge, drowsiness (0.3%) and irritability (0.6%)
Mason and colleagues[55] USA; 2004	Retrospective; 1264; 0.55 (0.25) yr	Oral pentobarbital 4–8 mg kg^{-1}	—	99.5	18 (11)	90 (35)	108 (35) min	Decrease in SpO_2 (0.2%); vomiting (0.3%); prolonged sedation (0.2%); unplanned admission (0.2%); after discharge, drowsiness (0.3%) and irritability (0.3%)
Rooks and colleagues[42]; USA; 2003	Prospective; 317; 6.9 (31) months	Oral pentobarbital 4 mg kg^{-1}	—	99.7	19 (14)	81 (34)	100 (35) min	Vomiting (1.6%); prolonged sedation (1.6%); SpO_2 decrease (1.6%)
Schlatter and colleagues[56]; France; 2018	Prospective; 81; 8 months to 8 yr	Oral pentobarbital 5 mg kg^{-1}	—	67	30 (21)	47 (23)	77 (32) min	Rejection of doses because of bad taste (30%)
Thiopental								
Alp and colleagues[57]; Turkey; 1999	Clinical; 30; 2–78 months	Rectal thiopental 36.7 mg kg^{-1}	—	96.7	15	30	—	<90% SpO_2 (10%); bradycardia (3.3%); hiccup (3.3%)
Alp and colleagues[52]; Turkey; 2002	Clinical; 30; 2–78 months	Rectal thiopental 36.7 mg kg^{-1}	Five-grade scale according to	76.5	15	30	60–180 min	Respiratory depression (10%);

Continued

Table 1 Continued

Authors; country location; year of publication	Study type; no. of patients; age	Medication	Sedation tool used	Success rate (%)	Onset time (min)	Sedation duration (min)	Recovery time	Adverse events
			Karl and colleagues					<90% SpO_2 (6.7%); bradycardia (6.6%)
Beebe and colleagues[19]; USA; 2000	Clinical; 172; >18 months	Rectal thiopental 25 mg kg^{-1}	—	86	—	69 (32)	61 (53) min	Defecation
Beekman and colleagues[58]; the Netherlands; 1996	Clinical; 83; 0–8 yr	Rectal thiopental 36.7 mg kg^{-1}	—	95.2	30	90	4 h	—
Glasier and colleagues[59]; USA; 1995	Clinical; 462; 3 months to 12 yr	Rectal thiopental 25 mg kg^{-1}	—	96	12.2	—	71.1 min	Nausea and vomiting (14%); decreased SpO_2 (11%); ataxia (13%)
Gómez-Ríos and colleagues[60]; Spain; 2017	RCT; 21; 3 months to 6 yr	Rectal thiopental 25 mg kg^{-1}	—	100	13.50 (2.6)	10.14 (3.3)	47.50 (8.7) min	Vomiting (20%); anal mucosa irritation
Nguyen and colleagues[61]; USA; 2001	Prospective; 525; 3 months to 14 yr	Rectal thiopental 25–40 mg kg^{-1}	—	96	16 (10)	58	—	Oxygen desaturation (1.9%)
Melatonin and combination								
Heida and colleagues[62]; the Netherlands; 2020	Retrospective; 64; 10 months to 5 yr	Oral melatonin 6 mg kg^{-1}	—	77	—	Procedure time 10–29 min	—	None
Johnson and colleagues[63]; UK; 2002	Prospective; 40; 14 months to 18 yr	Oral melatonin 10 mg kg^{-1}	—	57	35	—	5–10 min	None
Pasini and colleagues[64]; Croatia; 2018	Prospective; 15; 4.5 yr	Oral melatonin 10 mg	—	93	—	30	—	—
Picone and colleagues[65]; Italy; 2019	Retrospective; 110; 1–28 days	Oral melatonin10 mg; tryptophan 20 mg; vitamin B6 1.4 mg	(i) Awake/ tended to fall asleep (ii) Wake up if stimulated (iii) Awake (iv) Other	81% in 2 mg; 93% in 3 mg; 100% in 4 mg	25	Procedure time 25 min	—	None
Dexmedetomidine								
Ambi and colleagues[66]; India; 2012	Prospective; 28; 0–10 yr	Intranasal dexmedetomidine 2 μg kg^{-1}	UMSS	60	30	Procedure time 11	81.39 min	None
Fan and colleagues[67]; Singapore; 2021	Retrospective; 56; 8.5–40 months	Intranasal dexmedetomidine 2–4 μg kg^{-1}	Ramsay sedation score	34	—	—	—	None
Inserra and colleagues[53]; Italy; 2022	Prospective; 78; 38–41 weeks	Intranasal dexmedetomidine 3 μg kg^{-1}	N-PASS score	59	19	—	—	Bradycardia (10%); oxygen desaturations (3%)
Olgun and Ali[68]; USA; 2018	Retrospective; 52; 1–12 months	Intranasal dexmedetomidine 4 μg kg^{-1}	—	96	—	Procedure time 35–50	—	>20% Decrease in baseline HR (39%); >20% decrease in MABP (3.8%)

