

# Safety and efficacy of chloral hydrate for conscious sedation of infants in the pediatric cardiovascular intensive care unit

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## Abstract

This study evaluates the safety and efficacy of chloral hydrate administration for the conscious sedation of infants in the pediatric cardiovascular intensive care unit (PCICU).

We conducted a retrospective review of the charts of 165 infants with congenital heart disease who received chloral hydrate in our PCICU between January 2014 and December 2014. Chloral hydrate was administered orally or rectally to infants using doses of 50 mg/kg. We collected and analyzed relevant clinical parameters.

The overall length of time to achieve sedation was ranged from 5 to 35 min ( $10.8 \pm 6.2$  min); the overall mean duration of sedation was ranged from 15 to 60 min ( $33.5 \pm 11.3$  min); and the overall mean length of time to return to normal activity was 10 min to 6 h ( $34.3 \pm 16.2$  min). The length of the PCICU stay was ranged from 3 to 30 days ( $8.2 \pm 7.1$  days). Physiologically, there were no clinically significant changes in heart rate, mean arterial pressure, respiratory rate, or peripheral oxygen saturation before, during, or after use of the chloral hydrate. There were no significant differences regarding sedative effects in the subgroups (cyanotic vs acyanotic group, with pulmonary infection vs without pulmonary infection group, and with pulmonary hypertension vs without pulmonary hypertension group).

Our experience suggests that chloral hydrate is a safe and efficacious agent for conscious sedation of infants in the PCICU.

**Abbreviation:** PCICU = pediatric cardiovascular intensive care unit.

**Keywords:** chloral hydrate, infant, intensive care unit, sedation

## 1. Introduction

Infants with congenital cardiac malformations often have labile cardiovascular function during the perioperative period and may require sedation in the pediatric cardiovascular intensive care unit (PCICU) for several days to weeks. These infants are subject

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M-LC and QC have been contributed equally to this study and share first authorship.

M-LC and QC designed the study, collected the clinical data, performed the statistical analysis, participated in the operation, and drafted the manuscript. M-LC, QC, FX, J-XZ, X-YS, and X-ZT participated in the operation and revised the article. All authors read and approved the final manuscript.

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to a host of noxious and irritating stimuli and require an adequate level of sedation while minimizing medication-related complications, respiratory inhibition, cardiovascular depression, and excessive or prolonged neurologic compromise. Chloral hydrate is one of the most commonly used sedatives in the clinical setting despite the availability of other sedatives such as midazolam and pentobarbital.<sup>[1-4]</sup> It has the characteristics of ease of administration, high success rate, and transient and low prevalence of adverse reactions. Other traditional sedative agents (such as midazolam, propofol, and ketamine) can have negative effects on the respiratory drive or can have cardiovascular side effects. Based on available reports, these characteristics of chloral hydrate make it potentially useful in the treatment of infants who require sedation in a PCICU. During a 1-year period (2014), we used chloral hydrate for conscious sedation in infants in our PCICU; here we summarize our experiences and report the results.

## 2. Materials and methods

Approval was obtained from the Institutional Review Board of the University of Fujian Medical University, China, for a retrospective review of infant patients who received chloral hydrate for conscious sedation in the PCICU. Additionally, written parental informed consent was obtained from the parents of the patients.

### 2.1. Participants

Our PCICU can accommodate 20 patients, 10 professional doctors, and 60 professional nurses. In our department, the number of patients treated annually was about 800, and the

number of admissions usually was 100%. All infant patients for whom cardiovascular events were likely, as well as those who required respiratory support, postoperative treatment, or cardiopulmonary resuscitation, were required to be admitted to the PCICU. We reviewed the charts of 165 consecutive infants who were admitted to the PCICU between January 2014 and December 2014 and who received chloral hydrate. All the infants suffered from congenital cardiovascular disease and/or pulmonary infection and/or pulmonary hypertension. Due to the patients' poor condition, conscious sedation was needed for all the infants to prevent cardiorespiratory complications. Patients' standard demographic information was collected. There were 76 females and 89 males. The patients were aged from 1 to 12 months (mean  $\pm$  standard deviation,  $4.5 \pm 2.8$  months). Their weights ranged from 3.5 to 6.5 kg ( $4.6 \pm 1.3$  kg). Inclusion criteria including those patients were admitted to PCICU need conscious sedation, patients with any medical contraindications for sedation were excluded from the study. We also excluded those patients admitted to the PCICU > 30 days and used other sedative agents prior to the study.

