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REVIEW

Efficacy of chloral hydrate oral solution for sedation in pediatrics: a systematic review and meta-analysis

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Objective: Chloral hydrate (CH), as a sedation agent, is widely used in children for diagnostic or therapeutic procedures. However, it has not come into the market and is currently only used as hospital preparation in China. This review aims to systematically evaluate the efficacy of CH in children of all age groups for sedation before medical procedures.

Materials and methods: Seven electronic databases and three clinical trial registry platforms were searched and the deadline was September 2018. Randomized controlled trials (RCTs) evaluating the efficacy of CH for sedation in children were included by two reviewers. The extracted information included success rate of sedation, sedation latency and sedation duration. The Cochrane risk of bias tool was applied to assess the risk of bias. The outcomes were analyzed by Review Manager 5.3 software and expressed as relative risks (RR) or Mean Difference (MD) with 95% confidence interval (CI). Heterogeneity was assessed with I-squared (I^2) statistics.

Results: A total of 24 RCTs involving 3564 children of CH for sedation were included in the meta-analysis. Compared to placebo group, CH group had a significant increase in success rate of sedation when used for painless and painful procedure (RR=4.15, 95% CI [1.21, 14.24], P=0.02; RR=1.28, 95% CI [1.17, 1.40], P<0.01), which included 22 and 455 children for this analysis, respectively. Compared to midazolam group, CH group had a significant increase in success rate of sedation (RR=1.63, 95% CI [1.48, 1.79], I^2=0%, P<0.00001), sedation latency (MD=13.29, 95% CI [11.42, 15.16], I^2=0%, P<0.00001) and sedation duration (MD=17.52, 95% CI [10.3, 24.71], I^2=0%, P<0.05), which included 1052, 710 and 727 children for this analysis, respectively. Compared to diazepam, there was no significant difference in success rate of sedation (RR=0.93, 95% CI [0.80, 1.08], I^2=52%, P=0.32), which included 230 children for this analysis. Compared to dexmedetomidine, there was no significant difference in the success rate of sedation (RR=0.92, 95% CI [0.80, 1.06], I^2=48%, P=0.27) and sedation latency (RR=−1.09, 95% CI [−2.45, 0.26], I^2=26%, P=0.11), which included 512 and 371 children for this analysis, respectively. Compared to barbiturates, there was no significant difference in the success rate of sedation (RR=1.03, 95% CI [0.94, 1.13], I^2=50%, P=0.58) and sedation duration (MD=−0.72, 95% CI [−1.78, 0.34], I^2=38%, P=0.18), which included 749 and 210 children for this analysis, respectively.

Conclusions: From the extrapolation of the existing literature, CH oral solution is an appropriate effective alternative for sedation in pediatrics.

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

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Introduction

Sedation is defined as a drug-induced depression of consciousness, which is a continuum from wakefulness to anesthesia.[1] It assists in reducing anxiety, providing

pain control and reducing movement of the patient when undergoing a procedure. Children can easily become anxious during medical procedures. Pain and anxiety sometimes make the procedure more difficult to perform for the medical staff, due to movement or a lack of cooperation from the patient.[2] As a result, children frequently require sedation to undergo examination or diagnostic imaging.

Sedative medications are used to reduce pain and anxiety. They can be injected directly into the bloodstream, injected into muscle tissue, given as a nasal spray, or swallowed as a tablet or solution. Chloral hydrate (CH) is a central nervous system depressant and is one of the oldest sedatives (discovered in 1832). It is well absorbed orally as well as rectally and rapidly metabolized into the active metabolite trichloroethyl alcohol, which is responsible for its sedative and hypnotic effects.[3] It is one of the most frequently used sedative agents in pediatric ophthalmology, dentistry, radiology and so on. NICE 2010 guideline recommends that CH is considered for children under 15 kg who are unable to tolerate a painless procedure (for example, during diagnostic imaging), which have a wide margin of safety.[4] American College of Emergency Physicians 2008 guideline recommends that CH may be used to provide effective procedural sedation in pediatric patients undergoing painless diagnostic studies. However, children receiving CH should be properly monitored and managed by appropriately trained personnel due to the risk of respiratory depression and hypoxia.[5]

Contemporarily, CH has entered the pharmaceutical market in Japan, Australia, England and Switzerland, but it is only widely used as a hospital preparation in China. Meanwhile, there is no systematic review of the efficacy of CH for sedation in pediatrics. Henceforth, this review aims at systematically evaluating the efficacy of CH oral solution in pediatrics for sedation to provide evidence for health professionals who prescribe CH, as well as pharmaceutical research and development.