Continued

Table 1 Continued

Authors; country location; year of publication	Study type; no. of patients; age	Medication	Sedation tool used	Success rate (%)	Onset time (min)	Sedation duration (min)	Recovery time	Adverse events
Tug and colleagues[69]; Turkey; 2015	RCT; 30; 1–10 yr	Intranasal dexmedetomidine 3 μg kg^{-1}	Ramsay sedation score	30	31	72	56 min	None
Tug and colleagues[69]; Turkey; 2015	RCT; 30; 1–10 yr	Intranasal dexmedetomidine 4 μg kg^{-1}	Ramsay sedation score	70	30	65	46 min	None
Dexmedetomidine and combinations: midazolam and ketamine								
Boriosi and colleagues[70]; USA; 2019	Retrospective; 220; 5–18 yr	Buccal dexmedetomidine 2–3 μg kg^{-1}; oral midazolam 0.21–0.53 mg kg^{-1}	Children's Hospital of Wisconsin Sedation Scale	81	39.3 (12.7)	Procedure time 58.1 (26.1)	61.2 (30.4) min	Hypoxaemia (2%); vomiting (2%); vasovagal episode (3%)
Cozzi and colleagues[71]; Italy; 2017	Retrospective; 108; 4–209 months	Intranasal dexmedetomidine 3 μg kg^{-1}; oral midazolam 0.5 mg kg^{-1}	Ramsay sedation score	84	33	Procedure time 35	91 min	Oxygen desaturation (5%); hypotension (3%); bradycardia (8%); vomiting (2%)
Inserra and colleagues[53]; Italy; 2022	Prospective; 101; 38.1–40.4 weeks	Intranasal dexmedetomidine 3 μg kg^{-1}; midazolam 0.2 mg kg^{-1}	N-PASS score	88	15.2	—	—	Bradycardia (6%); oxygen desaturation (3%)
Sulton and colleagues[72]; USA; 2020	Retrospective; 224; 8–28.5 months	Intranasal dexmedetomidine 2.5–3 μg kg^{-1}; midazolam 0.29–0.39 mg kg^{-1}	—	100	—	—	—	None
Wu and colleagues[73]; China; 2020	RCT; 40; 0–8 yr	Intranasal dexmedetomidine 3 μg kg^{-1}; midazolam 0.3 mg kg^{-1}	Ramsay sedation score	95	8.53 (5.39)	118.0 (13.47)	—	Respiratory depression (3%); nausea and vomiting (3%); cough (5%); dysphoria (3%); decreased HR (3%)
Liu and colleagues[74]; China; 2021	RCT; 168; 40.4 (17.6) months	Intranasal dexmedetomidine 3 μg kg^{-1}; ketamine 2 mg kg^{-1}	MOAA/S	82.1	10.9 (2.7)	29.7 (18.1)	53.8 (15.2) min	Airway obstruction (1.2%); vomiting (1.2%); emergence agitation (1.2%); delayed awakening (1.2%)
Sevoflurane and combination								
De Sanctis Briggs[75]; Spain; 2005	Retrospective; 640; 0–12 months	Inhalation sevoflurane 7% induction; 1.8–2% maintenance	Steward test score	98	—	38	—	Vomiting (0.2%); respiratory depression (2%)
Gómez-Ríos and colleagues[60]; Spain; 2017	RCT; 21; 3 months to 6 yr	Inhalation sevoflurane 1–8% induction; 2% maintenance	—	100	1.93 (0.7)	6.80 (1.6)	27.83 (5.1) min	Agitation
			—	92	—	—	—	

Continued

Table 1 Continued

Authors; country location; year of publication	Study type; no. of patients; age	Medication	Sedation tool used	Success rate (%)	Onset time (min)	Sedation duration (min)	Recovery time	Adverse events
Sury and colleagues[76]; UK; 2005	Prospective; 13; 46 months	Inhalation sevoflurane 4% induction; 2% maintenance						Respiratory events (7.7%)
Liu and colleagues[74]; China; 2021	RCT; 168; 40.8 (17.4) months	Intranasal dexmedetomidine 3 μg kg^{-1}; sevoflurane 0.4% in oxygen at 6 L min^{-1}	MOAA/S	95.2	5.7 (0.5)	28.8 (17.1)	27.4 (6.3) min	Airway obstruction (0.6%); bradycardia (1.8%); emergence agitation (1.8%)
Other								
Bluemke and Breiter[20]; USA; 2000	Retrospective; 588; 0–3 yr	Oral diazepam 0.2 mg kg^{-1}	—	87	—	—	—	—
Eker and colleagues[77]; Turkey; 2017	Clinical; 112; 12 (9) days	Oral glucose solution 30%, 0.5–1 ml	Wisconsin Sedation Scale	79	—	Procedure time 21.55 (9.53)	—	None
Shepherd and colleagues[78]; USA; 1990	Prospective; 79; 6.2 yr	Oral trimeprazine 3 mg kg^{-1}; droperidol 0.7 mg $(4\ kg)^{-1}$	—	56	—	—	—	—
Sury and colleagues[49]; UK; 1999	Prospective; 950; 10–20; >20 kg	Oral temazepam 1 mg kg^{-1} and droperidol 0.25 mg kg^{-1}	—	66	—	—	—	—
Volle and colleagues[79]; Germany; 1996	Prospective; 780; 0–8 yr	Oral chlorprothixene 1.8 mg kg^{-1}	—	91	30–120	Procedure time 30–120	6–8 h	Decreased SpO_2 (0.2%); respiratory depression (0.2%)

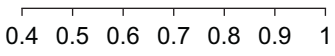
Table 2 Primary outcomes in pooled estimate and secondary outcomes in range per sedative. CI, confidence interval.

