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Efficacy and safety of rectal chloral hydrate for pediatric procedural sedation

A systematic review and meta-analysis

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Abstract

Background: To evaluate the efficacy and safety of rectal chloral hydrate (CH) in pediatric procedural sedation.

Methods: Seven electronic databases and 3 clinical trials registry platforms were searched, and the deadline was August 2022. Randomized controlled trials evaluating the efficacy and safety of rectal CH in pediatric procedural sedation were included by 2 reviewers. The extracted outcomes included the success rate of sedation, sedation latency, sedation duration, and adverse events. The Cochrane risk of bias tool was used to assess the risk of bias. The outcomes were analyzed using Review Manager 5.3 software.

Results: Forty-four randomized controlled trials with 8007 children were included in the meta-analysis. The success rate of sedation in the rectal CH group was significantly higher than that in the placebo group (risk ratio [RR], 2.60 [95% confidence interval [CI], 1.74–3.89]; $P < .01$; RR, 1.24 [95% CI, 1.01–1.54]; $P = .04$), oral CH group (RR, 1.12 [95% CI, 1.09–1.14]; $I^2 = 36\%$; $P < .001$; number needed to treat [NNT] = 10), diazepam group (RR, 1.21 [95% CI, 1.10–1.33]; $I^2 = 0\%$; $P < .001$; NNT = 6), phenobarbital group (RR, 1.24 [95% CI, 1.13–1.35]; $I^2 = 12\%$; $P < .001$; NNT = 6), and ketamine group (RR, 1.39 [95% CI, 1.20–1.60]; $I^2 = 20\%$; $P < .001$; NNT = 5). There was no significant difference in the success rate of sedation between the rectal CH group and the midazolam group (RR, 0.98 [95% CI, 0.86–1.11]; $I^2 = 51\%$; $P > .05$). The sedation latency was significantly shorter in rectal CH group than that in the oral CH group (mean difference [MD], −6.36 [95% CI, −7.04 to −5.68]; $I^2 = 49\%$; $P < .001$) and the phenobarbital group (MD, −7.64 [95% CI, −9.12 to −6.16]; $P < .00001$). The sedation duration in the rectal CH group was significantly longer than in the oral CH group (MD, 6.43 [95% CI, 4.39–8.47]; $I^2 = 0\%$; $P < .001$). The overall incidence of adverse events was significantly lower with rectal CH than with oral CH (RR, 0.21 [95% CI, 0.16–0.29]; $I^2 = 45\%$; $P < .001$) and ketamine (RR, 0.26 [95% CI, 0.12–0.60]; $I^2 = 0\%$; $P = .001$). There was no significant difference in the overall incidence of adverse events with rectal CH compared with intramuscular midazolam (RR, 0.55 [95% CI, 0.23–1.28]; $P = .17$) and intranasal midazolam (RR, 3.00 [95% CI, 0.66–13.69]; $P = .16$).

Conclusion: The available evidence suggests that rectal CH cloud be an effective and safe sedative agent for pediatric procedural sedation.

Abbreviations: CH = chloral hydrate, CI = confidence interval, MD = mean difference, NNT = number needed to treat, RCT = randomized controlled trial, RR, risk ratio.

Keywords: children, chloral hydrate, efficacy, meta-analysis, safety, sedation.

1. Introduction

Advances in the treatment of childhood illness have led to an increase in the number of painful or distressing diagnostic or therapeutic procedures for which many children require effective sedation.[1] The goals of sedation in children during diagnostic or therapeutic procedures include reducing fear and anxiety, improving pain control, and reducing movement. Nowadays, commonly used medicines for procedural sedation include benzodiazepines (such as midazolam and diazepam), barbiturates (such as phenobarbital and pentobarbital),

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All data generated or analyzed during this study are included in this published article and its supplementary information files.

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aldehydes (such as chloral hydrate [CH]), etc. For children, clinical guidelines recommend procedural sedatives including CH, midazolam, ketamine, dexmedetomidine, and pentobarbital.[1–3]

CH is a central nervous system depressant and one of the oldest sedatives (discovered in 1832).[2] Rectal administration of CH is one of the most commonly used methods of sedation in pediatrics. It is widely used in children with febrile seizures, intracranial disorders, and ancillary examinations, such as B-ultrasound and computed tomography. CH is quickly absorbed from the intestinal mucosa after rectal administration and is then rapidly metabolized by alcohol dehydrogenase in the liver and erythrocytes to trichloroethanol.[4] The trichloroethanol has a strong inhibitory effect on the central nervous system, a rapid hypnotic effect, and generally acts within 20 minutes to induce near-normal physiological sleep. After waking up, there are no symptoms of drowsiness or dizziness, which is easily accepted by the children' families.

Currently, the British National Formulary for Children (2022–2023) states that CH is administered by mouth or by rectum (if the oral route is not available).[3] The National Institute for Health and Care Excellence 2018 guideline reports that oral midazolam produces less effective sedation than CH for children undergoing noninvasive diagnostic procedures, and CH may be effective for sedation during auditory brainstem response testing.[4] Rectal administration of CH is a common route of pediatric sedation in some countries, such as Japan and China. Before 2019, CH had entered the pharmaceutical market in Japan and was only widely used as a hospital preparation in China. By 2019, CH had entered the pharmaceutical market in China.

However, there is no systematic review of the efficacy and safety of rectal CH in pediatric procedural sedation. Therefore, this review aims to systematically evaluate the efficacy and safety of rectal CH compared to placebo, no intervention, or other sedative hypnotics in pediatric procedural sedation, providing evidence for clinical use and postmarketing surveillance by the pharmaceutical industry.

2. Materials and methods

2.1. Literature search

Our search included 7 electronic literature databases (PubMed, Embase, Cochrane Library, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, VIP Database for Chinese Technical Periodicals, and Wanfang Database) and 3 clinical trial registry platforms (the ClinicalTrials.gov, the World Health Organization Clinical Trials Registry Platform, and Cochrane Central Registry of Controlled Trials). The deadline for all retrieval was August 2022. The search terms were ("chloral hydrate" OR "somnos" OR "nycton" OR "dormal") AND ("child" OR "newborn" OR "infant" OR "neonate" OR "toddler" OR "teenager" OR "adolescent" OR "pediatric").[5] The exact search strategy for 7 electronic literature databases was added in Table 1, Supplemental Digital Content, http://links.lww.com/MD/N447.

2.2. Inclusion criteria

The following studies were included: participants: children (0–18 years) requiring procedural sedation; intervention: rectal CH; comparison: placebo, no intervention, or other sedative hypnotics; outcomes: success rate of sedation (the ratio of the number of people who successfully complete the examination or surgery to the total number of people), sedation latency (the time from completion of medication to the state of falling asleep), sedation duration (the time from sleep to response to instruction), and adverse events; and study type: randomized controlled trials (RCTs). The following studies were excluded: trials with incomplete or missing information, such as abstracts only, and non-Chinese or non-English literature, such as Japanese literature.

2.3. Data extraction

Two independent reviewers screened all the titles and abstracts to identify potentially eligible articles. They applied the eligibility criteria independently to make the final selection. Any disagreements were resolved by discussion or by a third reviewer. Data were extracted independently by 2 reviewers using a standard form,[6] including the year of publication, basic information about the included patients (such as sample size, and age), interventions (such as medicine name, dosage, and method of administration), outcomes (such as success rate of sedation and sedation latency), etc.