Materials and methods

Search strategy

Our research comprises three English electronic databases (PubMed, EMBase, Cochrane Library) and four Chinese electronic databases (China National Knowledge Infrastructure, WanFang Database, Chinese Biomedical Literature Database, VIP Database for Chinese Technical Periodicals). Three clinical trial registry platforms were used to find additional studies, including ClinicalTrials.gov, the World Health Organization Clinical Trials Registry Platform and Cochrane Central Registry of Controlled Trials.

The search strategy was specific for each database and included a combination of the medical subject headings and free text terms for ("chloral hydrate" or "somnos" or "nycton" or "dormal") and ("child" or "newborn" or "infant" or "neonate" or "toddler" or "teenager" or "adolescent" or "pediatric"). We looked for additional studies in reference lists of selected articles and contacted with authors for unclear information. The deadline of all retrieval was September 2018.

This protocol was registered with the international prospective register of systematic review: CRD42018108967.

Inclusion criteria

The following studies were included: (1) Participants: pediatric patients (0–18 years) needed sedation before diagnostic procedures, which were classified according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Criteria: preterm newborn infants, term newborn infants (birth to 27 days), infants and toddlers (28 days to 23 months), children (24 months to 11 years) and adolescents (12–18 years)[6]. (2) Intervention: chloral hydrate oral solution. (3) Comparison: placebo, no intervention or other sedative hypnotics.[7] (4) Outcomes: success rate of sedation, sedation latency, sedation duration.[8] (5) Type of study: randomized controlled trial (RCT).

Exclusion criteria

The following studies were excluded: (1) Studies with incomplete or missing information. (2) Not Chinese or English literature. (3) Comparative study of different routes of administration of chloral hydrate.

Data extraction

Data were extracted from all included studies. Extracted information included: study information (author, published time of included studies, country), method (study design, information of quality evaluation), intervention (sample size, medicine, administration route, dose), outcomes (success rate of sedations, sedation latency, sedation duration).

Two independent reviewers screened all the titles and abstracts to determine potential eligible articles. They independently applied the eligibility criteria to perform

the final selection. When discrepancies occurred between both reviewers regarding the inclusion of the articles, they would discuss and identify the reasons to either include or exclude the articles and then make the final decision. If they could not reach an agreement, the final decision would be based on a third reviewer.

Risk of bias assessment

We used the Cochrane risk of bias tool for RCT studies.

Data analysis

Meta-analysis was conducted with RevMan 5.3. The data were pooled and expressed as relative risks (RR) or Mean Difference (MD) with 95% confidence interval (CI). Heterogeneity assessment was done by I-squared (I^2) statistics. A fixed effects model was initially conducted. If significant heterogeneity existed among trials (I^2>50%), potential sources of heterogeneity were considered, and where appropriate a random effects model was used.

Results

Characteristics of the included studies

A total of 2045 records were identified for initial screening and 24 eligible studies published between 2000 and 2017 were included in this meta-analysis (Figure 1). A total of 3564 children were enrolled in this study. The dose range of CH oral solution is 25–100 mg/kg (Table 1).

Quality assessment

According to Cochrane risk of bias estimation, the seven items including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias of these were evaluated. 54.2% of studies (13/24) used an adequate method of random sequence generation, such as using a random number table or a computer-generated random number table. Only one study mentioned allocation concealment. 25% of studies (6/24) performed on blinding of participants and personnel, such as using computer distribution in the center. 66.7% of studies (16/24) reported complete outcomes. 62.5% of studies (15/24) reported no selective reporting with checking protocols. Blinding of outcome assessment and other bias were vague in the majority of trials (Figure 2).

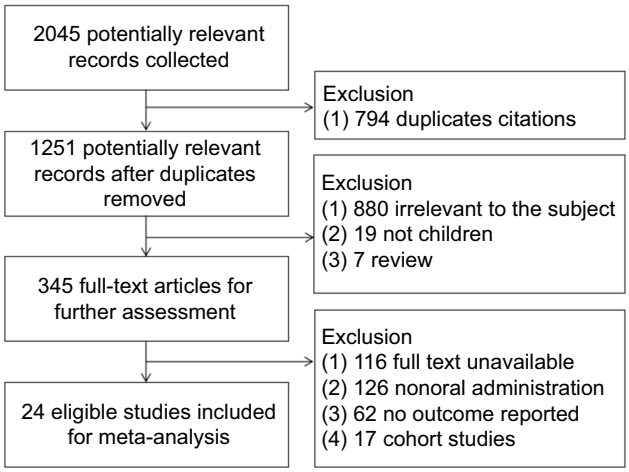

Figure 1 Flow diagram of selecting study.