Sedative	Route of administration	Dosage	Success rate [95% CI]	Onset time (min)	Sedation duration (min)	Recovery time (min)
Chloral hydrate	Oral	30–105 mg kg^{-1}	0.94 [0.91–0.96]	15–45	34–165	22–278
Chloral hydrate+hydroxyzine	Oral	40+2 mg kg^{-1}	0.77	19	34	69
Chloral hydrate+midazolam	Oral	40+0.5 mg kg^{-1}	0.74	22	39	82
Chloral hydrate+thioridazine	Oral	50–100+2–4 mg kg^{-1}	0.89	30 min+2 h	—	—
Chloral hydrate+melatonin	Oral	50–100+3 mg kg^{-1}	1.00	39	—	—
Chloral hydrate+dexmedetomidine	Oral	50 mg kg^{-1}+0.4–2.0 μg kg^{-1}	0.95 [0.92–0.97]	13–17	—	46–92
Midazolam	Rectal/oral/intranasal	0.2–1.0 mg kg^{-1}	0.36 [0.14–0.65]	9–53	59–76	60–113
Midazolam+diphenhydramine	Oral	0.5+1.25 mg kg^{-1}	0.82	20	31	28
Pentobarbital	Oral	4–8 mg kg^{-1}	0.99 [0.90–1.00]	18–30	47–90	77–108
Thiopental	Rectal	25–40 mg kg^{-1}	0.92 [0.85–0.96]	12–30	10–90	48–240
Melatonin	Oral	6–10 mg kg^{-1}	0.75 [0.54–0.89]	35	30	5–10
Melatonin+tryptophan+vitamin B6	Oral	4 mg	1.00	25	—	—
Dexmedetomidine	Intranasal	2–4 μg kg^{-1}	0.62 [0.38–0.82]	19–31	65–72	46–81
Dexmedetomidine+midazolam	Intranasal or buccal Intranasal or oral	2–3 μg kg^{-1} +0.21–0.53 mg kg^{-1}	0.94 [0.78–0.99]	9–39	118	61–91
Dexmedetomidine+sevoflurane	Intranasal and inhalation	3 μg kg^{-1}+0.4% in oxygen at 6 L min^{-1}	0.95	5.7	28.8	27.4
Dexmedetomidine+ketamine	Intranasal	3 μg kg^{-1}+2 mg kg^{-1}	0.82	10.9	29.7	53.8
Sevoflurane	Inhalation	1–8% induction; 1.8–2%	0.98 [0.97–0.99]	2	7–38	28
Glucose solution	Oral	0.5–1.0 ml 30%	0.79	—	21.55	—
Chlorprothixenes	Oral	1.8 mg kg^{-1}	0.91	30–120	30–120	6–8 h
Diazepam	Oral	0.2 mg kg^{-1}	0.87	—	—	—
Trimeprazine+droperidol	Oral	3 mg kg^{-1}+0.7 mg (4 kg)$^{-1}$	0.56	—	—	—
Temazepam+droperidol	Oral	1+0.25 mg kg^{-1}	0.66	—	—	—

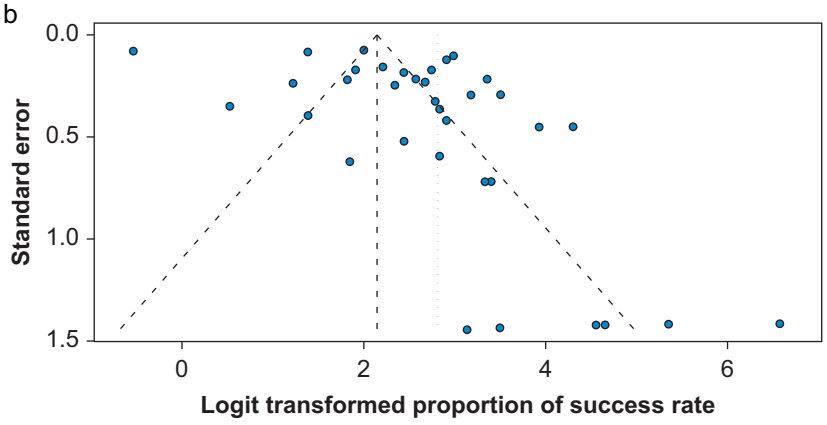
a

Study	Events	Total	Proportion	95% CI
Ahktar and colleagues 2007	301	324	0.93	[0.90–0.96]
Bailey and colleagues 2016	105	105	1.00	[1.00–1.00]
Beebe and colleagues 2000	148	172	0.86	[0.81–0.91]
Bluemke and Breiter 2000	1981	2081	0.95	[0.94–0.96]
Bracken and colleagues 2012	631	653	0.97	[0.95–0.98]
Chung and colleagues 2000	16	16	1.00	[1.00–1.00]
Cortellazzi and colleagues 2007	710	888	0.80	[0.77–0.83]
D'Agostino and Terndrup 2000	11	11	1.00	[1.00–1.00]
Dalal and colleagues 2006	78	101	0.77	[0.69–0.85]
Delgado and colleagues 2015	1500	1703	0.88	[0.87–0.90]
Finnemore and colleagues 2014	399	411	0.97	[0.95–0.99]
Goo and colleagues 2011	51	54	0.94	[0.88–1.00]
Greenberg and colleagues 1994	288	300	0.96	[0.94–0.98]
Hijazi and colleagues 2014	136	144	0.94	[0.91–0.98]
Hubbard and colleagues 1992	254	259	0.98	[0.96–1.00]
Keengwe and colleagues 1999	250	677	0.37	[0.33–0.41]
Kimiya and colleagues 2017	110	116	0.95	[0.91–0.99]
Lee and colleagues 2012	367	399	0.92	[0.89–0.95]
Litman and colleagues 2010	1302	1373	0.95	[0.94–0.96]
Malviya and colleagues 2000	263	302	0.87	[0.83–0.91]
Malviya and colleagues 2004	22	35	0.63	[0.47–0.79]
Marchi and colleagues 2004	52	52	1.00	[1.00–1.00]
Marti-Bonmati and colleagues 1995	46	50	0.92	[0.84–1.00]
Marti-Bonmati and colleagues 1995	47	47	1.00	[1.00–1.00]
Mason and colleagues 2004	369	374	0.99	[0.97–1.00]
Morriss and colleagues 2007	19	22	0.86	[0.72–1.00]
Morriss and colleagues 2007	60	62	0.97	[0.92–1.00]
Ronchera and colleagues 1992	162	172	0.94	[0.91–0.98]
Ronchera-Oms and colleagues 1994	560	596	0.94	[0.92–0.96]
Rooks and colleagues 2003	358	358	1.00	[1.00–1.00]
Schmalfuss 2005	290	310	0.94	[0.91–0.96]
Sury and colleagues 1999	187	205	0.91	[0.87–0.95]
Vade and colleagues 1995	56	58	0.97	[0.92–1.00]
Woodthorpe and colleagues 2007	410	455	0.90	[0.87–0.93]
Zhang and colleagues 2016	32	40	0.80	[0.68–0.92]
Fixed-effect model		**12925**	**0.90**	**[0.89–0.90]**
Random effects model			**0.94**	**[0.91–0.96]**
Prediction interval				**[0.56–1.00]**