2.4. Quality assessment

Two independent reviewers (ZC and FQ) were required to finish the retrieval work. We used the risk of bias assessment tool in the Cochrane Handbook for Systematic Reviews of Interventions to assess the quality of the included studies. The quality assessment included whether the random sequence generation was correct, whether there was an allocation concealment scheme, whether the blinding method was used, whether the blinding of outcome assessment was used, etc. Each indicator was divided into 3 levels: "yes" (low risk of bias), "no" (high risk of bias), and "unclear" (lack of relevant information). Disagreements were well resolved by discussion between 2 reviewers or with a third reviewer.

2.5. Statistical analysis

Meta-analysis was performed using Review Manager 5.3. The risk ratio (RR) with 95% confidence interval (CI) was used for dichotomous variables. The mean difference (MD) with 95% CI was used for continuous data. Heterogeneity was assessed using I^2 statistics. A fixed effects model was initially conducted. If there was significant heterogeneity among trials ($I^2 > 50\%$), potential sources of heterogeneity were considered, and where appropriate, a random effects model was used. If the heterogeneity of the random effects model was still >50%, descriptive analysis was used to evaluate the efficacy and safety of CH rectal solution in children. The number needed to treat (NNT) analyses were calculated with the main outcome (success rate of sedation).

2.6. Ethical statement

As all analyses were based on previous publications, ethical approval was not necessary.

3. Results

3.1. Characteristics of the included studies

A total of 2732 records were identified in the initial screening. Forty-four RCTs published between 2003 and 2020 were included in this meta-analysis (Fig. 1). A total of 8007 children were included. The dose of rectal CH ranged from 20 to 80 mg/kg (Table 1).

3.2. Quality assessment

We assessed clinical heterogeneity using the Cochrane risk of bias estimation tools; 90.91% of studies (40/44) reported no selective reporting; 84.09% of studies (37/44) reported complete outcome data; and 93.18% of studies (41/44) reported no other

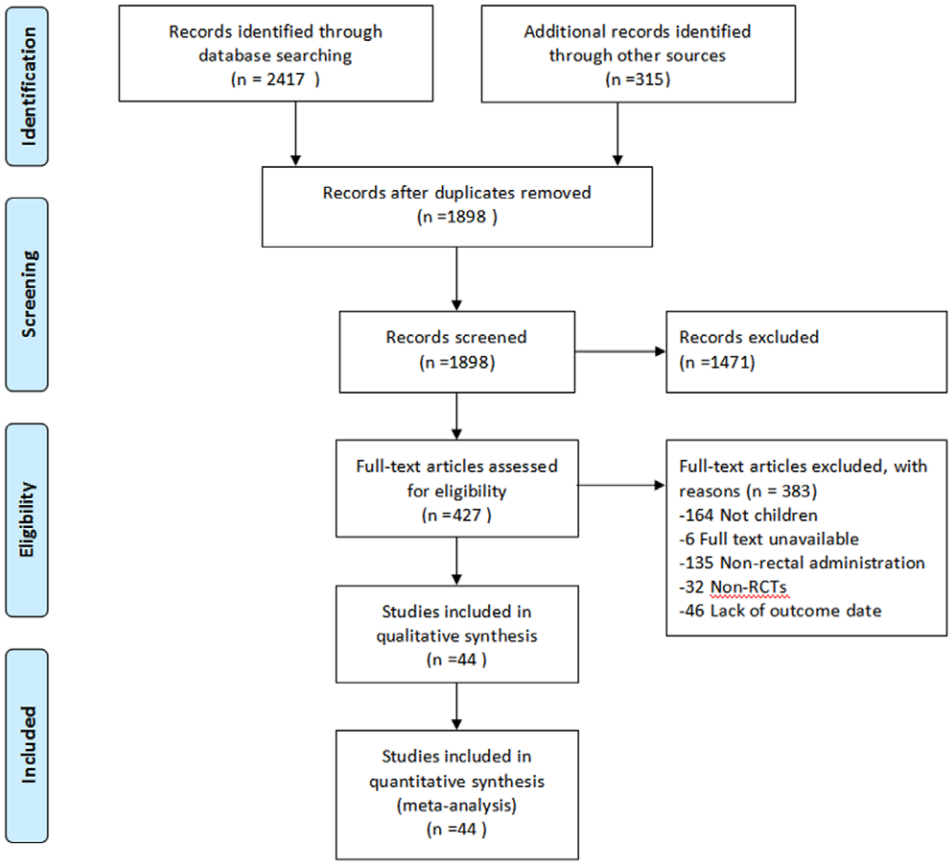

Figure 1. Flow diagram of study selection. RCT = randomized controlled trial.

bias. Most studies did not clearly report on random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment (Table 2).

3.3. Efficacy

3.3.1. Success rate of sedation. Of the 44 RCTs, 2 studies with 137 children compared rectal CH with placebo.[7,8] Compared with the placebo group, the success rate of sedation increased significantly in the rectal CH group (RR, 2.60 [95% CI, 1.74–3.89]; $P < .01$; RR, 1.24 [95% CI, 1.01–1.54]; $P = .04$).

Thirty-two studies with 5236 children compared rectal CH with oral CH.[9–38] Before sensitivity analysis, 3 studies had significant heterogeneity. After sensitivity analysis, the success rate of sedation increased significantly in the rectal CH group than in the oral CH group, with no heterogeneity (RR, 1.12 [95% CI, 1.09–1.14]; $I^2 = 36\%$; $P < .001$; NNT = 10)[10,11,13–15,19,20,22,23,25–29,31–34,36,38] (Fig. 2).

Two studies with 335 children compared rectal CH with midazolam.[7,39] There was no significant difference in the success rate of sedation between the rectal CH group and the midazolam group (RR, 0.98 [95% CI, 0.86–1.11]; $I^2 = 51\%$; $P > .05$).

Five studies with 704 children compared rectal CH with diazepam.[27,39,40,42,51] Before sensitivity analysis, 3 studies had significant heterogeneity.[27,39,51] After sensitivity analysis, the success rate of sedation in the rectal CH group was higher than in the diazepam group (RR, 1.21 [95% CI, 1.10–1.33]; $I^2 = 0\%$; $P < .001$; NNT = 6)[40,42] (Fig. 3).

Four studies with 547 children compared rectal CH with phenobarbital.[32,39,40,43] Before sensitivity analysis, 1 subgroup had significant heterogeneity.[32] After sensitivity analysis, the success rate of sedation was higher in the rectal CH group than in the phenobarbital group (RR, 1.24 [95% CI, 1.13–1.35]; $I^2 = 12\%$; $P < .001$; NNT = 6)[39,40,43] (Fig. 4).

Three studies with 375 children compared rectal CH with ketamine.[44–46] The success rate of sedation was higher in the rectal CH group than in the ketamine group, with no heterogeneity (RR, 1.39 [95% CI, 1.20–1.60]; $I^2 = 20\%$; $P < .001$; NNT = 5; Fig. 5).

3.3.2. Sedation latency. Of the 44 RCT studies, 6 studies with 1160 children compared rectal CH with oral CH.[7,19,23,24,33,34] Before sensitivity analysis, 1 study had significant heterogeneity.[24] After sensitivity analysis, sedation latency was significantly shorter in the rectal CH group than in the oral CH group, with no heterogeneity (MD, −6.36 [95% CI, −7.04 to −5.68]; $I^2 = 49\%$; $P < .001$)[17,19,23,33,34] (Fig. 6).