Outcomes

CH versus placebo

Success rate of sedation

Among the 24 RCT studies, 2 studies with 477 children contributed to this analysis. Compared to placebo group, the success rate of sedation increased significantly in CH group when used for painless and painful procedure [RR=4.15, 95% CI (1.21, 14.24), P=0.02; RR=1.28, 95% CI (1.17, 1.40), P<0.01].[13,28]

CH versus midazolam

Success rate of sedation

Among the 24 RCT studies, 8 studies with 1052 children contributed to this analysis.[8,9,14,18,21–23,26] Before sensitivity analysis, three studies had significant heterogeneity.[9,18,26] After sensitivity analysis, compared to midazolam group, the success rate of sedation increased significantly in CH group with no heterogeneity [RR=1.63, 95% CI (1.48, 1.79), I^2=0%, P<0.00001] (Figure 3).[8,14,21–23]

Group

Sedation latency

Among the 24 RCT studies, 5 studies with 710 children contributed to this analysis.[8,14,18,21,26] Before sensitivity analysis, two subgroups had significant heterogeneity.[8,26] After sensitivity analysis, the sedation latency in CH group was longer than in midazolam group with no heterogeneity [MD=13.29, 95% CI (11.42, 15.16), I^2=0%, P<0.00001] (Figure 4).[14,18,21]

Sedation duration

Among the 24 RCT studies, 4 studies with 727 children contributed to this analysis.[8,21,23,26] Before sensitivity analysis,

Table 1 Characteristics of included studies

Author/Year	Sample size	Interventions	Age (Years)	Weight(kg)	Examination types	Success rate of sedation (%)	Sedation latency (min)	Sedation duration (min)
Ashrafi MR et al, 2013[9]	198	T: chloral hydrate, oral, 1 mL/kg (n=98) C: midazolam, oral, 0.5 mg/kg (n=100)	0.1–10	—	Electrocardiography	T:100% C:100%	—	—
Azizkhani R et al, 2014[10]	140	T: chloral hydrate, oral, 50 mg/kg (n=70) C: thiopental sodium, clysis, 25 mg/kg (n=70)	2–6	T:14.54±4.33 C:15.80±4.44	CT	T:82.86% C:87.14%	—	T:12.9±2.8 C:13.7±2.6
Cao Q et al, 2017[11]	142	T: chloral hydrate, oral, 80 mg/kg (n=71) C: dexmedetomidine, nasal drip, 2 μg/kg (n=71)	0.3–3	T:10.5 (9.5–12) C:10 (8–12)	Ophthalmic testing	T:64.29% C:85.92%	—	—
Bektas O et al, 2014[12]	259	T: chloral hydrate, oral, 26.38±14.73 mg/kg (n=147) C: hydroxyzine, oral, 1.43±0.74 mg/kg (n=112)	0–18	—	Electrocardiography	T:89.80% C:88.39%	T:32.34±26.83 C:34.68±30.75	—
Hijazi OM et al, 2014[8]	286	T: chloral hydrate, oral, 75 mg/kg (n=144) C: midazolam, oral, 0.5 mg/kg (n=142)	0–12	T:11.15±3.76 C:11.90±5.84	CT et al.	T:94.44% C:61.97%	T:24.3±16.96 C:53.12±40.94	T:75.9±38.37 C:58.98±35.05
Da CL et al, 2007[13]	22	T: chloral hydrate, oral, 75 mg/kg (n=13) C: placebo (n=9)	0–5	—	Dental examination	T:92.31% C:22.22%	—	—
Fallah R et al, 2013[14]	60	T: chloral hydrate, oral, 100 mg/kg (n=30) C: midazolam, nasal drip, 0.2 mg/kg (n=30)	0–10	T:12.08±5.7 C:11.66±4.34	CT	T:76.67% C:40%	T:23.75±15.09 C:10.92±4.23	—
Gumus H et al, 2015[15]	160	T1: chloral hydrate, oral, 50 mg/kg (n=36) T2: chloral hydrate, oral, 100 mg/kg (n=40) C1: dexmedetomidine, oral, 2 μg/kg (n=42) C2: dexmedetomidine, oral, 3 μg/kg (n=42)	1–9	13.8±3.7	Electrocardiography	—	T1:34.0±4.6 T2:28.9±4.0 C1:35.9±3.5 C2:34.5±4.0	—
Malviya S et al, 2004[16]	70	T: chloral hydrate, oral, 75 mg/kg (n=35) C: pentobarbital, intravenous injection, 2–5 mg/kg (n=35)	2–12	—	MRI	T:97.14% C:91.43%	—	T:45±23 C:40±14
Kantovitz KR et al, 2007[17]	20	T: chloral hydrate, oral, 40 mg/kg (n=9) C: diazepam, oral, 5 mg (n=11)	3–7	16	Dental examination	T:63.64% C:44.44%	—	—
Wheeler DS et al, 2001[18]	40	T: chloral hydrate, oral, 75 mg/kg (n=15) C: midazolam, oral, 0.5 mg/kg (n=25)	—	T:9.21±2.79 C:8.96±3.17	Electrocardiography	T:93.33% C:88%	T:25±4.7 C:27.3±2.9	—

(*Continued*)

Table 1 (Continued).

