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Efficacy of Reconstituted Oral Chloral Hydrate from Crystals for Echo Sedation

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Abstract

Background—Chloral hydrate has been the drug of choice for uncooperative infants and children requiring sedation for echocardiography. Recently, the commercially available liquid formulation was discontinued by the manufacturer, and the only oral form of chloral hydrate available was made using reconstituted crystals.

Objective—To compare sedation efficacy before and after this change in chloral hydrate formulas.

Methods—Consecutive patients presenting for echo sedation during the transition from the manufacturer-derived old formulation (OLD) to the locally-reconstituted new formulation (NEW) were retrospectively reviewed for time to onset of level 3 sedation, duration of level ≥3 sedation, requirement for additional sedative medications, sedation failure, ability to complete the echocardiogram and adverse events related to the sedatives.

Results—The cohort included 124 patients (63 OLD, 61 NEW). Although the mean age at sedation was younger for the NEW group, the weight and average dose of chloral hydrate used were not significantly different. There were no adverse events in either group. Time to onset of sedation was the same between the 2 formulations, but the duration of sedation was significantly shorter for the NEW group (42.4±24.5 vs. 55.3±26.2 min, p=0.01). In addition, the need for secondary sedating agents because of inadequate sedation and sedation failure were significantly greater using the NEW compared to the OLD formulation.

Conclusion—Chloral hydrate reformulation using reconstituted crystals results in a shorter duration of sedation, more frequent requirement for a secondary sedative agent, more frequent sedation failure and occasional inability to complete the echocardiogram compared to the manufacturers' formulation.

Keywords

Pediatric; Echocardiography; Chloral hydrate; Sedation

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Introduction

Transthoracic echocardiography, while the mainstay of diagnosis and surveillance for pediatric patients with heart disease, can be difficult to perform in infants and toddlers due to lack of cooperation and anxiety. Use of sedation in this age group improves image quality and reduces diagnostic errors, particularly in those with more complex disease(1). Chloral hydrate has been the medication of choice for many pediatric echo labs due to its low cost, oral availability (100mg/mL solution) and safety profile. However, chloral hydrate is no longer produced in the United States(2) and no clearly superior alternative has emerged without intravenous access and anesesthesiologist present. The pharmacy at the Children's Hospital of Wisconsin has been preparing an oral formulation of chloral hydrate from reconstituted crystals (50mg/mL) since December 2013 as a replacement for the commercially available drug. We sought to compare efficacy of the pharmacy-reconstituted (NEW) formulation with the manufacturer-derived (OLD) formulation for their ability to provide adequate sedation to perform a complete echocardiogram in an otherwise uncooperative patient.

Methods

Consecutive patients presenting to the echo sedation lab before and after the transition, occurring in December 2013, were retrospectively reviewed in compliance with institutional review board requirements for a quality improvement initiative. As this was a quality improvement initiative, no patients were excluded. Data were collected on patient characteristics and sedation parameters. Chloral hydrate dosing is done by the individual physician supervising the echo lab on the day of the sedation, with recommended guidelines as follows:

-infants < 3 month 50 mg/kg

-infants 3-9 months 75 mg/kg

-infants and children >9 months 100 mg/kg up to a maximum dose of 1000 mg

These guidelines were available as part of the ordering algorithm in the electronic medical record and were utilized by all staff during the entire study duration. Sedation score was assessed during direct nurse monitoring based on the Ramsay sedation scale(3) as part of an institutional sedation protocol (Table 1). Sedation failure was defined as failure to reach level 3 sedation on the Ramsay sedation scale. Adverse events were considered any complication requiring intervention, excluding additional sedation, or admission. Descriptive data are presented as number with percent of total, mean ± standard deviation or median with range. Patients receiving the OLD were compared to those receiving the NEW by Fisher's exact test or Wilcoxon rank sum test. The primary outcome of interest was sedation failure. Other outcomes of interest were time to onset of level 3 sedation, duration of level ≤3 sedation, requirement for additional sedative medications, ability to complete the echocardiogram and adverse events related to the sedatives. Analyses were performed using StataIC13 (StataCorp, College Station, Texas) with a $p<0.05$ considered significant.