Two studies with 356 children compared rectal CH with midazolam.[17,48] Sedation latency was significantly longer in the rectal CH group than in the intranasal midazolam group (MD, 5.90 [95% CI, 3.82–7.98]; $P < .001$) and the intramuscular midazolam group (MD, 7.70 [95% CI, 5.75–9.65]; $P < .001$).

One study with 88 children compared rectal CH with phenobarbital.[46] Sedation latency was significantly shorter in the rectal CH group than in the phenobarbital group (MD, −7.64 [95% CI, −9.12 to −6.16]; $P < .00001$).

3.3.3. Sedation duration. Of the 44 RCTs, 4 studies with 442 children compared rectal CH with oral CH.[17,19,23,34] Before sensitivity analysis, 1 study had significant heterogeneity.[22] After sensitivity analysis, the sedation duration was significantly longer in the rectal CH group than in the oral CH group, with no heterogeneity (MD, 6.43 [95% CI, 4.39–8.47]; $I^2 = 0\%$; $P < .001$)[19,34,40] (Fig. 7).

Two studies with 356 children compared rectal CH with midazolam.[17,48] The sedation duration was significantly longer in

Table 1

Characteristics of included studies.

Author/Year	Sample size	Interventions	Age, mo	Examination types	Success rate of sedation, %	Sedation latency, min	Sedation duration, min	Adverse events
Huang 2017[7]	T: 40 C: 40	T: chloral hydrate, rectal, 0.6 mL/kg C: blank control	12–36	Lumbar puncture	T: 97.50% C: 37.50%			
Li 2011[8]	T: 30 C: 27	T: chloral hydrate, rectal, 0.5 mL/kg C: routine nursing care	13–85	Peripherally inserted central catheter	T: 96.67% C: 77.78%			
Yu 2005[9]	T: 30 C: 30	T: chloral hydrate, rectal, 0.2–0.4 mL/kg C: chloral hydrate, oral, 0.2–0.4 mL/kg	0–36	MRI	T: 80.00% C: 60.00%			
Fu 2009[10]	T: 60 C: 60	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	0.13–36		T: 91.67% C: 83.87%			
Yu 2013[11]	T: 60 C: 60	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	1–96	CT, EEG, MRI	T: 95.00% C: 78.33%			
Feng 2009[12]	T: 101 C: 102	T: chloral hydrate, rectal, 50 mg/kg C: chloral hydrate, oral, 50 mg/kg		Ultrasonography, ECG, CT, MRI, lumbar puncture	T: 86.14% C: 98.04%			
Liu 2010[13]	T: 46 C: 46	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	2–96	MRI, CT, ECG, ultrasonography	T: 97.83% C: 82.61%			
Liu 2007[14]	T: 50 C: 50	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg		MRI	T: 98.00% C: 82.00%			T: vomiting (n = 0), bucking (n = 0) C: vomiting (n = 38), bucking (n = 5)
Liu 2011[15]	T: 30 C: 30	T: chloral hydrate, rectal, 0.5–0.8 mL/kg C: chloral hydrate, oral, 0.5–0.8 mL/kg	3–36	Sutures in cleft lip	T: 96.67% C: 86.67%			
Zhou 2005[16]	T: 51 C: 74	T: chloral hydrate, rectal, 0.4–0.5 mL/kg C: chloral hydrate, oral, 0.4–0.5 mL/kg	1.33–12	Hearing examination	T: 74.51% C: 93.24%			

(*Continued*)

Table 1

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Author/Year	Sample size	Interventions	Age, mo	Examination types	Success rate of sedation, %	Sedation latency, min	Sedation duration, min	Adverse events
Qu 2016[17]	T: 40 C1: 40 C2: 40 C3: 40	T: chloral hydrate, rectal, 0.4–0.6 mL/kg C1: chloral hydrate, oral, 0.4–0.6 mL/kg C2: midazolam, intramuscular, 0.2 mg/kg C3: midazolam, intranasal, 0.2 mg/kg	0–48	CT, MRI, lumbar puncture, ultrasonography,	T: 90.00% C1: 73.3% C2: 83.3% C3: 86.6%	T: 16.5 ± 4.8 C1: 21.9 ± 6.0 C2: 8.8 ± 2.6 C3: 10.6 ± 3.3	T: 63.7 ± 11.6 C1: 45.4 ± 9.3 C2: 45.2 ± 8.7 C3: 58.4 ± 12.4	T: poor oxygenation (n = 0), cardiovascular inhibition (n = 4), respiratory depression (n = 1), nausea/vomiting (n = 1) C1: poor oxygenation (n = 0), cardiovascular inhibition (n = 1), respiratory depression (n = 4), nausea and vomiting (n = 9) C2: poor oxygenation (n = 2), cardiovascular inhibition (n = 7), respiratory depression (n = 2), nausea, vomiting (n = 2) C3: poor oxygenation (n = 0), cardiovascular inhibition (n = 1), respiratory depression (n = 0), nausea and vomiting (n = 1)
Zhang 2016[18]	T: 120 C: 120	T: chloral hydrate, rectal, 0.4–0.6 mL/kg C: chloral hydrate, oral, 0.4–0.6 mL/kg	1–48	CT, MRI, ECG, etc	T: 95.0% C: 71.7%			
Zhang 2011[19]	T: 31 C: 31	T: chloral hydrate, rectal, 0.4–0.6 mL/kg C: chloral hydrate, oral, 0.4–0.6/kg	24–60	Debridement, suturing	T: 93.55% C: 83.87%	T: 24.48 ± 4.30 C: 29.13 ± 5.03	T: 57.67 ± 6.00 C: 51.67 ± 7.49	T: digestive reaction (n = 0) C: digestive reaction (n = 7)
Zhang 2010[20]	T: 60 C: 56	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	12–60	Gamma knife surgery	T: 100% C: 96.43%			T: digestive reaction (n = 0) C: digestive reaction (n = 16)
Peng 2010[21]	T1: 90 T2: 90 C: 90	T1: chloral hydrate, rectal, 0.5 mL/kg T2: chloral hydrate, rectal, 0.6 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	5–72	Ultrasonography	T1: 90.0% T2: 70.0% C: 91.11%			T1: vomiting (n = 0), bucking (n = 0), redness around mouth (n = 0), defecating (n = 50) T2: vomiting (n = 0), bucking (n = 0), redness around mouth (n = 0), defecating (n = 53) C: vomiting (n = 7), bucking (n = 14), redness around mouth (n = 17), defecating (n = 12)
Wen 2015[22]	T: 70 C1: 70 C2: 70	T: chloral hydrate, rectal, 0.5–0.8 mL/kg C1: chloral hydrate, oral, 0.5–0.8 mL/kg C2: chloral hydrate + glucose, oral, 0.5–0.8 mL/kg	1–72	CT, MRI, X-ray, ultrasonography	T: 62.86% C1: 57.14% C2: 78.57%			T: nausea, vomiting (n = 4), bucking (n = 6), defecating (n = 12) C1: nausea, vomiting (n = 18), bucking (n = 11), defecating (n = 8) C2: nausea, vomiting (n = 6), bucking (n = 4), defecating (n = 6)
Li 2015[23]	T: 100 C: 100	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	1–38	Ultrasonography, CT, MRI, ECG, lumbar puncture	T: 96% C: 82%	T: 19.76 ± 1.83 C: 26.24 ± 3.87	T: 41.42 ± 6.7 C: 58.62 ± 14.43	T: nausea, vomiting, bucking (n = 27) C: digestive reaction (n = 64)
Lin 2016[24]	T: 60 C: 60	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	6–24	Ultrasonography, CT, MRI	T: 86.67% C: 60.00%	T: 10.67 ± 3.97 C: 19.93 ± 4.57		T: digestive reaction (n = 6) C: digestive reaction (n = 15)
Fan 2014[25]	T: 75 C: 75	T: chloral hydrate, rectal, 50–80 mg/kg C: chloral hydrate, oral, 50–80 mg/kg	4–36	NA	T: 96.00% C: 80.00%			