## 2.2. Study design and setting

Chloral hydrate was administered in aliquots, first, to achieve a level of sedation adequate for placement in a bed and, second, to maintain adequate sedation throughout the procedure or examination. All infants were weighed to enable calculation of the appropriate drug dose. Infants were given nothing by mouth before sedation; this period was at least 1 or 2 h for liquids. Chloral hydrate was administered orally or rectally to infants at doses of 50 mg/kg; 112 infants were administered chloral hydrate orally, and the other 53 infants were dosed rectally to alleviate noncooperation or significant shortness of breath. If the initial dose did not achieve satisfactory results after 30 min, an augmentation dose of 25 mg/kg of the same medication was given orally to the infants. If the medicinal effect was considered inadequate despite incremental infusion doses, a rescue agent was administered. Rescue agents were also administered if immediate sedation was needed to avoid a complication (respiratory function depression, significant hypertension, etc.). The rescue agents included midazolam, dexmedetomidine, and fentanyl.

On becoming sleepy, the infant was placed in the bed. Sedation was judged to be successful if the patient kept quiet and was unable to produce potentially self-injurious behaviors such as displacement of intravenous catheters or other medical devices. Similarly, sedation was judged to be successful when the patient cooperated with a complete echocardiographic examination, was not agitated, and appeared to be comfortable.

## 2.3. Objectives and outcome measures

During sedation, the pediatric intensivist continuously monitored the patient for any problems involving the airway, the respiratory organs, or the hemodynamic situation. The length of time required to achieve sedation, the duration of sedation, the length of time required to return to normal activity, and whether sedation was successful were recorded. Continuous peripheral oxygen saturation, heart rate, and respiratory rate with telemetry and automated noninvasive mean arterial pressure monitoring were recorded throughout the procedure and during the postprocedure recovery period. All the recorded clinical parameters are shown in Table 1. The first record was obtained before the patient was given sedative drugs. Ten to fifteen minutes after the chloral hydrate was started, the second record was

**Table 1**

**Changes in clinical data from the patients undergoing sedation with chloral hydrate.**

Items	Before sedation	During sedation	After recovery
Heart rate, beats/min	112.3 $\pm$ 5.2	105.2 $\pm$ 4.8	111.5 $\pm$ 6.8
Mean arterial pressure, mm Hg	84.5 $\pm$ 5.9	83.8 $\pm$ 4.8	83.6 $\pm$ 5.1
Respiratory rate	25.2 $\pm$ 5.3	24.3 $\pm$ 6.5	25.7 $\pm$ 6.1
Peripheral oxygen saturation, %	99.1 $\pm$ 0.5	99 $\pm$ 0.6	99.1 $\pm$ 0.4

taken. The third record was taken while the patients were successfully recovering for 10 to 15 min. Antecubital venous access with an intravenous cannula was prepared in case of the need to administer intravenous fluids. A nurse was present at all times to assist with the procedures, and equipment for cardiorespiratory resuscitation was readily available.

All episodes of desaturation, cardiorespiratory dysfunction, and other complications, such as nausea, vomiting, or prolonged sedation, were recorded. Desaturation was defined as a drop in transcutaneous oxygen saturation <90% in the noncyanotic patients and a decrease of >5% of the initial oxygen saturation values in the cyanotic patients. In this study, prolonged sedation was defined as a lack of return to the patient's normal baseline state of awareness within 4 h of drug administration. Those children with severe cyanotic congenital heart disease, chronic cardiac insufficiency, severe pulmonary hypertension, or severe pulmonary infection were maintained on 1 L supplemental oxygen via a standard or humidified low-flow nasal cannula. All participants were followed up until chloral hydrate was stopped or they were discharged from the PCICU.