Results

During the 4 month period, 124 patients underwent sedation in the echocardiography sedation lab at the Children's Hospital of Wisconsin. The median age was 7 months (2 weeks – 30 months) with a median weight of 6.8 kg (2.6 – 13.2 kg). The OLD formulation was used in 63 patients and the NEW formulation in 61 patients. Comparison between the OLD and NEW groups can be seen in Table 2. There were no adverse events in either group, including those receiving secondary sedative agents. Although the mean age at sedation was younger for the NEW group, the weight and average dose of chloral hydrate used were not significantly different between groups. The mean time of onset to sedation between the OLD and NEW groups (23 ± 10.8 vs. 24.4 ± 9.9 minutes, p=0.22) was similar, but the duration of sedation was significantly shorter for the NEW group (42.4±24.5 vs. 55.3±26.2 min, p=0.01). While time to onset of adequate sedation was similar between groups, Figure 1 demonstrates a shift with the NEW formulation towards later onset. Figure 2 demonstrates the shift toward shorter duration of level 3 sedation with the NEW formulation. The need for secondary sedating agents (midazolam 0.2-0.3 mg/kg intranasal) because of inadequate sedation and sedation failure were significantly greater using the NEW compared to the OLD formulation.

Discussion

Oral chloral hydrate has a long history of safe use for sedation in children undergoing transthoracic echocardiography for congenital and acquired heart disease. It allows completion of echocardiographic study in over 90% of all children and >99% of those under 3 years of age (4-6), and reports of adverse events are very rare. Most difficulties with chloral hydrate are with administration due to its bitter taste, relatively large volume and resultant emesis (4, 5). However, commercially available production of the oral chloral hydrate suspension was discontinued in the United States in 2012 due to “business reasons” (2), requiring labs to reconstitute an oral suspension at their local pharmacy from crystals available from pharmaceutical supply companies (Fargon, Inc., St. Paul, Minnesota). This review comparing the 2 formulations demonstrates some advantages of the OLD commercially available formulation of chloral hydrate (100mg/ml) compared to the NEW pharmacy reconstituted formulation (50mg/ml) produced at the Children's Hospital of Wisconsin. The advantages of the old formulation include decreased need for a secondary sedative agent and successful sedation to echo completion in all patients compared to the new formulation. In addition, due to inability to concentrate the NEW formulation further, the OLD formulation requires half the volume of sedative compared to the NEW, which is important in a 10 kg child who now must drink 20 mL of the 50 mg/mL NEW formulation (rather than 10 mL of the 100 mg/mL OLD) to receive the recommended 1000 mg dose.

The increased need for a secondary sedative agent with the NEW formulation, which in our lab is midazolam 0.2-0.3 mg/kg given intranasally, is concerning. While it was infrequent, occurring in 5 cases (8.2%) with the NEW formulation compared to none with the OLD formulation, use of more than one sedative agent increases the risk for adverse events. A retrospective review of adverse events with sedation found that no particular drug category or route of administration was associated with adverse events but that almost half of the

adverse events were associated with use of multiple sedative agents(7). In a separate review of >16,000 sedations for radiologic procedures, use of multiple agents was associated, in multivariable analysis, with an odds ratio of 4.9 for adverse events compared to use of a single agent(8). Drug-drug interactions with additive negative cardiorespiratory consequences are the likely cause of this increased risk(7).