(*Continued*)

Table 1

(*Continued*)

Author/Year	Sample size	Interventions	Age, mo	Examination types	Success rate of sedation, %	Sedation latency, min	Sedation duration, min	Adverse events
Jiang 2012[26]	T: 88 C: 88	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	6–48	CT, EEG, ECG, ultrasonography	T: 90.91% C: 76.14%			
Tang 2011[27]	T1: 30 T2: 30 T3: 30 C1: 30 C2: 30	T1: chloral hydrate, rectal, 0.5 mL/kg T2: chloral hydrate, rectal, 0.5 mL/kg T3: chloral hydrate, rectal, 0.5 mL/kg C1: chloral hydrate, oral, 0.5 mL/kg C2: diazepam, inject 0.100 μg/kg	5–84	MRI	T1: 90% T2: 96.7% T3: 100% C1: 93.3% C2: 93.3%			
Wang 2008[28]	T: 25 C: 24	T: chloral hydrate, rectal, 0.05 mL/kg C: chloral hydrate, oral, 0.05 mL/kg		Ultrasonography	T: 100.0% C: 100.0%			T: digestive reaction (n = 0) C: digestive reaction (n = 22)
Bai 2005[29]	T: 50 C: 50	T: chloral hydrate, rectal C: chloral hydrate, oral			T: 92.00% C: 80.00%			T: vomiting and bucking (n = 0) C: vomiting and bucking (n = 30)
Qin 2007[30]	T: 150 C: 150	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	1.33–12	Hearing examination	T: 76.00% C: 93.33%			
Zhao 2010[31]	T: 213 C: 212	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	12–60	CT	T: 96.24% C: 89.15%			
Guo 2015[32]	T1: 24 T2: 24 T3: 24 C1: 24 C2: 24	T1: chloral hydrate, rectal, 0.5 mL/kg T2: chloral hydrate, rectal, 0.5 mL/kg T3: chloral hydrate, rectal, 0.5 mL/kg C1: chloral hydrate, oral, 0.5 mL/kg C2: phenobarbital, intramuscular, 5 mg/kg	5–84	MRI	T1: 90% T2: 100% T3: 100% C1: 95% C2: 95%			
Jin 2008[33]	T: 450 C: 148	T: chloral hydrate, rectal, 0.3–0.5 mL/kg C: chloral hydrate, oral, 0.3–0.5 mL/kg	0.18–48	CT	T: 95.11% C: 87.84%	T: 19.03 ± 9.58 C: 25.01 ± 10.34		T: digestive reaction (n = 0) C: digestive reaction (n = 23)

(*Continued*)

Table 1

(*Continued*)

Author/Year	Sample size	Interventions	Age, mo	Examination types	Success rate of sedation, %	Sedation latency, min	Sedation duration, min	Adverse events
Zhong 2010[34]	T: 60 C: 60	T: chloral hydrate, rectal, 0.4–0.6 mL/kg C: chloral hydrate, oral, 0.4–0.6 mL/kg	12–48	Dental examination	T: 95% C: 80%	T: 16.1 ± 5.6 C: 25.5 ± 8.8	T: 54.7 ± 9.0 C: 50.3 ± 6.5	T: digestive reaction (n = 0) C: digestive reaction (n = 13)
Chen 2004[35]	T: 40 C: 37	T: chloral hydrate, rectal, 50–80 mg/kg C: chloral hydrate, oral, 50–80 mg/kg	3–60	CT	T: 92.50% C: 51.35%			T: digestive reaction (n = 0) C: digestive reaction (n = 5)
Chen 2015[36]	T: 110 C: 110	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	0.27–72	MRI, CT, etc	T: 92.73% C: 81.82%			
Gao 2016[37]	T1: 120 T2: 120 C: 120	T1: chloral hydrate, rectal, 50 mg/kg T2: chloral hydrate, rectal, 50 mg/kg C: chloral hydrate, oral, 50 mg/kg	2–35	ECG	T: 91% C: 73%			T: adverse reaction (n = 18) C: adverse reaction (n = 27)
Gao 2006[38]	T: 213 C: 204	T: chloral hydrate, rectal, 50 mg/kg C: chloral hydrate, oral, 50 mg/kg		Ultrasonography, ECG, CT	T: 90.61% C: 82.84%			
Li 2015[39]	T1: 110 T2: 105 C1: 108 C2: 97	T1: chloral hydrate, rectal, 0.5–0.8 mL/kg T2: midazolam, rectal, 0.1–0.3 mL/kg C1: diazepam, intravenous,0.3–0.5 mg/kg C2: phenobarbital, intramuscular, 5 mg/kg	3–108		T1: 85.45% T2: 95.20% C1: 93.50% C2: 74.23%			
Ma 2015[40]	T: 80 C1: 80 C2: 80	T1: chloral hydrate, rectal, 0.5 mL/kg C1: phenobarbital, oral, 5 mg/kg C2: diazepam, inject 0.3 mg/kg			T1: 100% C1: 78.8% C2: 82.5%			
Guo 2018[41]	T: 42 C: 42	T: chloral hydrate, rectal, 0.5 mL/kg C: midazolam, intramuscular, 0.03 mg/kg	17–29	MRI	T: 81% C: 95%	T: 16.85 ± 2.39 C: 24.49 ± 4.4		
Wang 2003[42]	T: 65 C: 55	T: chloral hydrate, rectal, 0.2–0.4 mL/kg C: diazepam, intramuscular, 0.4 mg/kg		MRI	T: 84.61% C: 69.09%			T: adverse reaction (n = 0) C: adverse reaction (n = 0)

(*Continued*)

Table 1

(*Continued*)