## 2.4. Statistical analysis

Continuous data are presented as means  $\pm$  standard deviations and ranges. Clinical parameters were compared with the independent samples *t* test. Nominal variables were compared using Fisher exact test. The success rates were analyzed by the Chi-squared test. A *P* value of < 0.05 was defined as statistically significant.

## 3. Results

Successful sedation with adequate sedation levels was achieved in 158 (95.8%) of 165 cases. In all infants, chloral hydrate was started within 4 h of admission to the PCICU. All patients were spontaneously breathing before receiving chloral hydrate. The overall mean length of time to achieve sedation was 5 to 35 min ( $10.8 \pm 6.2$  min); the overall mean duration of sedation was 15 to 60 min ( $33.5 \pm 11.3$  min); and the overall mean length of time to return to normal activity was 10 min to 6 h ( $34.3 \pm 16.2$  min). The overall length of stay in the PCICU was 3 to 30 days ( $8.2 \pm 7.1$  days). In 51.5% of cases, chloral hydrate was indicated to control agitation, and in 48.5%, it was indicated for examination sedation. Rescue agents were administered a total of 7 times (4.2%). Midazolam was the most common rescue drug used. Because of the additive effect of chloral hydrate, the rescue boluses given were lower than the usual requirements: midazolam 0.03 mg/kg, fentanyl 0.2  $\mu$ g/kg, or dexmedetomidine (bolus dose of 0.3  $\mu$ g/kg followed by an infusion of 0.2–0.3  $\mu$ g/kg per h).

Table 1 shows the changes in the clinical data for the patients who underwent sedation with chloral hydrate. Although overall there was a slight trend toward lower blood pressure and lower

**Table 2****Comparison of the clinical data attributed to chloral hydrate administration between the groups of cyanotic and acyanotic cases.**

Items	Cyanotic cases (n=35)	Acyanotic cases (n=130)	P
Sex, M:F	19:16	68:62	0.835
Age, mo	4.8±1.8	4.2±2.7	0.239
Weight, kg	4.2±1.2	4.8±2.1	0.165
The success rates, %	94.3	96.1	0.06
Length of time to achieve sedation, min	10.2±8.9	10.9±11.4	0.701
Duration time of sedation, min	32.6±10.4	34.8±11.2	0.592
Length of time to recovery, min	31.3±13.2	36.5±12.8	0.815

heart rate compared with the initial conditions, this was not clinically significant and did not require supportive therapy. All patients remained warm and well-perfused throughout the procedure. Ten infants had slight hypotension that resolved by venous liquid perfusion. Each of the patients was breathing spontaneously during the sedation procedure.

The overall prevalence of side effects was <7% in all the infants. Prolonged sedation was observed in 5 infants who received 2 doses of chloral hydrate because of noncooperation. Other patients were arousable within 1 h and were fully awake within 2 h after administration of chloral hydrate. Initially, movement was a notable problem with the sedation. Three infants with complex congenital heart disease who needed a longer inspection time required administration of an augmentation dose of chloral hydrate because of uncooperative movements. In 5 infants with cyanotic congenital heart disease and severe pulmonary infection, pulse oximetry recordings during sedation revealed an episode of oxygen desaturation that resolved completely after awakening, suctioning the secretions in the upper airway, positioning the head, and the transitory administration of 100% blow-by oxygen. These children remained cooperative without further sedation, and no additional episodes of desaturation were observed during the remainder of the examination. Two infants vomited upon wakening from sedation. One was 6 months old, and the other was 7 months old; both had received a standard dose of 50 mg/kg. The vomiting resolved without any intervention. These 2 infants were able to tolerate oral fluids and a light meal 4 h later. There were no respiratory adverse events, and none of the patients required intubation during the sedation procedure. No other complications (desaturation requiring endotracheal intubation, hypotension, hypertension, bradycardia, apnea, or abnormal movements) occurred.