Author/Year	Sample size	Interventions	Age (Years)	Weight(kg)	Examination types	Success rate of sedation (%)	Sedation latency (min)	Sedation duration (min)
Yuen VM et al, 2017[19]	194	T: chloral hydrate, oral, 50 mg/kg (n=107) C: dexmedetomidine, nasal sprays, 3 μg/kg (n=87)	1–3	T:11.6 (10.0–13.7) C:12.0 (10.4–15.0)	CT	T:75.70% C:73.56%	T:22.4±7.8 C:19.6±6.6	—
Zhang W et al, 2016[20]	150	T: chloral hydrate, oral, 25 mg/kg (n=50) C1: dexmedetomidine, nasal drip, 2 μg/kg (n=50) C2: dexmedetomidine, nasal drip, 1 μg/kg (n=50)	0–0.5	T:6.1±1.6 C:5.5±1.2	MRI	T:80% C1:94% C2:98%	T:14.6±4.3 C1:15.1±3.2 C2:14.1±3.1	—
Layangool T et al, 2008[21]	264	T: chloral hydrate, oral, 50 mg/kg (n=132) C: midazolam, sublingually, 0.3 mg/kg (n=132)	0.5–5	T:9.3±2.8 C:9.4±2.8	Electrocardiography	T:93.18% C:56.06%	T:25.1±20.2 C:11.13±8.6	T:54.6±26.8 C:30.5±29.4
Stephen MC et al, 2015[22]	82	T: chloral hydrate, oral, 25–50 mg/kg (n=41) C: midazolam, nasal drip, 0.5 mg/kg (n=41)	1–6	T:12.41±3.62 C:11.95±3.5	Hearing test	T:95.12% C:51.22%	—	—
D'Agostino J et al, 2000[23]	33	T: chloral hydrate, oral, 75 mg/kg (n=11) C: midazolam,oral, 0.5 mg/kg (n=22)	0.17–8	T:12.9±4.7 C:11.9±5.6	MRI	T:100% C:52.38%	—	T:95±26 C:76±3
Zhou GL et al, 2011[24]	156	T: chloral hydrate, oral, 0.5 mL/kg (n=78) C: phenobarbital, injection, 5 mg/kg (n=78)	0.08–2	—	—	T:92.31% C:80.77%	—	—
Chen ZY et al, 2016[25]	150	T: chloral hydrate, oral, 0. 5 mL/kg (n=50) C1: chloral hydrate, oral, 0. 5 mL/kg + midazolam, intravenous injection, 0. 2 mg/kg (n=50) C2: midazolam, intravenous injection, 0.2 mg/kg (n=50)	4–12	13–35	Fiberoptic bronchoscopy	—	—	—
Qu SQ et al, 2016[26]	90	T: chloral hydrate, oral, 0.4–0.6 mL/kg (n=30) C1: midazolam,intramuscular injection, 0. 2 mg/kg (n=30) C2: midazolam,nasal drip, 0. 2 mg/kg (n=30)	0–4	—	CT, MRI, electrocardiography, lumbar puncture	T:73.33% C1:83.3% C2:86.7%	T:21.9±6 C1:8.8±2.6 C2:10.6±3.3	T:45.4±9.3 C1:45.2±8.7 C2:58.4±12.4
Wang Q, 2004[27]	232	T: chloral hydrate, oral, 0.8–1.0 mL/μg (n=120) C: phenobarbital, intramuscular injection, 5 mg/kg (n=112)	0.1–6	—	Dental examination	T:75% C:79.46%	—	
Zhang P, 2000[28]	455	T: chloral hydrate, oral, 40–60 mg/kg (n=223) C: placebo (n=232)	0.67–4	—	Intravenous injection	T:92.85% C:72.41%	—	—

(*Continued*)

Table 1 (Continued).

Author/Year	Sample size	Interventions	Age (Years)	Weight(kg)	Examination types	Success rate of sedation (%)	Sedation latency (min)	Sedation duration (min)
Zong SJ, 2010[29]	110	T: chloral hydrate, oral, 0.5 mL/kg (n=63) C: diazepam, intramuscular injection, 0.1–0.2 mg/kg (n=47)	4.5–7.7	—	Minimally invasive suture of the face	T:93.65% C:95.74%	—	—
Qiong L, 2002[30]	100	T: chloral hydrate, oral, lmL/year(n=46) C: diazepam, intravenous injection, 0.3–0.5 mg/kg (n=54)	0.25–7	—	Lumbar puncture examination	T:80.43% C:96.30%	—	—
Zhang L et al, 2003[31]	151	T: chloral hydrate, oral, 50 mg/kg (n=90) C: phenobarbital, intramuscular injection, 5 mg/kg (n=61)	0.08–l	—	Brain, chest and abdomen examination	T:97.78% C:52.46%	—	—

Abbreviations: T, treatment group; C, control group; NR, not reported; RCT, randomized controlled trials; CT, computed tomography; MRI, magnetic resonance imaging.