There were 2 patients in the NEW formulation group in whom a study could not be completed. These 2 patients were also sedation failures and required intranasal midazolam as a secondary agent. The first patient was an 18 month old infant followed with a mild unrepaired coarctation of the aorta. His weight at that time was 13.1 kg and he was given 1000mg of NEW chloral hydrate (76 mg/kg). During the echocardiogram he was at level 4 or 5 (minimal) sedation and the study could not evaluate coronary artery origins or all pulmonary veins. Given previous studies, this study was adequate to warrant referral for surgical repair. The second patient was a 3 month old with a cleft lip and palate, inguinal hernia and hypothyroidism who was evaluated for a murmur. His weight was 4.35 kg and he received 350 mg (80 mg/kg). He remained at level 4-5 sedation during the study. The echocardiogram was able to identify a patent foramen ovale and a secundum atrial septal defect but could not identify the right coronary artery and demonstrated only 2 pulmonary veins returning to the left atrium. He was rescheduled for repeat cardiology evaluation and echocardiogram when sedation would not be necessary for study completion.

Numerous alternatives to chloral hydrate for non-invasive diagnostic procedures in infants and children have been evaluated, but all have deficiencies. Distraction techniques, such as video viewing can be successful to obtain complete echocardiographic studies(9) but more recent data have shown that sedation results in higher quality studies and reduces the risk of preventable diagnostic errors, particularly in patients with moderate or high complexity disease(1). It is our general policy to sedate patients needing complete echocardiograms between 1 month and 2 years of age and use distraction techniques above this age. Other options for sedative medications have included pentobarbital sodium, midazolam and inhaled anesthetics. Oral pentobarbital sodium has proven to be at least as safe and efficacious as chloral hydrate for echocardiograms or radiologic procedures(10-13) but has significantly higher cost, with a hospital cost 28 times that of chloral hydrate. While midazolam may offer the benefits of quicker onset of action and shorter recovery time, it is primarily an anxiolytic rather than a sedative and results in more frequent sedation failure and inability to complete the study (6, 14). A final alternative is the use of anesthetic gas, which should result in elimination of sedation failures and provides for anesthesia staff monitoring for serious adverse outcomes during drug delivery. The need for an anesthesiologist and anesthesia cart, however, can increase the cost of the echocardiogram by almost $1500 (15). Additionally it can be difficult to ensure that there is consistent need for anesthesia given the variable ages of patients needing echocardiograms.

This initiative was undertaken to determine the efficacy of our pharmacy-derived formulation of chloral hydrate. While the efficacy of the NEW formulation did not meet that of the original commercially available formulation with more failed sedations and the 2 incomplete studies, there were also benefits to the NEW formulation. The NEW formulation had similar time to onset, and although not statistically significant, had fewer patients with

prolonged sedation of > 60 minutes (figure 2). The shorter duration of sedation seen with the NEW formulation may be a benefit in some cases where echocardiograms are simple and can be completed quickly, such as murmur evaluations, but a disadvantage with more complex disease that requires more extensive evaluation. The NEW formulation demonstrated similar safety profile as the OLD formulation without adverse events in either group. Finally, subjective feedback from the sedation nurses has been that while sedation onset has not changed, the frequency of post-sedation irritability is reduced with the NEW. In the sedation lab at the Children's Hospital of Wisconsin, based on these results and available alternatives, we have continued to use the NEW formulation with midazolam intranasal as a secondary agent. It has become rare that midazolam has been required, possibly reflecting more effective delivery of the larger volume of drug by the sedation nurses over time. For those very rare cases where a full echocardiogram cannot be completed, the study is either deferred until the child is old enough so that sedation is no longer necessary or performed in special procedures with anesthesia performing sedation. This determination is made on a case by case basis depending on the age of the patient and the information required.

This study is limited by a small sample size. It was not designed to be a comparison of patient outcomes but rather a quality improvement initiative to determine whether the NEW formulation was providing adequate sedation for completion of echocardiographic studies or whether it would be beneficial to use alternative medications. There was an abrupt transition from the OLD to NEW formulation and therefore there was no blinding to patients/parents or providers; this has the potential to introduce bias in those assessing time to onset and duration of sedation, which can be subjective. One patient in the NEW formulary group did not receive the full dose as they spat out some of what was given. This resulted in a sedation failure and requirement for a secondary agent. This was categorized as such as it may potentially have resulted from the increased volume required with the NEW formulation.