Author/Year	Sample size	Interventions	Age, mo	Examination types	Success rate of sedation, %	Sedation latency, min	Sedation duration, min	Adverse events
Yang 2018[43]	T: 42 C: 42	T: chloral hydrate, rectal, 0.5 mL/kg C: phenobarbital, intramuscular	0–36	Ultrasonography				T: adverse reaction (n = 5) C: adverse reaction (n = 15)
Guo 2012[44]	T: 50 C: 50	T: chloral hydrate, rectal, 0.25–0.75 mL/kg C: phenobarbital, intramuscular, 3–5 mg/kg	12–72	Lumbar puncture, bone marrow aspiration	T: 96% C: 62%			T: laryngospasm (n = 0), asthma (n = 0), increased salivary secretion (n = 0) C: laryngospasm (n = 2), asthma (n = 1), increased salivary secretion (n = 1)
Huang 2014[45]	T: 76 C: 79	T: chloral hydrate, rectal, 0.25–0.75 mL/kg C: ketamine, intramuscular, 3–5 mg/kg	12–84	Puncture	T: 93.42% C: 65.82%			T: laryngospasm (n = 2), asthma (n = 1), increased salivary secretion (n = 3) C: laryngospasm (n = 7), asthma (n = 5), increased salivary secretion (n = 9)
Ji 2018[46]	T: 50 C: 50	T: chloral hydrate, rectal, 0.5 mL/kg C: ketamine, intranasal, 1.00 mL/kg	2–39.6	MRI, CT, brainstem auditory evoked potential	T: 28.00% C: 30.00%			T: diarrhea (n = 2), hallucination (n = 5), dysphoria (n = 13), nausea (n = 9), SpO2 lower than 90%(n = 6) C: diarrhea (n = 0), hallucination (n = 0), dysphoria (n = 15), nausea (n = 10), SpO2lower than 90%(n = 8)
Yang 2009[47]	T: 236 C: 187	T: chloral hydrate, rectal, 0.5 mL/kg C: chloral hydrate, oral, 0.5 mL/kg	0.07–12	CT				T: nausea and vomiting (n = 0), bucking (n = 0), defecating (n = 17) C: nausea and vomiting (n = 53), bucking (n = 24), defecating (n = 0)
Cheng 2019[48]	T: 117 C: 119	T: chloral hydrate, rectal, 0.5 mL/kg C: midazolam, intramuscular, 0.03 mg/k	10–30	ECG		T: 17 ± 6 C: 7 ± 4	T1: 125 ± 39 C1: 71 ± 24	T: nausea (n = 3), vomiting (n = 1), somnolence (n = 2) C: nausea (n = 3), vomiting (n = 2), somnolence (n = 2)
Wang 2019[49]	T: 50 C: 50	T: chloral hydrate, rectal C: chloral hydrate, oral	1–36		T: 98% C: 90%			
Liu 2020[50]	T: 250 C: 250	T: chloral hydrate, rectal C: chloral hydrate, oral	3–36	MRI	T: 96% C: 92%			
Qi 2011[51]	T: 43 C: 43	T: chloral hydrate, rectal C: diazepam, intramuscular			T: 100% C: 53.49%			

CT = computed tomography, ECG = electrocardiogram, EEG = electroencephalography, MRI = magnetic resonance imaging.

the rectal CH group than in the intramuscular midazolam group (MD, 18.50 [95% CI, 14.10–22.90]; $P < .01$). However, there was no significant difference between the rectal CH group and the intranasal midazolam group (MD, 5.30 [95% CI, −0.78 to 11.38]; $P = .09$).

Table 2

Quality assessment of included studies.

Items	Low risk of bias	Unclear risk of bias	High risk of bias
Random sequence generation	7 (15.91%)	34 (77.27%)	3 (6.82%)
Allocation concealment	0 (0%)	44 (100%)	0 (0%)
Blinding of participants and personnel	0 (0%)	39 (88.64%)	5 (11.36%)
Blinding of outcome assessment	0 (0%)	44 (100%)	0 (0%)
Incomplete outcome data	37 (84.09%)	7 (15.91%)	0 (0%)
Selective reporting	40 (90.91%)	4 (9.09%)	0 (0%)
Other bias	41 (93.18%)	3 (6.82%)	0 (0%)

3.4. Safety

Relevant adverse events associated with rectal CH were reported in 20 RCTs. The most common adverse events were respiratory system (mainly manifested as respiratory depression and cough), digestive system (mainly manifested as defecation), and cardiovascular system (mainly manifested as cardiovascular depression).

3.4.1. Overall incidence of adverse events. Fifteen studies with 2712 children contributed data on the incidence of adverse events for rectal CH compared to oral CH.[14,17,19–24,28,29,34,35,37,39,47] Before sensitivity analysis, 7 studies had significant heterogeneity.[14,21–23,28,29,33] After sensitivity analysis, the overall incidence of adverse events was significantly lower in the rectal CH group than in the oral CH group with no heterogeneity (RR, 0.21 [95% CI, 0.16–0.29]; $I^2 = 45\%$; $P < .001$)[17,19,20,24,34,35,37,47] (Fig. 8).

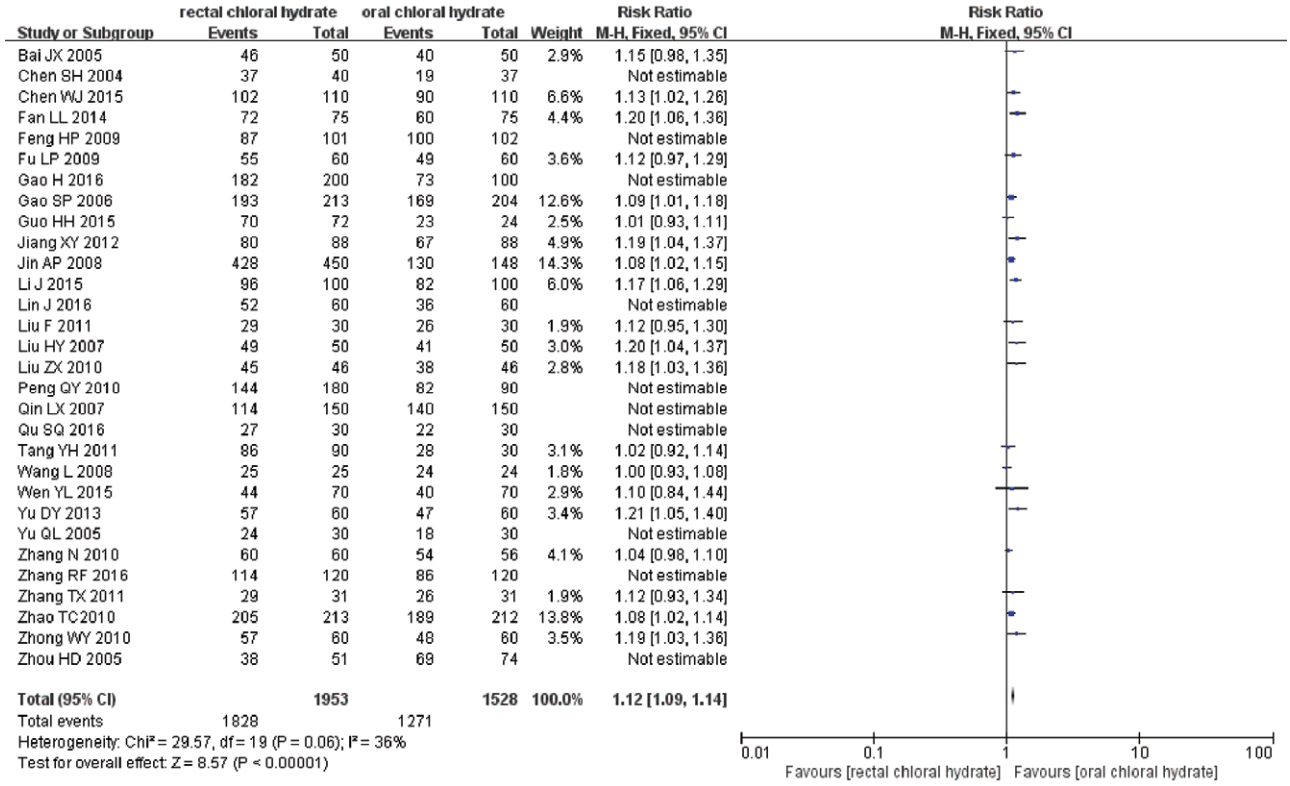

Figure 2. The success rate of sedation between rectal chloral hydrate and oral chloral hydrate. CI = confidence interval, M-H = Mantel-Haenzel.