Cyanotic heart disease was present in 35 of 165 patients (21.2%) but did not affect the success rate of sedation (94.3% vs 96.1% successful rate for cyanotic and acyanotic patients,

respectively) or the prevalence of side effects in this study. In the groups, we do not have to consider whether the 2 groups of patients with pulmonary infection. There were no significant differences in length of time required to achieve sedation, duration of sedation, or length of time to recovery in both the cyanotic and acyanotic groups (Table 2).

Table 3 compares the subgroup with pulmonary infection (24.8% cases) and the subgroup without pulmonary infection (75.2% cases) (meanwhile, we do not have to consider whether the 2 groups of patients with cyanotic or acyanotic heart disease). Table 4 compares the subgroup with ventricular septal defects with pulmonary hypertension (39.4% cases) and the subgroup with ventricular septal defect without pulmonary hypertension (18.2% cases) (moderate to severe pulmonary hypertension was assessed by transthoracic echocardiography, and the presence of pulmonary artery systolic pressure 45–90 mm Hg). In both subgroups, the results showed no significant differences in the success rate of sedation, length of time to achieve sedation, duration of sedation, and length of time to recovery.

Compared with another group of 145 other cases with congenital cardiovascular disease in our division who were previously administered dexmedetomidine for sedation (unpublished data), the results showed no notable differences in patient distribution, the success rates, or the Ramsey Sedation Scores in both groups ( $P > 0.05$ ). But the dexmedetomidine group required a significantly shorter time to achieve sedation and length of time to recovery than the chloral hydrate group ( $1.5 \pm 3.3$  vs  $11.5 \pm 9.5$  min and  $31.2 \pm 12.3$  vs  $2.1 \pm 1.2$  min,  $P < 0.05$ ). The cost, however, was significantly higher in the dexmedetomidine group compared to that of the chloral hydrate group ( $215.5 \pm 110.9$  vs  $1.5 \pm 2.3$  RMB,  $P < 0.05$ ) (Supplemental Table 5, <http://links.lww.com/MD/B494>).

The total follow-up period ranged from 3 to 5 days ( $3.8 \pm 0.8$  days). None of the patients presented delayed side effects. None

**Table 3****Comparison of the clinical data attributed to chloral hydrate administration between the groups with and without pulmonary infection.**

Items	With pulmonary infection (n=41)	Without pulmonary infection (n=124)	P
Sex, M:F	23:18	64:60	0.618
Age, mo	4.6±2.1	4.5±1.9	0.516
Weight, kg	4.2±1.2	4.8±2.1	0.114
The success rates, %	95.1	96.0	0.329
Length of time to achieve sedation, min	10.3±8.5	11.1±9.5	0.676
Duration time of sedation, min	31.5±10.5	34.9±13.2	0.505
Length of time to recovery, min	30.2±11.2	31.4±12.1	0.907

**Table 4****Comparison of the clinical data attributed to chloral hydrate administration between the subgroup of ventricular septal defect with and without pulmonary hypertension.**

Items	With pulmonary hypertension (n=65)	Without pulmonary hypertension (n=30)	P
Sex, M:F	35:30	16:14	0.963
Age, mo	4.1±2.5	4.3±2.8	0.959
Weight, kg	4.3±1.5	4.6±2.0	0.428
The success rates, %	93.8	93.3	0.649
Length of time to achieve sedation, min	12.1±8.6	11.9±10.2	0.520
Duration time of sedation, min	31.5±10.2	33.6±11.1	0.593
Length of time to recovery, min	30.5±12.3	32.1±11.5	0.844

of the patient outcomes required unplanned intensive care unit admission or subsequent medical attention.