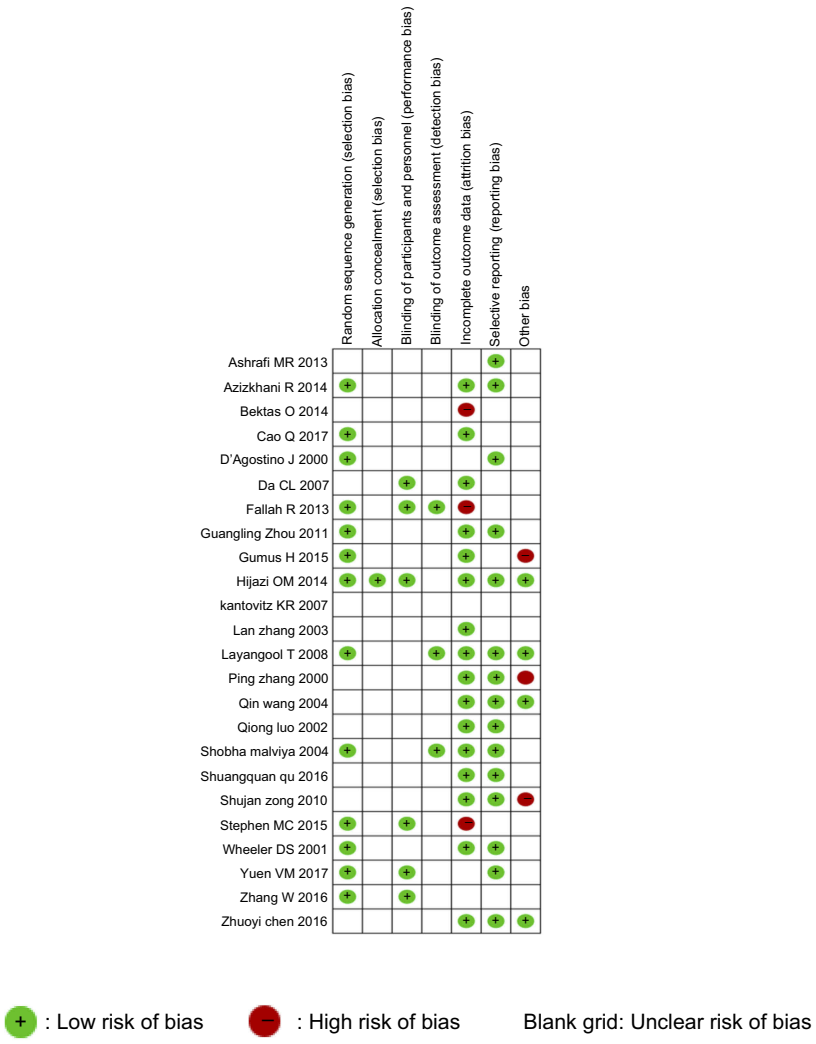

Figure 2 Quality assessment of included studies.

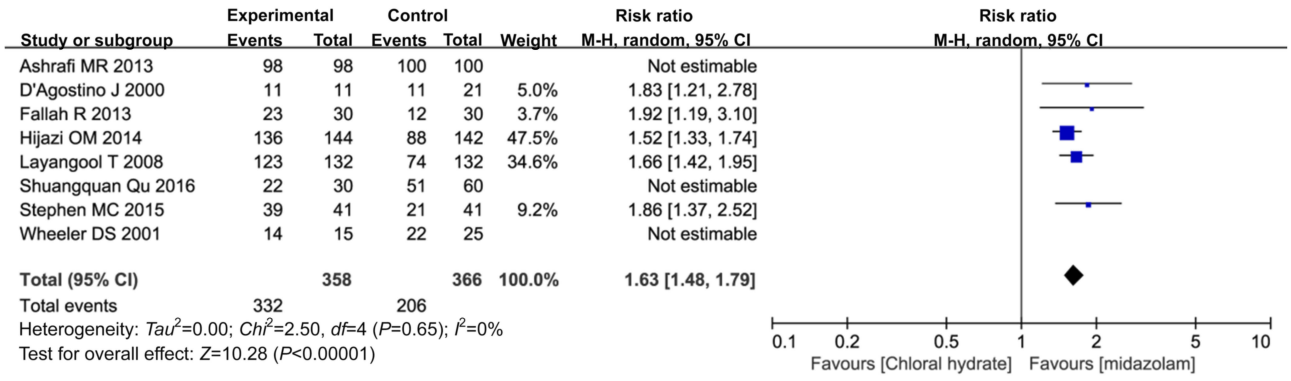

Figure 3 The success rate of sedation between chloral hydrate group and midazolam.