Heterogeneity: I^2=98%, τ^2=1.5224, P<0.01



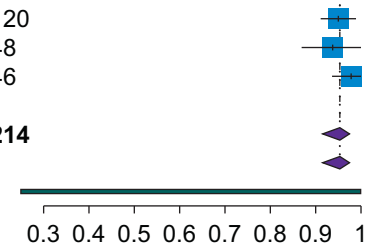
b



c

Study	Events	Total	Proportion	95% CI
Zhang and colleagues 2016	114	120	0.95	[0.91–0.99]
Zhang and colleagues 2015	45	48	0.94	[0.87–1.00]
Zhang and colleagues 2015	45	46	0.98	[0.94–1.00]
Fixed-effect model		**214**	**0.95**	**[0.92–0.97]**
Random effects model			**0.95**	**[0.92–0.97]**
Prediction interval				**[0.25–1.00]**

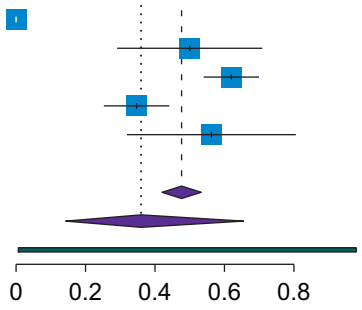
Heterogeneity: I^2=0%, τ^2=0, P=0.64



d

Study	Events	Total	Proportion	95% CI
Alp and colleagues 2002	0	20	0.00	[0.00–0.00]
D'Agostino and Terndrup 2000	11	22	0.50	[0.29–0.71]
Hijazi and colleagues 2014	88	142	0.62	[0.54–0.70]
Inserra and colleagues 2021	34	98	0.35	[0.25–0.44]
Schmalfuss 2000	9	16	0.56	[0.32–0.81]
Fixed-effect model		**298**	**0.48**	**[0.42–0.53]**
Random effects model			**0.36**	**[0.14–0.65]**
Prediction interval				**[0.01–0.98]**

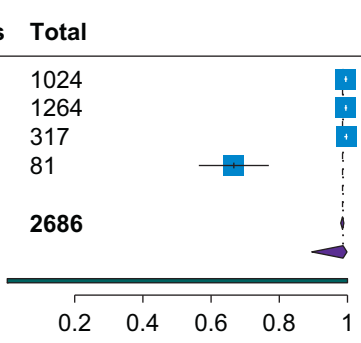
Heterogeneity: I^2=76%, τ^2=1.5676, P<0.01



e

Study	Events	Total	Proportion	95% CI
Mason and colleagues 2004	1019	1024	1.00	[0.99–1.00]
Mason and colleagues 2004	1258	1264	1.00	[0.99–1.00]
Rooks and colleagues 2003	316	317	1.00	[0.99–1.00]
Schlatter and colleagues 2018	54	81	0.67	[0.56–0.77]
Fixed-effect model		**2686**	**0.99**	**[0.98–0.99]**
Random effects model			**0.99**	**[0.90–1.00]**
Prediction interval				**[0.00–1.00]**

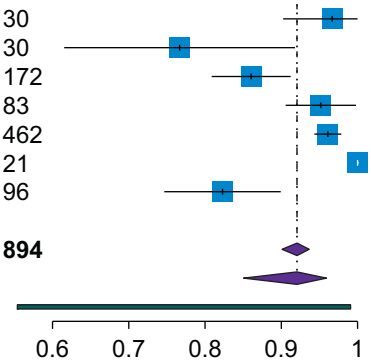
Heterogeneity: I^2=98%, τ^2=4.6120, P<0.01



f

Study	Events	Total	Proportion	95% CI
Alp and colleagues 1999	29	30	0.97	[0.90–1.00]
Alp and colleagues 2002	23	30	0.77	[0.62–0.92]
Beebe and colleagues 2000	148	172	0.86	[0.81–0.91]
Beekman and colleagues 1996	79	83	0.95	[0.91–1.00]
Glasier and colleagues 1995	444	462	0.96	[0.94–0.98]
Gómez-Ríos and colleagues 2017	21	21	1.00	[1.00–1.00]
Nguyen and colleagues 2001	79	96	0.82	[0.75–0.90]
Fixed-effect model		**894**	**0.92**	**[0.90–0.94]**
Random effects model			**0.92**	**[0.85–0.96]**
Prediction interval				**[0.55–0.99]**

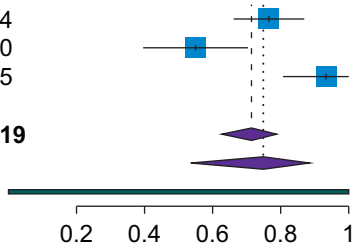
Heterogeneity: I^2=83%, τ^2=0.6232, P<0.01



g

Study	Events	Total	Proportion	95% CI
Heida and colleagues 2020	49	64	0.77	[0.66–0.87]
Johnson and colleagues 2002	22	40	0.55	[0.40–0.70]
Pasini and colleagues 2018	14	15	0.93	[0.81–1.00]
Fixed effect model		**119**	**0.71**	**[0.63–0.79]**
Random effects model			**0.75**	**[0.54–0.89]**
Prediction interval				**[0.00–1.00]**