#### 4. Discussion

Several drugs have been used for years in clinical practice for the conscious sedation of infants, and today's sedation practices vary considerably among various centers. The ideal sedating agent would be safe, efficacious, painless, reversible, and easy to administer, would provide consistent sedation and rapid onset and offset of action, and would have minimal or no side effects.<sup>[5]</sup> Considering the potential higher risk of desaturation and adverse sedation-related events, general anesthesia should be given to children of under 1 year old and patients with ASA Class III to IV.<sup>[6,7]</sup> However, it should also be noted that intubation and ventilation with general anesthesia could cost a long time and increase the risk of adverse incidents. Even the short-lived incidents of this kind may lead to airway trauma and atelectasis.

The selection of sedatives for infants undergoing conscious sedation varies remarkably from one geographical area to another, and the most suitable agents for this purpose are still being investigated.<sup>[8–11]</sup> In our study, all patients had potential or significant congenital heart disease and would be stratified at high risk during either moderate or deep sedation. Chloral hydrate is a widely used oral sedative hypnotic drug that has been used for several decades in pediatrics, which may be due in part to its ease of administration, apparent safety, and efficacy.<sup>[18,9]</sup> The gastrointestinal tract rapidly absorbs chloral hydrate after oral or rectal administration. The time from oral administration of chloral hydrate to onset of sedation averages 15 to 60 min.<sup>[12,13]</sup> Chloral hydrate is a relatively mild sedative that, when administered orally in doses of 50 to 75 mg/kg, induces sleep without untoward respiratory or hemodynamic complications in most infants.<sup>[14]</sup>

The number of studies investigating pediatric conscious sedative agents in the PICU has also increased recently. Reeves et al used propofol for conscious sedation of 16 children who were undergoing intrathecal chemotherapy and bone marrow aspirations. They found an increased risk of adverse events when children undergo deep sedation.<sup>[15]</sup> Finnemore et al reported a series of 411 infants who were sedated with chloral hydrate for magnetic resonance imaging. In their study, 17 (3.1%) cases had self-limiting desaturations or responded to additional inspired oxygen. They determined that using chloral hydrate sedation in infants had a relatively low risk.<sup>[16]</sup> Nicolson et al compared the use of oral chloral hydrate (n=297) with face-mask administration of sevoflurane anesthesia (n=210) for transthoracic echocardiography. They offered mask anesthesia as an alternative strategy.<sup>[17]</sup> Wheeler et al compared the use of chloral hydrate vs oral midazolam sedation in children undergoing echocardiography. They concluded that the children in the chloral hydrate group had a significantly deeper level of sedation and were more likely to receive a nearly comprehensive echocardiographic evaluation.<sup>[2]</sup> Coskun et al used chloral hydrate for sedation of 360 children and reported 342 (95%) of the patients achieved successful sedation and confirmed that chloral hydrate was a safe and successful drug for use in children.<sup>[18]</sup>

In our center, we also had experience about midazolam and dexmedetomidine for conscious sedation of infants. Some papers reported that dexmedetomidine administration in children following cardiac surgery appeared to be safe and was associated with decreased inotropic support<sup>[19–21]</sup>. Other authors claimed

that the safety of clonidine given early after cardiac surgery as alternative to midazolam merits.<sup>[22]</sup> Compared with chloral hydrate, all the sedatives can yield safe and effective results, but the chloral hydrate group had no need intravenous injection. Furthermore, in our study, we compared chloral hydrate with dexmedetomidine for conscious sedation of infants and concluded that both sedatives can yield safe and effective results, but the chloral hydrate group had better economic benefits. Chloral hydrate may be preferable in third-world settings because of its cost advantage.

Like previous investigators, we found chloral hydrate to be a useful adjunct for managing sedation in infants in the PICU. At first, chloral hydrate was chosen primarily as a supplement for infants in whom midazolam failed to achieve adequate sedation or for infants who developed clinically significant tolerance to it or other sedatives. With increased experience, some clinicians began to select it as the initial sedative. Our study was also in accordance with the results of previous studies that confirmed that sedation with chloral hydrate provided an optimal environment in which to perform medical care in infants. The overall sedation success rate in all infants was 95.8% in our study. The patients remained calm and cooperated with medical treatment during the sedation procedure. Our results also showed no difference of sedative effects in the subgroups, which further confirmed the effectiveness and safety of chloral hydrate in infants with congenital heart disease.