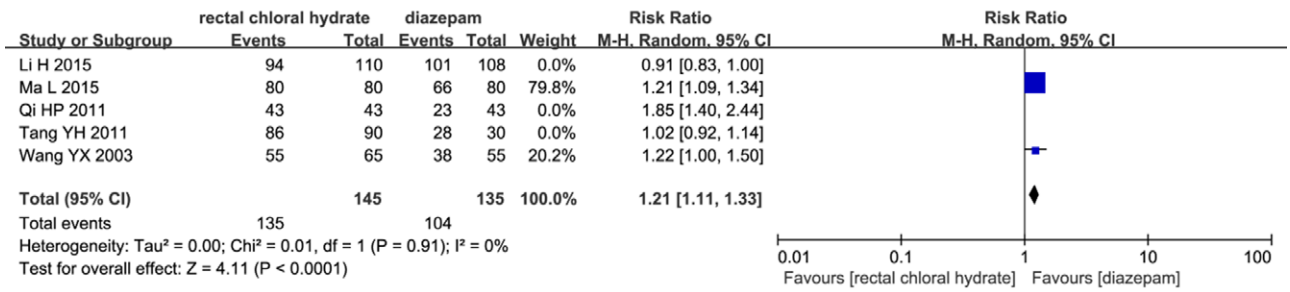

Figure 3. The success rate of sedation between rectal chloral hydrate and diazepam. CI = confidence interval, M-H = Mantel-Haenzel.

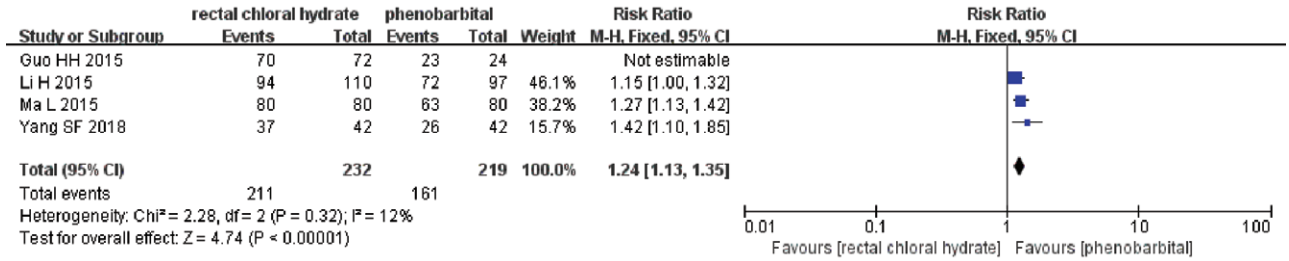

Figure 4. The success rate of sedation between rectal chloral hydrate and phenobarbital. CI = confidence interval, M-H = Mantel-Haenzel.

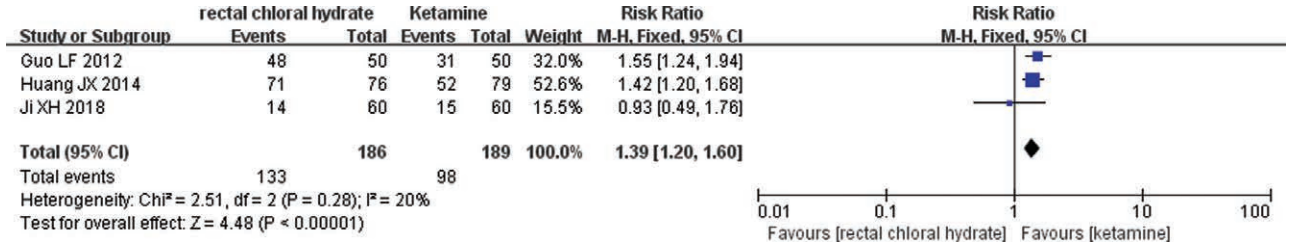

Figure 5. The success rate of sedation between rectal chloral hydrate and ketamine. CI = confidence interval, M-H = Mantel-Haenzel.

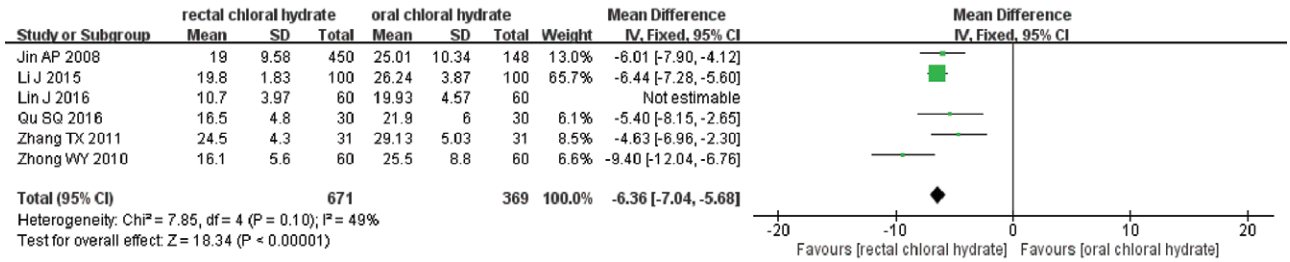

Figure 6. The sedation latency between rectal chloral hydrate and oral chloral hydrate. CI = confidence interval, SD = standard deviation.

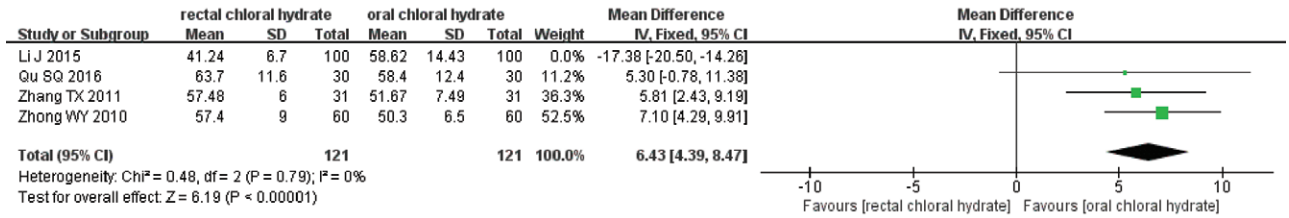

Figure 7. The sedation duration between rectal chloral hydrate and oral chloral hydrate. CI = confidence interval, SD = standard deviation.

One study with 90 children contributed data on the incidence of adverse events for rectal CH versus midazolam.[17] There was no significant difference in the overall incidence of adverse events with rectal CH compared with intramuscular midazolam (RR, 0.55 [95% CI, 0.23–1.28]; $P = .17$) and intranasal midazolam (RR, 3.00 [95% CI, 0.66–13.69]; $P = .16$).

Three studies with 355 children contributed data on the incidence of adverse events for rectal CH versus ketamine.[44,45] Before sensitivity analysis, 1 study had significant heterogeneity.[46] After sensitivity analysis, the overall incidence of adverse events was significantly lower in rectal CH than in the ketamine group, with no heterogeneity (RR, 0.26 [95% CI, 0.12–0.60]; $I^2 = 0\%$; $P = .001$)[44,45] (Fig. 9).