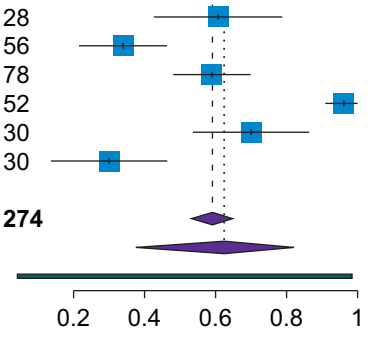
Heterogeneity: I^2=76%, τ^2=0.4362, P=0.01



h

Study	Events	Total	Proportion	95% CI
Ambi and colleagues 2012	17	28	0.61	[0.43–0.79]
Fan and colleagues 2021	19	56	0.34	[0.22–0.46]
Inserra and colleagues 2021	46	78	0.59	[0.48–0.70]
Olgun and Ali 2018	50	52	0.96	[0.91–1.00]
Tug and colleagues 2015	21	30	0.70	[0.54–0.86]
Tug and colleagues 2015	9	30	0.30	[0.14–0.46]
Fixed-effect model		**274**	**0.59**	**[0.53–0.65]**
Random effects model			**0.62**	**[0.38–0.82]**
Prediction interval				**[0.04–0.98]**

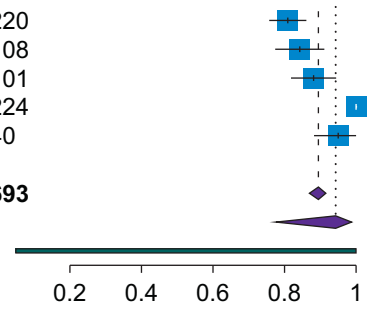
Heterogeneity: I^2=87%, τ^2=1.4517, P<0.01



i

Study	Events	Total	Proportion	95% CI
Boriosi and colleagues 2019	178	220	0.81	[0.76–0.86]
Cozzi and colleagues 2017	91	108	0.84	[0.77–0.91]
Inserra and colleagues 2021	89	101	0.88	[0.82–0.94]
Sulton and colleagues 2020	224	224	1.00	[1.00–1.00]
Wu and colleagues 2020	38	40	0.95	[0.88–1.00]
Fixed-effect model		**693**	**0.89**	**[0.87–0.92]**
Random effects model			**0.94**	**[0.78–0.99]**
Prediction interval				**[0.05–1.00]**

Heterogeneity: I^2=33%, τ^2=2.6548, P=0.20



j

Study	Events	Total	Proportion	95% CI
De Sanctis Briggs and colleagues 2005	627	640	0.98	[0.97–0.99]
Gómez-Ríos and colleagues 2017	21	21	1.00	[1.00–1.00]
Sury and colleagues 2005	12	13	0.92	[0.78–1.00]
Fixed-effect model		**674**	**0.98**	**[0.97–0.99]**
Random effects model			**0.98**	**[0.97–0.99]**
Prediction interval				**[0.60–1.00]**

Heterogeneity: I^2=0%, τ^2=0, P=0.43

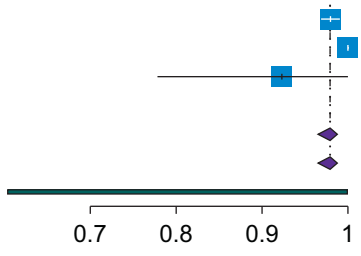


Fig 2. (a) Meta-analysis: forest plot of chloral hydrate. (b) Funnel plot of the logit transformed proportion of successful sedation with chloral hydrate. (c–j) Meta-analyses: forest plots of (c) chloral hydrate and dexmedetomidine, (d) midazolam, (e) pentobarbital, (f) thiopental, (g) melatonin, (h) dexmedetomidine, (i) dexmedetomidine and midazolam, and (j) sevoflurane. CI, confidence interval.

months was 100%, in children 1–3 yr was 76%, and in children 4–8 yr was 42%.[56] In addition, 30% of the failed sedations could be ascribed to children's rejection of pentobarbital because of its unpleasant taste.[56] Vomiting and oxygen desaturations occurred in 0.2–1.6% of cases.[38,42,55] Prolonged sedation was reported in 0.1–1.6%[38,42,55] and unplanned admission in 0.2%.[55] After discharge, 0.3% of patients experienced drowsiness and 0.3–0.6% of patients irritability.[38,55]

The meta-analysis of pentobarbital shows a pooled proportion of success of 0.99 (95% CI: 0.90–1.00; $P<0.01$; $I^2=98\%$) (Fig 2e).

Thiopental

Rectal thiopental 25–40 mg kg^{-1} was used as a sedative in seven studies ($n=1323$; Table 1).[19,52,57–61] The sedation success rate was 76.5–100% with an onset time of 12–30 min. Sedation duration lasted between 10 and 90 min; the recovery time varied between 47.5 and 180 min. Bradycardia occurred in 3.3–6.6%,[52,57] respiratory depression in 10%,[52] and oxygen desaturations in 1.9–11%[52,57,59,61] of the patients. Rectal irritation or defecation occurred in two studies[19,60] and vomiting in 14–20% of the patients.[59,60] One study reported hiccups in 3.3% of the patients[57]; another study reported ataxia in 13% of the patients.[59]

The meta-analysis of thiopental shows a pooled proportion of success of 0.92 (95% CI: 0.85–0.96; $P<0.01$; $I^2=83\%$) (Fig 2).