two subgroups had substantial heterogeneity.[21,26] After sensitivity analysis, the sedation duration in CH group was longer than in midazolam group with no heterogeneity [MD=17.52, 95% CI (10.3, 24.71), I^2=0%, P<0.05] (Figure 5).[8,23]

CH versus diazepam

Success rate of sedation

Among the 24 RCT studies, 3 studies with 230 children contributed to this analysis.[17,29,30] There was no significant

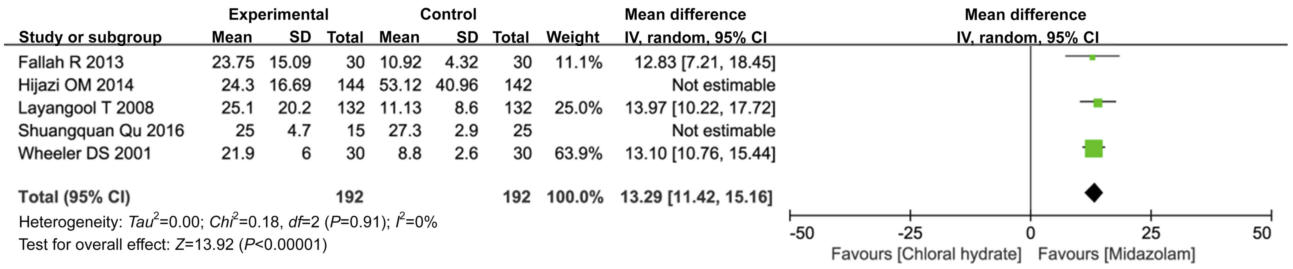

Figure 4 The sedation latency between chloral hydrate group and midazolam group.

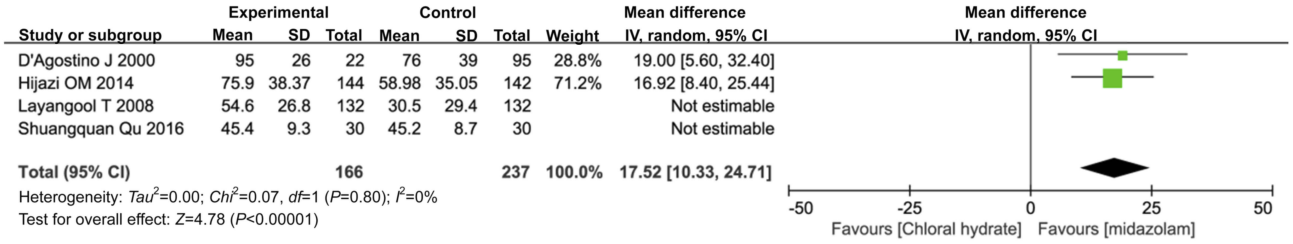

Figure 5 The sedation duration between chloral hydrate group and midazolam group.

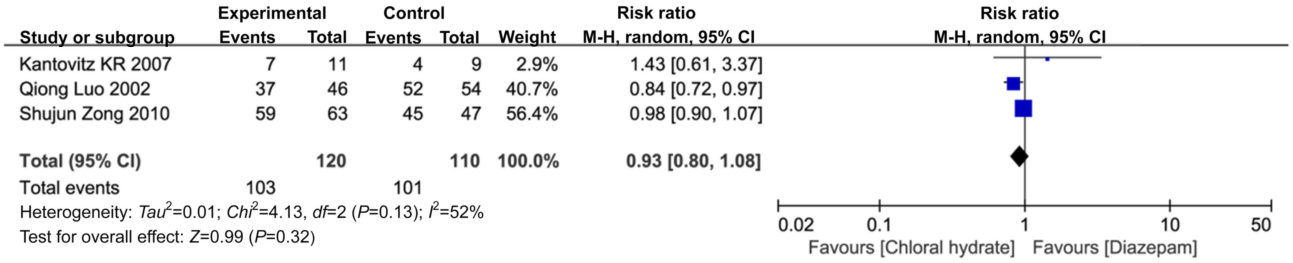

Figure 6 The success rate of sedation between chloral hydrate group and diazepam group.

difference in success rate of sedation between CH group and diazepam group [RR=0.93, 95% CI (0.80, 1.08), I^2=52%, P=0.32] (Figure 6).

CH versus dexmedetomidine

Success rate of sedation

Among the 24 RCT studies, 4 studies with 512 children contributed to this analysis.[11,15,19,20] Before sensitivity analysis, one subgroup had significant heterogeneity.[11] After sensitivity analysis, there was no significant difference in success rate of sedation between CH group and dexmedetomidine group [RR=0.92, 95% CI (0.80, 1.06), I^2=48%, P=0.27] (Figure 7).