Many reports have described various adverse effects associated with pediatric sedation with chloral hydrate. The most commonly reported side effects are nausea and vomiting.<sup>[16,23–25]</sup> The palatability of oral medications is relatively important in the care of infants. Because of the bitter taste of chloral hydrate, infants frequently resist taking this bad-tasting liquid and may vomit the drug or cough and potentially aspirate it. For these reasons, our nurses often mixed chloral hydrate with breast milk or sweet liquid before feeding the infant and then carefully checked the patient's response. Some patients still vomited a little drug, which may make accurate dosing impossible and may lead to potential underdosing. Such events also added to the stress experienced by the nursing staff. In this circumstance, administration of a small and appropriate amount of added dose was necessary to ensure the therapeutic effect. Some patients cannot tolerate oral drug administration, so an alternative is rectal dosing, which also helps ensure the proper dose and drug absorption. Our nurses also used music therapy as a complementary medical treatment for infants' sedation. The use of music seemed to provide comfort for the infants, and this method could be a safe, cost-effective means of relaxation, and a risk-free complement to sedation.<sup>[26]</sup>

According to published reports, other adverse effects associated with the use of chloral hydrate included respiratory depression, cardiac arrhythmias, motor imbalance, agitation, and local skin and mucosal lesions.<sup>[27–30]</sup> But such adverse events occurred infrequently in our study. The few adverse events that did occur were managed expeditiously and did not result in a poor outcome for any patient, although temporary slight hypotension and bradycardia were noted in some patients who required higher doses of chloral hydrate. These patients remained well perfused throughout the procedure, and their blood pressure and heart rate recovered to baseline in about 30 min after the sedation procedure. Therefore, we emphasize the importance of caring for those patients with severe congenital heart disease in a specific setting with continuous cardiorespiratory monitoring and appropriate attending supervision.

Adequate ancillary support should be prepared when sedation is applied to patients with severe cyanotic congenital heart disease, chronic cardiac insufficiency, severe pulmonary hypertension, and severe pulmonary infection. Napoli et al reported a study that included 64 cyanotic heart disease of 405 children. They concluded that there were no significant differences in sedation results between the cyanotic and acyanotic groups.<sup>[31]</sup> In our opinion, for this group of patients, the procedure should be performed using a sedative agent that can best support the hemodynamic stability. In this study, we observed no respiratory compromise in any of the patients. Two of our infants with cyanotic congenital heart disease and severe pulmonary infection experienced an episode of oxygen desaturation that resolved completely upon being awakened, suctioning of the secretions in the upper airway, positioning of the head, and the transitory administration of 100% blow-by oxygen. During the process, cardiologists and nurses should be in charge of the sedation and monitoring. A functioning intravenous catheter should be in place and monitoring indexes such as heart rate, saturation of oxygen, periodic noninvasive measurement of blood pressures, etc., should be needed for those patients. Proper equipment should be installed to deal with emergency such as urgent management of airway and cardiac resuscitation. From our data, we found that the presence of cyanotic congenital heart disease had had no influence on the safety and efficacy of chloral hydrate.

Like any retrospective study, ours included a bias associated with data collection and incomplete data for some patients. Although the small number of children in the study precluded reaching statistical significance for all study end-points, important differences were demonstrated. Much larger numbers of patients must be evaluated to establish the uses of chloral hydrate for conscious sedation in infants. This study was limited to one institution, and other institutions may find different results.

In conclusion, our experience suggested that orally administered chloral hydrate, because of its ease of administration, high success rate, and transient and low prevalence of adverse reactions, was a safe and efficacious agent in the conscious sedation of infants with congenital heart disease.

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