Melatonin and combinations

The use of oral melatonin is described in three studies ($n=119$; Table 1).[62–64] Doses of melatonin 3 mg for children 10 months to 1 yr, 5 mg for children 1–4 yr, and 10 mg for children 4–5 yr resulted in a 77% success rate.[62] A dose of 10 mg in two other studies resulted in a success rate of 57–93%.[63,64] The onset time was 35 min, the duration was 30 min, and the recovery time was 5–10 min.

A combination of melatonin 1 mg with tryptophan 20 mg and vitamin B6 1.4 mg[65] resulted in a 100% sedation success rate when a total of 4 mg was administered, with an onset sedation time of 25 min.

The meta-analysis of melatonin shows a pooled proportion of success of 0.75 (95% CI: 0.54–0.89; $P<0.01$; $I^2=76\%$) (Fig 2g).

Dexmedetomidine and combinations

The use of intranasal dexmedetomidine only for MRI procedures is described in six studies (274 patients; Table 1), of which one study reported two subgroups.[53,66–69] The success sedation rate varied from 60% in the study that used intranasal dexmedetomidine 2 μg kg^{-1},[66] to 30–59% in the studies that used 3 μg kg^{-1},[53,69] 70–96% in the studies that used intranasal dexmedetomidine 4 μg kg^{-1},[68,69] and 34% in the study that used 2–4 μg kg^{-1}.[67] The onset time of sedation was reported in three studies[53,66,69] and was 19–30 min. The sedation duration ranged from 11 to 72 min and the recovery time from 46 to 82 min. In addition, 39% of the patients in one study[68] showed a >20% decrease in baseline HR as an adverse event, 10% experienced bradycardia, and 3% oxygen desaturation.[53] The meta-analysis of dexmedetomidine shows a pooled proportion of success of 0.62 (95% CI: 0.38–0.82; $P<0.01$; $I^2=87\%$) (Fig 2h).[66,68,69]

Combinations of sedatives with dexmedetomidine have been described in five studies (693 patients) using midazolam,[53,70–73] one study (168 patients) using sevoflurane,[74] and one study (168 patients) using ketamine (Table 1).[74] The success sedation rate varied between these studies from 81.4% when using buccal dexmedetomidine 2–3 μg kg^{-1} and oral midazolam 0.21–0.53 mg kg^{-1},[70] to 84% when using intranasal dexmedetomidine 3 μg kg^{-1} and oral midazolam 0.5 mg kg^{-1},[71] to 95% when using intranasal dexmedetomidine 3 μg kg^{-1} and midazolam 0.3 mg kg^{-1},[73] to 100% when using intranasal dexmedetomidine 2.5–3 μg kg^{-1} and midazolam 0.29–0.39 mg kg^{-1},[72] to 88% when using intranasal dexmedetomidine 3 μg kg^{-1} and midazolam 0.2 mg kg^{-1}.[53] The reported onset sedation time was 9–39 min and the sedation duration 58–118 min. Recovery time was recorded as 61–91 min. Adverse events were hypoxaemia, vomiting, and vasovagal episodes in 3% of the patients.[70] Nausea and vomiting, cough, dysphoria, decreased HR, and respiratory depression were recorded in 2.5–5% of the patients.[73] Oxygen desaturation occurred in 3–5%, hypotension in 3%, bradycardia in 6–8%, and vomiting in 2% of the patients.[53,71]

The use of intranasal dexmedetomidine 3 μg kg^{-1} and intranasal ketamine 2 mg kg^{-1} was associated with a success rate of 82.1% with an onset time of 10.9 (sd 2.7) min, sedation duration of 29.7 (sd 18.1) min, and recovery time of 53.8 (sd 15.2) min.[74] Adverse events, such as airway obstruction, happened in 1.2%, vomiting in 1.2%, emergence agitation in 1.2%, and delayed awakening in 1.2% of the patients.

The combination of dexmedetomidine and midazolam shows a pooled proportion of success of 0.94 (95% CI: 0.78–0.99; $P=0.23$; $I^2=33\%$) (Fig 2i).

Sevoflurane and combinations

Three studies (674 patients; Table 1) reported the use of sevoflurane as a sedative technique for MRI.[60,75,76] These studies used an $ETCO_2$ concentration of sevoflurane 1.8–2% with a peak concentration of 1–8% at induction whilst patients were spontaneously breathing through a face mask (Oximask; Vecmedical, Barcelona, Spain) fixated with an elastic band over their heads *via* an anaesthetic circuit or Mapleson C system, or a Smart CapnoLine™ (Proact Medical Ltd, Kettering, Northamptonshire, UK) in both nostrils fixed to the cheeks with adhesive tape. In all three studies, 2 L O_2 min^{-1} was used. This resulted in 92–100% sedation success rate. The onset time was approximately 1.93 (sd 0.7) min, and the sedation duration varied from 6.8 to 38 min. Recovery lasted 28 (sd 5) min. During the procedure, 1.5% of the patients experienced minor to severe hypoxia, and 0.1% had an episode of vomiting.[75] A respiratory event occurred in 7.7% of the patients.[76]

The meta-analysis of sevoflurane shows a pooled proportion of success of 0.98 (95% CI: 0.97–0.99; $P<0.01$; $I^2=0\%$) (Fig 2j).

The use of sevoflurane 0.4% applied through a face mask in oxygen at 6 L min^{-1} in combination with dexmedetomidine 3 μg kg^{-1} was associated with a success rate of 95.2%.[74] The onset time was 5.7 (sd 0.5) min, the sedation duration was 28.8 (sd 17.1) min, and the recovery time was 27.4 (sd 6.3) min. Adverse events were airway obstruction in 0.6%, bradycardia in 1.8%, and emergence agitation in 1.8% of patients.