Sedation latency

Among the 24 RCT studies, 3 studies with 371 children contributed to this analysis.[15,19,20] Before sensitivity analysis, one subgroup had significant heterogeneity.[19] After sensitivity analysis, there was no significant difference in sedation latency between CH group and dexmedetomidine group [RR=−1.09, 95% CI (−2.45,0.26), I^2=26%, P=0.11] with no heterogeneity (Figure 8).[15,20]

CH versus barbiturates

Success rate of sedation

Among the 24 RCT studies, 5 studies with 749 children contributed to this analysis.[10,16,24,27,31] Before sensitivity analysis, one subgroup had significant heterogeneity.[31] After sensitivity analysis, there was no significant difference in success rate of sedation between CH group and barbiturates group [RR=1.03, 95% CI (0.94, 1.13), I^2=50%, *P*=0.58] (Figure 9).

Group

Sedation duration

Among the 24 RCT studies, 2 studies with 210 children contributed to this analysis.[10,16] There was no significant

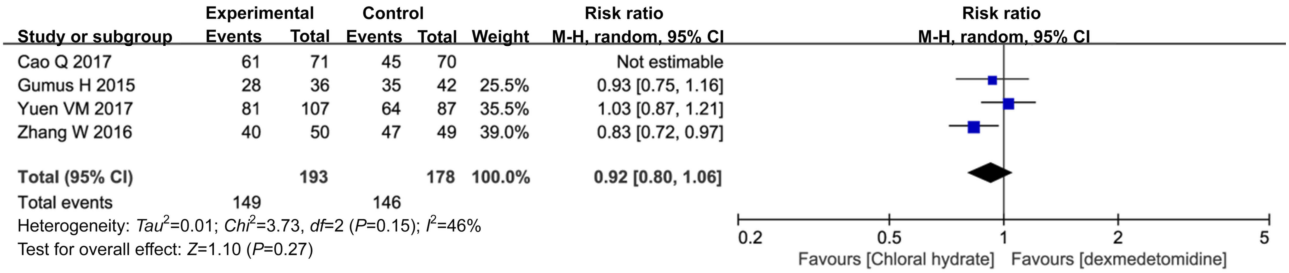

Figure 7 The success rate of sedation between chloral hydrate group and dexmedetomidine group.

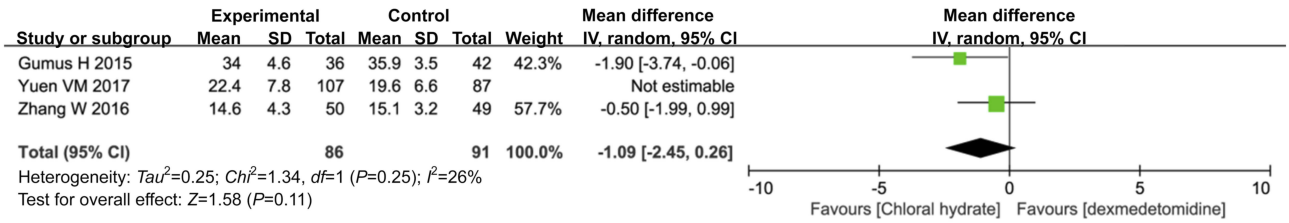

Figure 8 The sedation latency between chloral hydrate group and dexmedetomidine group.

difference in sedation duration in CH group and barbiturates group [MD=−0.72, 95% CI (−1.78, 0.34), I^2=38%, P=0.18] (Figure 10).

Discussion

Sedating children for diagnostic and therapeutic procedures continues to pose challenges.[8] The methodology of sedation is needed to decrease patients' anxiety, movement and radiation exposure, which ultimately elevate the quality of procedural outcomes. Commonly used sedative hypnotics including benzodiazepines (such as midazolam, diazepam, triazolam), aldehydes (such as CH), barbiturates (such as thiopental), imidazole pyridine derivatives (such as zolpidem), benzene ring piperidine derivatives (ketamine) are prevalently prescribed in the current clinical diagnostic and therapeutic procedures. Moreover, within these categories of sedatives, CH, midazolam, dexmedetomidine are recommended for sedation in children in the guideline.[4,5]

The present study was a meta-analysis to evaluate the efficacy of CH oral solution for sedation in pediatrics. Based on the existing evidence from 24 RCTs, the analysis indicated that the sedative effect of CH was better than midazolam, which was consistent with the results of Wilson ME et al.[1] Additionally, there was no significant difference between the CH and diazepam, dexmedetomidine, barbiturates in the success rate of sedation. Meanwhile, children aged 0–18 were with a prospering success rate of sedation that ranges from 63.61% to 100% in this study. Consequently, the sedation success rate of hearing test, electrocardiography, MRI, ophthalmic testing, lumbar puncture examination, CT and dental examination with a significant expression were 95.12%,

