Chloral Hydrate as a Sedating Agent for Neurodiagnostic Procedures in Children

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Introduction

Neuroimaging and electroencephalography (EEG) are important for the diagnosis, prognosis and development of interventional strategies in paediatric neurodevelopmental disorders. Due to the need of the child to remain still during the imaging exam and sleep EEG, performing these tests is often a challenge. Thus, the use of an adequate sedative agent is paramount for the success of the neurodiagnostic procedures.

The National Institute for Health and Care Excellence (NICE) and the American College of Emergency Physicians guidelines recommend chloral hydrate for moderate sedation during painless procedures in children.[1,2] However, they do not claim its superiority compared to other sedative agents. Some studies suggest that chloral hydrate is ineffective in a significant proportion of children.[3,4] On the other hand, there are concerns about its safety, and gastrointestinal, cardiovascular, respiratory and carcinogenic effects have been reported.[5-7]

Aim

In this Cochrane Corner, we present and discuss the results of a systematic review from the Cochrane Database of Systematic Reviews published in 2017, which summarised and updated the existing evidence on the efficacy and safety of chloral hydrate as a sedative agent in paediatric neurodiagnostic procedures.[8]

Methods

Randomised or quasi-randomised controlled trials of children (under 18 years old) who electively underwent neuroimaging or sleep EEG requiring sedation were included. The administration of oral or rectal chloral hydrate was compared to other sedative/sleep-inducing agents, alternative therapies or no intervention.

The primary outcomes included the proportion of children who successfully completed a neurodiagnostic procedure without awakening, the proportion of children who required a further dose of either the same sedative agent or the addition of a different sedative agent, and the time to adequate sedation in minutes.

The secondary outcomes were the proportion of children with sedation failure or inadequate level of sedation, the sedation duration, sleep onset latency, EEG and neuroimaging artefact findings, and adverse effects attributable to therapy.

The review followed Cochrane's standardised methodology, with a systematic search of studies published up to July 2017 in MEDLINE, CENTRAL, EMBASE and Cochrane Epilepsy Group Specialized Register databases. Unpublished and ongoing studies, references, guidelines, review articles and abstracts of relevant scientific meetings were identified.

The risk of bias of the included studies was assessed using the Cochrane Risk of Bias Tool (2011) and the quality of evidence for the main outcomes was assessed using the GRADE approach. Authors assessed clinical heterogeneity due to clinical and methodological factors, and statistic heterogeneity was quantified by the measurement of inconsistency (I^2).

Different effect measures were used depending on the outcome, including risk ratio (RR) for dichotomous variables and mean differences (MDs) for continuous variables. The results were presented with 95% confidence intervals (95% CI).

The meta-analysis was based on a fixed-effects model, using a random-effects model in the presence of moderate to high heterogeneity.

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Results

Thirteen studies conducted in Iran, Turkey, the United States, Israel, Chile and Spain, with a total of 2,390 children, were included. Five studies used sedation for neuroimaging (computed tomography and/or magnetic resonance imaging). In the remainder, sedation was used for EEG.

The quantitative analysis included only 10 studies and 1,262 children after the exclusion of three studies for methodological reasons.

Of the 10 comparisons performed, seven compared oral (six studies) or rectal (one study) chloral hydrate with other sedative agents (oral dexmedetomidine, hydroxyzine, promethazine and melatonin; oral, intranasal and rectal midazolam; intravenous pentobarbital), and one study compared it with music therapy. Chloral hydrate doses ranged from 25 to 100 mg/kg orally and 50 mg/kg rectally. Two studies compared two doses of oral chloral hydrate (100 mg/kg vs. 50-70 mg/kg).

The methodological aspects of randomisation, allocation concealment and blinding of participants and researchers were adequate in seven (53%), three (23%) and three (23%) studies, respectively. Three studies were at low risk of bias in all domains.

Nine studies evaluated the time to adequate sedation. The remaining primary outcomes were not reported. Regarding secondary outcomes, failure and duration of sedation (eight and seven studies, respectively) and adverse effects (eight studies) were reported. Selected results are shown below and in Table 1.

Time to adequate sedation

Oral chloral hydrate showed shorter time to adequate sedation compared with dexmedetomidine (MDs -3.86; 95% CI -5.12 to -2.60), hydroxyzine (MDs -7.50; 95% CI -7.85 to -7.15), promethazine (MDs -12.11; 95% CI -18.48 to -5.74) and rectal midazolam (MDs -95.70; 95% CI -114.51 to -76.89). This time was significantly longer compared with intravenous pentobarbital (MDs 19; 95% CI 16.61 to 21.39) and intranasal midazolam (MDs 12.83; 95% CI 7.11 to 18.44). There was no significant difference between oral chloral hydrate and music therapy. The 100 mg/kg dose was associated with a shorter time onset to adequate sedation compared with 50 mg/kg (MDs -7.00; 95% CI -7.62 to -6.38) and 70 mg/kg (MDs -5.10; 95% CI -7.05 to -3.15).