Conclusions

Chloral hydrate reformulation using reconstituted crystals results in a shorter duration of sedation and more frequent requirement for a secondary sedative agent. It is also associated with more frequent sedation failure and occasional inability to complete the echocardiogram compared to the manufacturers' formulation. Optimal techniques for echo sedation have been made more challenging with the loss of this drug from the marketplace. Given the deficiencies of other medications for sedated echocardiograms, reconstituted chloral hydrate remains a suitable alternative and direct comparison of this reconstituted formulation with other sedative medications is warranted.

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Abbreviations

NEW	pharmacy-reconstituted chloral hydrate formulation
OLD	manufacturer-derived chloral hydrate formulation

Highlights

- Two forms of chloral hydrate for pediatric echo sedation were compared
- The pharmacy-derived version was less effective than manufacturer-derived version
- The pharmacy-derived version had more use of secondary agents and sedation failure

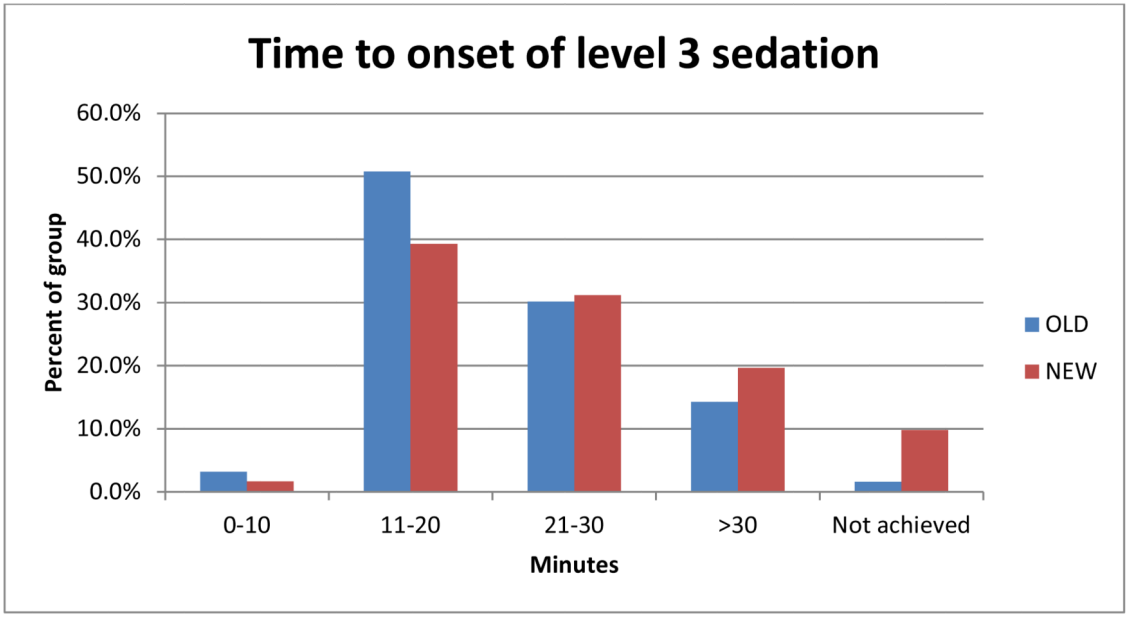

Figure 1.
Comparison of time (minutes) to onset of level 3 sedation between OLD and NEW formulations of chloral hydrate.