3.4.2. Incidence of respiratory adverse events. Six studies with 1093 children contributed data on the incidence of respiratory adverse events for rectal CH versus oral CH.[14,17,21,22,29,47] Before sensitivity analysis, 1 study had significant heterogeneity.[22] After sensitivity analysis, the incidence of respiratory adverse events was significantly lower in the rectal CH group than in the oral CH group with no heterogeneity (RR, 0.03 [95% CI, 0.01–0.10]; $I^2 = 15\%$; $P < .001$)[14,17,21,29,47] (Fig. 10).

One study with 90 children contributed data on the incidence of respiratory adverse events for rectal CH versus midazolam.[17] There was no significant difference in the incidence of respiratory adverse events between rectal CH and midazolam (RR, 1.00 [95% CI, 0.18–5.59]; $I^2 = 0\%$; $P = 1.00$).

Three studies with 355 children contributed data on the incidence of respiratory adverse events for rectal CH versus ketamine.[44–46] The incidence of respiratory adverse events was significantly lower in the rectal CH group than in the ketamine group with no heterogeneity (RR, 0.41 [95% CI, 0.20–0.84]; $I^2 = 19\%$; $P = .02$; Fig. 11).

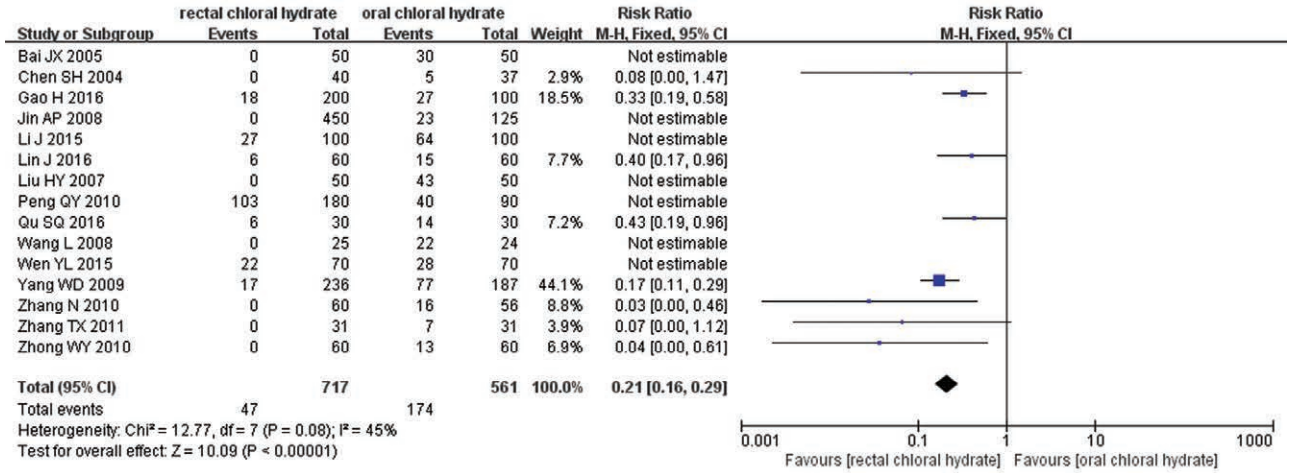

Figure 8. The overall incidence of adverse events between rectal chloral hydrate and oral chloral hydrate. CI = confidence interval, M-H = Mantel-Haenzel.

Figure 9. The overall incidence of adverse reactions between rectal chloral hydrate and ketamine. CI = confidence interval, M-H = Mantel-Haenzel.

3.4.3. Incidence of digestive adverse events. Thirteen studies with 2212 children contributed data on the incidence of digestive adverse events for rectal CH versus oral CH.[14,17,19–22,24,28,29,33–35,47] Before sensitivity analysis, 5 studies had significant heterogeneity.[14,21,22,29,33] After sensitivity analysis, the incidence of digestive adverse events was significantly lower in the rectal CH group than in the oral CH group with no heterogeneity (RR, 0.16 [95% CI, 0.11–0.24]; $I^2 = 43\%$; $P < .001$)[17,19,20,24,28,34,35,47] (Fig. 12).

One study with 90 children contributed data on the incidence of digestive adverse events for rectal CH versus midazolam.[17] There was no significant difference in the incidence of digestive adverse events between rectal CH and midazolam (RR, 0.67 [95% CI, 0.12–3.85]; $I^2 = 0\%$; $P = .65$).

One study with 100 children contributed data on the incidence of digestive adverse events for rectal CH versus ketamine. There was no significant difference in the incidence of digestive adverse events between rectal CH and ketamine (RR, 1.10 [95% CI, 0.51–2.36]; $P = .81$).

3.4.4. Incidence of cardiovascular adverse events. One study with 60 children contributed data on the incidence of cardiovascular adverse events for rectal CH versus oral CH.[36] There was no significant difference in the incidence of cardiovascular adverse events between rectal CH and oral CH (RR, 4.00 [95% CI, 0.47–33.73]; $P = .20$).

One study with 90 children contributed data on the incidence of cardiovascular adverse events for rectal CH versus midazolam.[17] There was no significant difference in the incidence of cardiovascular adverse events between rectal CH and intramuscular midazolam (RR, 0.44 [95% CI, 0.15–1.29]; $P = .14$) and intranasal midazolam (RR, 4.00 [95% CI, 0.47–33.73]; $P = .20$).

4. Discussion

This review aims to evaluate the efficacy and safety of rectal CH for pediatric procedural sedation. Based on the available evidence from 44 RCTs, the analysis indicated that the success rate of sedation with rectal CH ranged from 62.9% to 100%. Rectal CH significantly increased the success rate of sedation than oral CH, which was consistent with the results of Ding et al.[52] Rectal CH significantly increased the success rate of sedation than diazepam, phenobarbital, and ketamine. There was no significant difference in the success rate of sedation between rectal CH and midazolam.

The relevant adverse events associated with rectal CH were reported in 20 RCTs. The most common adverse events were respiratory system (mainly manifested as respiratory depression and cough), digestive system (mainly manifested as defecation), and cardiovascular system (mainly manifested as cardiovascular depression). The overall incidence of adverse events in rectal CH was significantly lower than that of oral CH and ketamine, which was consistent with the results of Ding et al.[52] There was no significant difference in the overall incidence of adverse events in rectal CH compared with intramuscular midazolam and intranasal midazolam.

According to the available secondary evidence, the National Institute for Health and Care Excellence 2018 guideline reports that oral midazolam produces less effective sedation than CH for children undergoing noninvasive diagnostic procedures, and CH may be effective for sedation during auditory brainstem response testing.[4] The British National Formulary for Children (2022–2023) states that CH could be administered by mouth or by rectum (if an oral route is not available).[3] An expert consensus of this existing secondary evidence suggested a CH solution for rectal administration.[49] The meta-analysis by Ding et al[52] showed that rectal CH had better sedative effects and fewer adverse reactions on the digestive and respiratory systems than oral CH. However, rectal CH may stimulate the rectum and cause a defecation reaction. In addition, the appropriate intubation depth was 5 to 10 cm according to the characteristics of pediatric rectal anatomy.[52] Clinically, oral CH could cause nausea and vomiting in some children, leading to severe coughing, resulting in inaccurate dosing. For these children, rectal CH was a better choice. In conclusion, the CH solution for rectal administration could be used as a sedative in children.