Sedation duration

A longer duration of sedation was observed with rectal chloral hydrate compared with rectal midazolam, but not with chloral hydrate compared with oral midazolam

Table 1. Comparison of chloral hydrate with midazolam and between different doses of chloral hydrate

Comparison and secondary outcomes	Participants (studies)	Mean differences (95% CI)	Risk ratio (95% CI)	Quality of evidence (GRADE)
Oral chloral hydrate (75-100 mg/kg) vs. oral midazolam (0.5 mg/kg)				
Sedation duration (minutes)	33 (1)	19 (-3.40 to 41.40)		Low
Sedation failure	33 (1)		0.17 (0.02 to 1.12)	Low
Adverse effects – overall	198 (1)		0.20 (0.01 to 4.0)	Low
Oral chloral hydrate (75-100 mg/kg) vs. intranasal midazolam (0.2 mg/kg)				
Sedation failure	60 (1)		0.39 (0.19 to 0.79)	Moderate
Adverse effects – nausea and vomiting	93 (2)		5.29 (0.84 to 33.14)	n.a.
Adverse effects – behavioural changes	60 (1)		0.33 (0.01 to 7.87)	Moderate
Oral chloral hydrate (50 mg/kg) vs. rectal midazolam (1 mg/kg)				
Sedation duration (minutes)	59 (1)	15.1 (3.35 to 26.85)		n.a.
Dose comparison (100 mg/kg vs. 70 mg/kg)				
Sedation duration (minutes)	97 (1)	8 (5.81 to 10.19)		n.a.
Sedation failure	97 (1)		0.46 (0.19 to 1.09)	n.a.
Adverse effects – overall	97 (1)	1.06 (0.49 to 2.32)		n.a.
Dose comparison (100 mg/kg vs. 50 mg/kg)				
Sedation duration (minutes)	76 (1)	17.8 (8.50 to 27.10)		n.a.
Sedation failure	76 (1)		0.23 (0.05 to 0.99)	n.a.
Adverse effects – overall	76 (1)		2.25 (0.77 to 6.55)	n.a.
Adverse effects – nausea and vomiting	76 (1)		2.10 (0.59 to 7.52)	n.a.
Adverse effects – oxygen desaturation	76 (1)		0.90 (0.06 to 13.87)	n.a.
Adverse effects – behavioural changes	76 (1)		4.51 (0.22 to 90.96)	n.a.

95% CI – 95% confidence interval; n.a. – not assessed.

(Table 1). Sedation was longer with oral chloral hydrate compared with hydroxyzine (MDs 3.1; 95% CI 2.23 to 3.97) and music therapy (MDs 160; 95% CI 121.07 to 198.93). The duration was shorter with oral chloral hydrate compared with dexmedetomidine (MDs 16.31; 95% CI 9.15 to 23.46). Higher doses were associated with a longer duration of sedation (Table 1).

Adverse effects

Oral chloral hydrate was associated with a higher risk of nausea and vomiting compared with dexmedetomidine (RR 12.04; 95% CI 1.58 to 91.96). There was no significant difference in overall and specific adverse effects (nausea, vomiting, arterial hypotension, bradycardia, desaturation, behavioural changes) between chloral hydrate and midazolam (Table 1) or other sedative agents. Overall adverse effects were not different between doses (Table 1).

Conclusion

In children undergoing neurodiagnostic procedures, oral chloral hydrate was as effective as a sedative agent as oral dexmedetomidine, hydroxyzine and midazolam, with similar failure rates, and was more effective than oral promethazine and intranasal midazolam. However, the authors state that the quality of the evidence does not permit presenting solid conclusions. There was a higher risk of adverse effects with oral chloral hydrate compared to oral dexmedetomidine. The authors recommend using chloral hydrate with caution until new safety studies are available.

Comments

The results of this review are in line with other European guidance documents, where chloral hydrate is deemed to be the preferred sedative agent in painless procedures, as it is effective and has a good safety profile.[1,2,9] Chloral hydrate has a moderate sedative effect, without respiratory or haemodynamic complications in most children.[5-7] However, the incidence of adverse effects can vary between 1.7% and 20%, which most often are nausea and vomiting.[5-7,10] Some observational studies describe infrequent and transient episodes of bradycardia, arterial hypotension, bradypnea and desaturation.[5,6] Thus, like other sedatives, it should be used by qualified professionals with assessement of vital signs at regular intervals and continuous pulse oximetry during and after the procedure.[11-14] On the other hand, studies in animals have identified genotoxic action and a carcinogenic potential of chloral hydrate, which has led to the cessation of its use in some countries.[15,16] Nevertheless, the few epidemiological studies which have been conducted in humans do not support this finding.[17,18]

NICE guidelines recommend the use of oral chloral hydrate or intravenous midazolam in children up to 15 kg for painless procedures, such as neuroimaging due to their good safety profile.[2,19,20] In contrast, the US guidelines favor intravenous sedatives for neuroimaging, and oral/intranasal midazolam or intranasal dexmedetomidine for other painless procedures such as EEG.[21] Chloral hydrate is no longer recommended due to the above-mentioned safety concerns, as potentially more effective and safe alternatives are available.[19,20]

In Portugal, the 2012 Portuguese Directorate-General of Health guidelines of pain control in paediatric invasive procedures recommend the use of drugs such as chloral hydrate and midazolam in painless diagnostic procedures that require the cooperation of the child.[12] The least invasive routes of administration (oral and intranasal) are preferred. Note that dexmedetomidine and pentobarbital are not authorised or available for human use for this indication in Portugal. As to the applicability in an emergency setting, observational studies have found that sedation with chloral hydrate in imaging procedures after mild head trauma was safe and effective, with uncommon and usually mild adverse events (vomiting).[22,23]

In spite of the conclusions pointed out in this review, it is important to stress that evidence is scarce and its quality is low. There is limited data relating to adverse effects, and more studies with adequate methods and relevant outcomes are needed to evaluate its efficacy and safety. There is a need to study Portuguese practices in this field and to promote rational use according to current evidence.

Keywords: Child; Chloral Hydrate/administration & dosage; Chloral Hydrate/adverse effects; Conscious Sedation; Electroencephalography; Hypnotics and Sedatives; Magnetic Resonance Imaging; Neuroimaging; Tomography, X-Ray Computed

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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