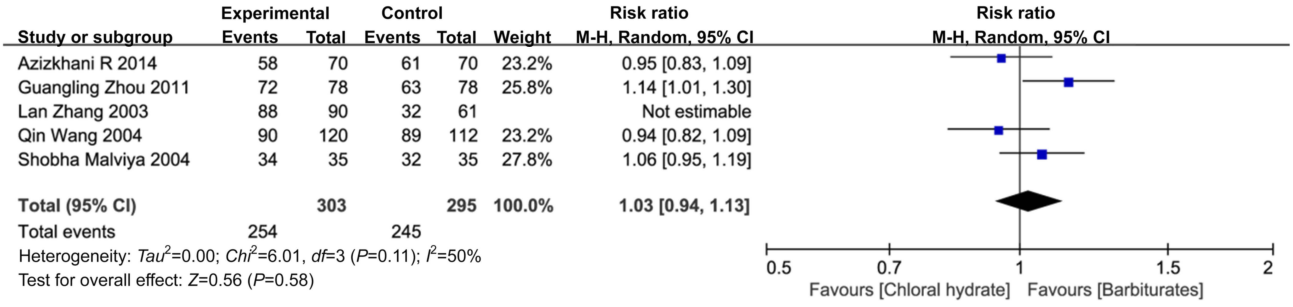

Figure 9 The success rate of sedation between chloral hydrate group versus barbiturates.

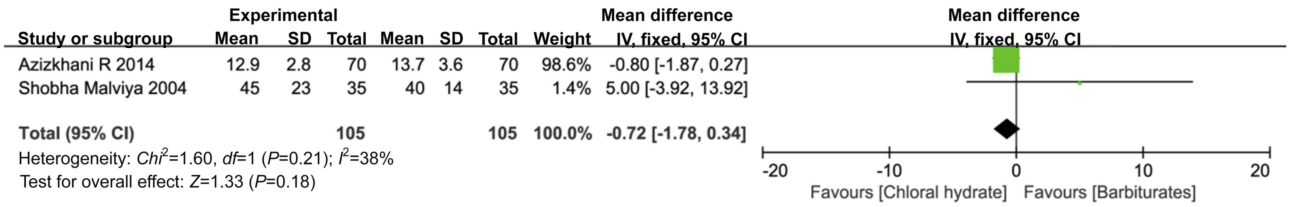

Figure 10 The sedation duration between chloral hydrate group versus barbiturates.

93.62%, 88.54%, 85.92%, 80.43%, 78.26%, 76.05%, respectively.

From the existing secondary evidence, CH recommended by the NICE 2010 guideline for children under 15 kg who are unable to tolerate a painless procedure had a wide margin of safety.[4] The American College of Emergency Physicians 2008 guideline suggested that CH could be used to provide effective procedural sedation in pediatric patients undergoing painless diagnostic studies (level A recommendation).[5] Two experts' consensus recommended CH could be used for sedation before non-invasive procedure and imaging examination in China.[32,33] The systematic review of Asimina Mataftsi et al indicated that despite the paucity of high-quality evidence, the existing literature suggested that the use of CH for procedural sedation in children appears to be an effective alternative to general anesthesia.[34] This is due to its ability to be safely administered in the hospital setting with appropriate monitoring and vigilance for intervention.[16] Therefore, these above evidences suggested that CH oral solution could be used for sedation in pediatrics.

We also recognized the limitations of this study. Firstly, only 25% of studies (6/24) were performed on blinding of participants and personnel assessment. Blinding of outcome assessment, allocation concealment and other bias were ambiguous in the majority of trials. These results indicated the overall quality of the included literature was not satisfactory. Due to only 6 studies being blinded, we did sensitivity analysis of the main outcome indicator of success rate of sedation and the results indicated no differences in the success rate of sedation between CH and midazolam or dexmedetomidine. Furthermore, before sensitivity analysis, some studies had compelling levels of heterogeneity, which might be caused by the quality of the studies, the dose of the treatment and control group, the sample size, the age of the child, the type of examination, etc. Thirdly, this study only included Chinese or English literature and there might be varying degrees of language bias. Although this systematic review and meta-analysis retrieved the mainstream databases, there might still be cases of missed detection. Additionally, this study only reported the efficacy of CH oral solution for sedation in pediatrics; the safety of CH oral solution for sedation in pediatrics would be reported in another manuscript.

Conclusion

From the extrapolation of the existing literature, CH oral solution is an appropriate effective alternative for sedation in pediatrics.

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Author contributions

Zhe Chen conducted data analysis and wrote the manuscript. Mao Lin and Zongyao Huang retrieved and screened the literature, as well as extracted data. Linan Zeng, Liang Huang and Dan Yu established inclusion and exclusion criteria, as well as outcome indicators. Lingli Zhang designed the study and resolved the problems in research process. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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