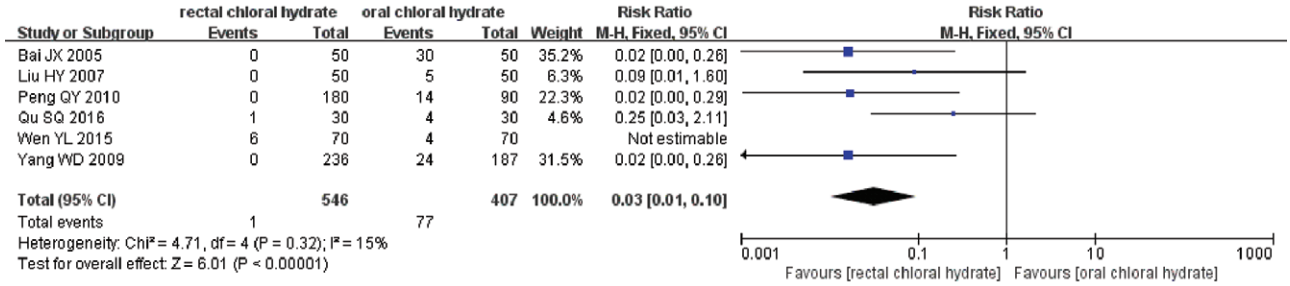

Figure 10. Incidence of respiratory adverse events between rectal chloral hydrate and oral chloral hydrate. CI = confidence interval, M-H = Mantel-Haenzel.

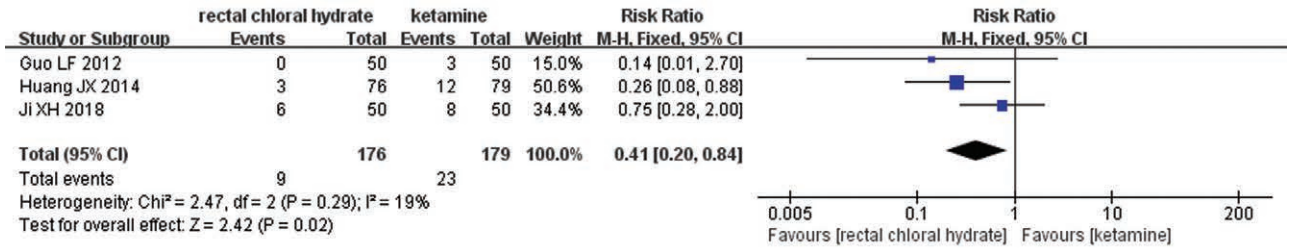

Figure 11. Incidence of respiratory adverse events between rectal chloral hydrate and ketamine. CI = confidence interval, M-H = Mantel-Haenzel.

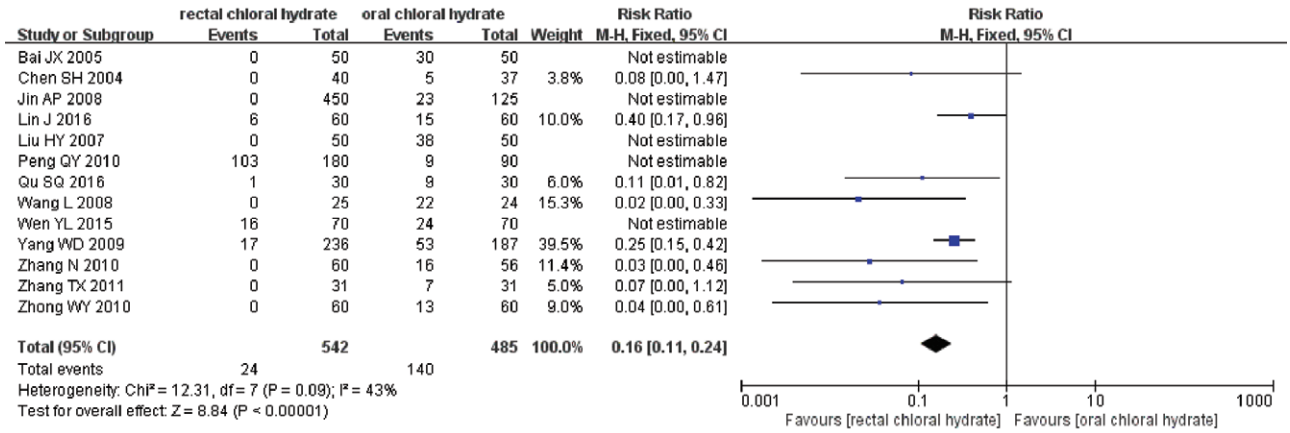

Figure 12. Incidence of digestive adverse events between rectal chloral hydrate and oral chloral hydrate. CI = confidence interval, M-H = Mantel-Haenzel.

There were still some limitations to this review. First, there was some heterogeneity in the included RCTs, which could be caused by differences in the quality of the included study, the dose and administration route of the control group, the sample size, the type of examination, etc. For example, compared with oral CH, the sedation duration of rectal CH was more heterogeneous, which might be due to differences in rectal administration depth and dose. For another example, in 2 studies comparing rectal CH with placebo, the success rate of sedation increased significantly in the rectal CH group.[7,8] However, when the success rate of sedation in the 2 studies was meta-analyzed, the heterogeneity was high, which could be due to the low success rate of sedation in the placebo group of 1 included study, and the included children were younger and did not cooperate due to fear and pain, crying, and struggling. Thus, we did sensitivity analyses and subgroup analyses to address these issues of heterogeneity. Second, most of the studies did not clearly report on random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. Thus, we could not assess the quality of the study. In addition, some of the studies still had other issues, such as incomplete descriptions of the main outcomes, small sample sizes, and inconsistent dosage. Therefore, a large sample randomized controlled study with high-quality, multicenter, and standardized design methods could be carried out in the future to clarify the efficacy and safety of sedatives for pediatric procedural sedation.

5. Conclusion

The existing evidence suggests that rectal CH cloud be an effective and safe sedative agent for pediatric procedural sedation. In terms of efficacy, rectal CH could improve the success rate of sedation compared with placebo. Compared with oral CH, rectal CH could increase the success rate of sedation and decrease the time of sedation latency. The success rate of sedation and the time of sedation duration were similar in midazolam and rectal CH. Compared with diazepam, rectal CH could improve the success rate of sedation. Compared with barbiturates, rectal CH could improve the success rate of sedation and reduce the time of sedation latency. Compared with ketamine, rectal CH could improve the success rate of sedation. In terms of safety, the incidence of adverse events with rectal CH was comparable to midazolam and lower than with ketamine. The most common adverse event was reflex defecation.

Author contributions

Data curation: Zhe Chen, Fang Qin, Linan Zeng.
Formal analysis: Zhe Chen, Fang Qin.
Methodology: Zhe Chen, Fang Qin, Lingli Zhang.
Software: Zhe Chen, Fang Qin.
Visualization: Zhe Chen.
Writing – original draft: Zhe Chen, Fang Qin.
Validation: Fang Qin.
Conceptualization: Linan Zeng, Lingli Zhang.
Writing – review & editing: Linan Zeng, Lingli Zhang.

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