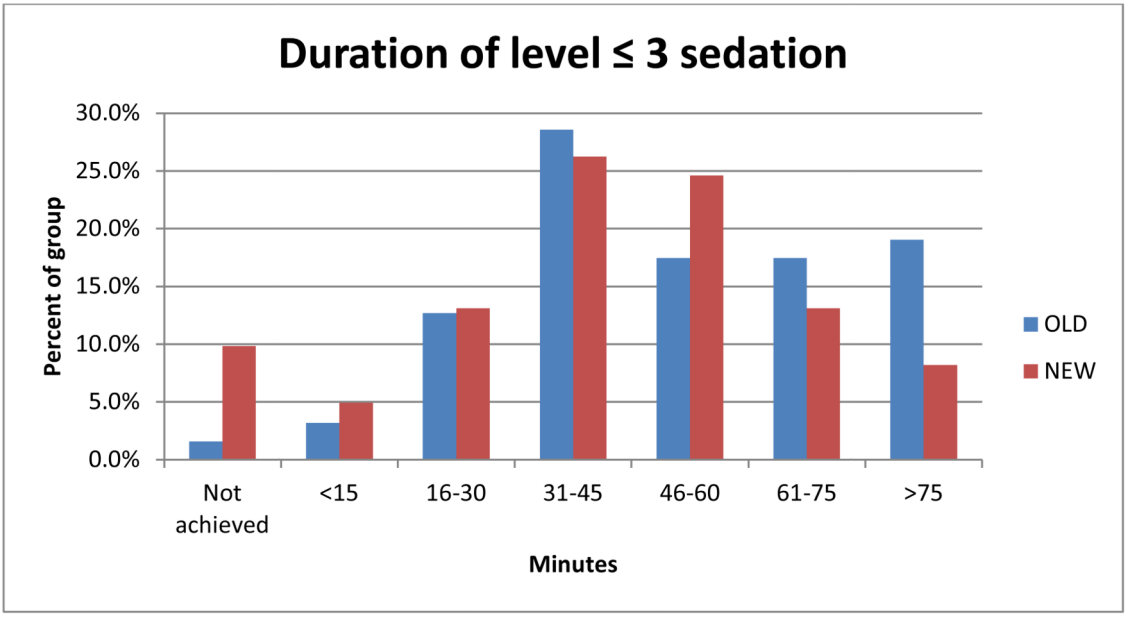

Figure 2.
Comparison of duration (minutes) of level ≤3 sedation between OLD and NEW formulations of chloral hydrate.

Table 1

Sedation Scoring Scale

Score	Sedation level	Description
6	None	Agitated, anxious, or in pain above baseline
5	Minimal	Spontaneously awake without stimulus; may exhibit anxiolysis
4		Drowsy but easily arouses to consciousness to light tactile or verbal/tactile stimulus
3	Moderate	Arouses to consciousness with moderate tactile or loud verbal stimulus
2	Deep	Arouses slowly to consciousness with sustained painful tactile stimulus
1		Arouses, but not consciousness, with painful stimulus
0		Unresponsive to painful stimulus

Sedation scoring based on the Ramsay sedation scale used to assess level of sedation after administration of the OLD and NEW formulations of chloral hydrate. Sedation failure was failure to reach level 3 sedation.

Table 2

Baseline characteristics and outcomes

	OLD formulation (n=63)	NEW formulation (n=61)	P value
Age (months)	10.3 ± 7.7	7.1 ± 5.4	0.04
Weight (kg)	7.5 ± 2.7	6.7 ± 2.2	0.16
Chloral hydrate dose (mg/kg)	75.9 ± 12.3	74.6 ± 16.7	0.71
Time to onset of sedation (min)	23 ± 10.8	24.4 ± 9.9	0.22
Duration of sedation (min)	55.3 ± 26.2	42.4 ±24.5	0.01
Sedation >60 minutes, n	23 (36.5%)	13 (21.3%)	0.08
Secondary agent required, n	0 (0%)	5 (8.2%)	0.03
Sedation failure, n	0 (0%)	8 (13.1%)	0.003
Incomplete echocardiogram, n	0 (0%)	2 (3.3%)	0.24

Comparison of patient characteristics and OLD and NEW chloral hydrate formulation efficacy