Other

Five other forms of pharmacological sedative techniques were reported in single studies (Table 1). Fifty-six newborns were given an oral glucose solution 30% in 0.5–1 ml, associated with a sedation success rate of 78.9%.[77] Oral chlorprothixene was given in a dose of 1.8 mg kg^{-1}, associated with a sedation

success rate of 91%.[79] Oral diazepam 0.2 mg kg^{-1} was associated with a success rate of 87%.[20] A combination of oral trimeprazine 0.3 mg kg^{-1} and droperidol 0.7 mg kg^{-1} was associated with a success rate of 56%.[78] Lastly, a combination of oral temazepam 1 mg kg^{-1} and droperidol 0.25 mg kg^{-1} was associated with a success rate of 66%.[49]

Discussion

This systematic review showed a large variation in medication type, dosage, route of administration, and success rates for sedation of children aged 0–8 yr undergoing an MRI procedure. The pooled success rate for oral chloral hydrate was 94%; for oral chloral hydrate and intranasal dexmedetomidine 95%; for rectal, oral, or intranasal midazolam 36%; for oral pentobarbital 99%; for rectal thiopental 92%; for oral melatonin 75%; for intranasal dexmedetomidine 62%; for intranasal dexmedetomidine and midazolam 94%; and for inhaled sevoflurane 98%.

The combination of intranasal dexmedetomidine 3 μg kg^{-1} and intranasal midazolam 0.3 mg kg^{-1} had varied success rates from 81% to 100%. The onset time lasted between 9 and 39 min, the duration between 58 and 118 min, and the recovery time between 61 and 91 min. In addition, adverse events, such as hypoxaemia, vomiting, respiratory depressions, and bradycardia, were rare (2–8%) compared with other sedatives. We were unable to perform any statistical analysis on the adverse events of the sedation methods used. The combination of intranasal dexmedetomidine 3 μg kg^{-1} and intranasal midazolam 0.3 mg kg^{-1} had the best success rate and least (serious) adverse events and might be the preferred needle-free pharmacological sedation technique.

Chloral hydrate was associated with a high success rate but also with a high incidence of adverse events, such as prolonged sedation, ataxia, hyperactivity, and nervousness. Chloral hydrate was used in approximately one-third of the included studies; therefore, the high incidence of adverse events associated with chloral hydrate could be biased because of over-registering of adverse events compared with other sedative techniques. Prolonged sedation was reported in 0.18–30% of the patients included in this systematic review. A previous review, not included in the present meta-analysis,[84] also reported serious adverse events in patients receiving oral chloral hydrate as sedation. The study reviewed 95 incidents, not all caused by chloral hydrate, but it states that patients receiving long half-life medication, such as chloral hydrate, had a higher risk of ending in injuries or death post-discharge. The authors concluded that chloral hydrate as a sedative agent requires supervision of skilled medical personnel and extended observation (time not defined) for long-acting sedatives, such as chloral hydrate.

Intranasal dexmedetomidine as a solo sedative was not effective over the duration of the MRI examination. Nevertheless, a systematic review on the effectiveness of dexmedetomidine *vs* chloral hydrate for diagnostic procedures in general[11] showed that intranasal dexmedetomidine is a superior alternative to chloral hydrate because it was more effective and better accepted for a large range of procedures. Our review was focused on MRI procedures, because CT, ophthalmic examination, and transthoracic echocardiography demand a different form of sedation varying between analgesic and anxiolytic effects. Furthermore, one study in this review, which used dexmedetomidine 4 μg kg^{-1}, reported a >20% decrease in baseline HR in 20 out of the 50 included patients.[68] Higher doses of dexmedetomidine might result in higher and acceptable success ratios but unavoidable and unacceptably increase the number of adverse events. Therefore, in contrast to the previously mentioned systematic review, we concluded from the results of the present systematic review that high-dose dexmedetomidine as a solo sedative might not be sufficient for sedation for an MRI procedure despite a success rate of 70–96%.

Sevoflurane was associated with a success rate of 92–100% but caused respiratory events.[76] Moreover, it is questionable whether the use of inhalation drugs can be labelled minimally invasive because a face mask is placed on the patient's face. Furthermore, leakage of sevoflurane vapour may be harmful to the personnel's health and the environment because usually the ventilation system in an MRI unit is less effective than that in an operating theatre.[85] At last, the end-tidal sevoflurane concentrations used for 'needle-free sedation' depending on the age of the child represent up to 1 minimum alveolar concentration. We think that this should be considered as general anaesthesia without airway control and with no i.v. access in case problems arise rather than sedation. Therefore, authors do not recommend this technique. Nevertheless, we chose to include this in the present systematic review because it fulfilled the inclusion criteria.

Whether the administration of the drug is minimally invasive is also questionable when using rectally administered medication. Again, we included these patients because they met our inclusion and exclusion criteria. However, children of different ages, for example the older children, and cultures can experience rectal insertion as uncomfortable or intrusive and should be considered when selecting a sedation technique.

Oral midazolam and melatonin as solo sedatives were associated with a success rate ranging from 0% to 93%. In view of this large variability, these sedatives are not very suitable for longer procedures, such as MRI examination. Rectal thiopental was associated with a relatively long recovery time and resulted in 10% respiratory depression. Moreover, one in five patients experienced episodes of nausea and vomiting. The incidence of vomiting associated with the use of oral pentobarbital was much lower (1.6%), but the downside was prolonged sedation, which can be a dangerous adverse event in outpatient MRI examinations. The combination of dexmedetomidine with sevoflurane or ketamine is promising but has only been studied once. Further research on its effectiveness and safety is required before this combination can be clinically implemented.

Multiple combinations of medication were only investigated by one or two studies, which might have hampered an objective comparison.

A limitation of this systematic review is the large heterogeneity of the 52 studies included in the meta-analysis. This heterogeneity varied between 0% and 98% and could be related to the differences in patient population, which means that patient selection does play a role in our opinion between the studies but also in the variety of sedation tool used, different definitions of adequate sedation, sedation duration, and recovery time.

Traditionally, a sedation encounter was considered successful when a procedure was completed without significant adverse events. The encounter was considered a failure if the MRI procedure was not completed, or there was a severe adverse event associated with the sedation. However, the quality of MRI as an outcome of 'success' is an equally important part of a successful sedation.[86] Regrettably, only

nine studies included an assessment of the quality of MRI. A variety of sedation tools, such as the Ramsay Sedation Scale, Skeie Scale, Wisconsin Sedation Scale, and University of Michigan Sedation Scale, were used to assess the level of sedation in these children. This could have resulted in discrepancies between the definitions of adequate sedation. The same applies to the definitions of sedation duration and recovery time. Some studies reported sedation duration as the time elapsed between administration and waking up, whilst other studies defined sedation duration as the time elapsed between adequate level of sedation and waking up. Adverse events were often not specified or mixed with their surrogates and could therefore be generally underreported. Also, the success rates of the prospective studies might be higher than those of the retrospective studies. Being included in a study might improve the success of the effect of that therapy compared with daily clinical practice—the so-called Hawthorn effect.

The quality assessment showed that only one quarter of the studies included a proper follow-up period of 24 h, which could have resulted in underreporting of adverse events. Moreover, only one quarter of the studies (Supplementary Appendix 2) included a prospective calculation of the necessary sample size, which makes it unclear if the effect found on the participants in the study can be extrapolated to population level.

Lastly, the use of non-pharmacological interventions, such as sleep deprivation in infants and feed and wrap in neonates, was explicitly mentioned only in nine studies. Application of these non-pharmacological interventions could have been of influence on the success rate.[87,88] However, these interventions were not always (fully) described in method sections and can vary per study. The same is true for the feasibility of dispensing sedation.[87,89] New techniques, such as motion correction of MRI images, may also influence success rates or sedation needs.[90] Therefore, a conclusion on the effects of non-pharmacological interventions on the primary outcome could not be drawn.

The result of the present review shows that there is a need for a higher standard of reporting, with more detailed outcome information.[91] Sedative drug trials should report the relative efficiency of their care, recovery times, the precise discharge criteria, etc. We recommend that future studies use the existing definitions as suggested by the International Committee for the Advancement of Procedural Sedation.[92]

Furthermore, satisfaction and perceptions of the child or parents have not been addressed in most studies. Sedation failure is distressing for the patient, family members, and all the staff involved, and it has cost implications because the children must be rescheduled for either repeat sedation or general anaesthesia. This again is an argument for careful selection of appropriate patients for sedation, recognising that general anaesthesia remains a safe alternative in those who fail the selection process.[8]

Future research could also be focused on the evaluation of clinical implementation of the use of intranasal dexmedetomidine 3 μg kg^{-1} and intranasal midazolam 0.3 mg kg^{-1} as sedatives for children aged 0–8 yr for MRI procedures. There is an increasing demand for sedation services in children for MRI imaging, which have a large demand on the available capacity and scheduling.[1] Safe and reliable needle-free sedation techniques would be extremely important in accommodating these needs, without putting excessive pressure on anaesthetic departments for 'sedation services' within radiology departments. The presence of well-organised teams, especially dedicated exclusively to paediatric sedation and dealing with relatively large numbers of patients, has shown to be a safe and practical solution.[1] Moreover, cost-effectiveness and organisational difficulty analysis could be done on the use of this technique compared with i.v. medication and general anaesthesia.[93] An interesting factor in this analysis could be the participation of non-anaesthesiologists, for example physician assistants, a paediatrician, or an anaesthetic nurse.[94] In children's hospitals, multidisciplinary sedation teams have demonstrated excellent success rates and safety records for sedation for radiological procedures.[30,95] The presence of these well-organised teams dedicated exclusively to paediatric sedation and dealing with relatively large numbers of patients appears to be more important than the use of a specific sedative or regimen.

Results of this systematic review reflect a historical evolution. Older drugs, such as chloral hydrate, were first extensively used and only years or even decades later closely studied for adverse events. This resulted in advice against its use. Meanwhile, the development of new drugs (i.e. the rise in the use of propofol in the past 25 yr and dexmedetomidine in the past 10 yr) and monitoring techniques continued, resulting in new protocols, standards, and guidelines.[96] Recently published reviews[97,98] analysed the trends in paediatric MRI sedation techniques. One study found a shift from propofol-only anaesthesia to propofol combined with dexmedetomidine as sedative drugs.[97] This same review nonetheless still shows an anaesthetic practice mainly focused on invasive (i.v. or volatile) anaesthesia and does not explore noninvasive ways like we aimed to do.

In conclusion, this systematic review is the first to focus on a specific procedure—MRI examination—and shows a large variation of 36–98% success rates. Furthermore, adequate sedation is possible, as a needle-free sedative technique for children aged 0–8 yr scheduled for this procedure is adequate and successful and can be an alternative to i.v. or i.m. medication.

Authors' contributions

Study concept/design: IdR, JW, JJD, SEH, JCdG
Development of search strategy: IdR, JW, WMB, JCdG
Clinical implementation: JCdG
Literature review: IdR, JW
Data analysis/interpretation: IdR, JW, SEH, JCdG
Article writing: IdR, JW, JCdG
Article revision: IdR, JW
Article critical revision: WMB, JCdG

Declaration of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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