RESEARCH ARTICLE

Use of Chloral Hydrate as a Sedative Agent before General Anesthesia in Pediatric Population Undergoing Eye Examination

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Background: Chloral hydrate (CH) is a sedative agent that is widely used in infants and children for several decades. The purpose of this study was to evaluate the safety and efficacy of CH before general anesthesia in pediatric population undergoing eye examination.

Methods: 165 pediatric patients with retinal tumor were examined from December 2014 to May 2015. 158 (95.7%) children were sedated by CH before general anesthesia. CH was used at a dose of 25 mg/kg with an augmentation dose, if necessary, in 20-30 minutes. We recorded the safety of CH, the success or fail of sedation, augmentation CH dose, time to sedation and complications of CH administration.

Results: In our study 158 (95.7%) children were sedated by CH and sixty four (40.5%) of these patients were under one year of age and ninety four (59.5%) were older. Successful sedation was achieved in 150/158 (94.9%) of the children. The success rate of sedation was higher in children below 1 year of age (63/64; 98.4%) compared to subjects older than 1 year (88/94; 93.6%) (P=0.01). The mean of time to sedation was 20.8±12.4 and 22.4±14.8 minutes in children below 1 year of age and older than 1 year respectively (p=0.91). Complications were observed in 4/158 (2.5%) of the children. We observed no episodes of desaturation after administration of CH in all subjects.

Conclusion: CH is a safe and effective sedative agent for children before general anesthesia provided it is used in a hospital setting with appropriately trained staff.

Keywords: chloral hydrate; pediatrics; sedation; general anesthesia

Eye examination in children for evaluation and course of treatment of retinoblastoma often requires general anesthesia. Because these patients undergo general anesthesia several times, sedation protocol can prevent psychological effects in this population. Chloral hydrate (CH) is a widely used oral sedative agent which has been administered in pediatrics for several decades [1-2]. We used CH as a sedative agent in children before general anesthesia in our department because its efficacy and low risk when used according to guideline for sedation in pediatrics population issued by the American Association of Pediatrics (AAP) [3]. CH is one of the oldest sedative agents that were synthesized in 1832 [4]. CH is used orally or rectally and rapidly absorbed from gastrointestinal tract and then metabolized to trichloroethanol, which is the active metabolite [5]. The mechanism of the sedation activity of CH is still unknown. It is justified that the hypnotic action of CH is mediated by trichloroethanol through its effect on the central nervous system by activation of gamma aminobutyric acid-A receptors (GABA). Moreover, it is shown that in cases of overdose with CH, use of flumazenil has been proven successful [6]. It is shown that the half-life of CH is a few minutes, but the half-life of the main metabolite of CH, trichloroethanol is longer (8-12 hours) [7]. Previous literatures recommend 20-100 mg/kg of CH in order to produce a sedative action, although for infants dose adjustment is required [4]. Side effects of CH such as nausea, vomiting, apnea, rash, respiratory distress, arrhythmia and hyperactivity have been reported [8]. Moreover, some experimental animal studies have reported that use of CH could have carcinogenic effects [9-10]. It is recommended that CH not is used in patients with a history of respiratory and hepatic disease, porphyria and gastric ulcer [9]. The aim of this study was to evaluate the safety and efficacy of CH as a sedative agent before general anesthesia in pediatric population undergoing eye examination for evaluation and treatment of retinal tumor.

Methods

165 pediatric patients with retinal tumor were examined at our department from December 2014 to May 2015. 158 (95.7%) children were sedated by CH before general anesthesia, whereas 7 (4.3%) children were relaxed to avoid

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sedation. Our subjects must have no contraindication for oral sedation with CH (Table 1). Approval from the hospital ethical committee and written consent from parents of patients were obtained. Based on our department protocol, instructions were given to all parents to bring their children to our department awake. Our protocol for fasting included: last solid feed 6 hours, last breastfeed 3 hours, last other than breast feed 4 hours and last clear fluids 2 hours prior to the appointment time. In addition, the parents are asked to bring milk for infants and juice, yogurt, cream or milk for older children in order to mix it with CH. Initial assessment on arrival of pediatrics to our department were clinical evaluation such as consciousness, heart rate, respiratory rate, blood pressure, fever and signs of common cold or other infectious disorder. Also, suitability for oral sedation and assessment regarding contraindications were evaluated. We used CH for children at a concentration of 5%, thirty minutes before general anesthesia. In our center CH is given at an initial dose of 25 mg/kg, if necessary repeat equal dose, to obtain adequate sedation after 20-30 minutes. Based on our protocol we used the minimum dose of CH for sedation in our center, because all subjects are outpatients and after sedation all of them undergo general anesthesia for eye examination. Moreover, we expect that with minimum dosage of CH we observe minimum side effects in our pediatrics population. CH was given to parents to mix it with milk or juice and then given to their children. After CH ingestion, our subjects remained in a quiet room adjacent to operating room with their parents until they were asleep. During stay in this room till transfer to operating room for general anesthesia, the pediatrics were under the care of the nurse of anesthesia who observed them for any events occurring due to ingestion of CH, such as deep sedation, respiratory distress, nausea, vomiting, apnea, arrhythmia and hyperactivity. After 30 minutes, the children were transferred to the operation room for eye examination under general anesthesia. We collected the following data for all our subjects: age, augmentation CH dose, time at which the augmentation dose was administered, success or fail of sedation, time to sedation (time from ingestion of the initial dose of CH to onset of sedation) and complications of CH administration. Moreover, the level of sedation, parents' satisfaction, postoperative nausea and vomiting, postoperative agitation and separation from parents at the time of transmission to operating room were evaluated by a nurse of anesthesia. Data were analyzed for the study group as a whole and in addition, for two subgroups; children below 1 year of age and children with older age. The children were brought to the operation room by parents and placed on the surgical bed and then leaving the operating room. Subsequently, the children were anesthetized with inhalation of sevoflurane 8% with spontaneous breathing till sleep, and then changed to isoflurane 2-2.5% for five minutes. Then, vascular line established and 1µg/kg fentanyl and 0.02 mg/kg midazolam were administered. Next, a laryngeal mask airway (LMA) with appropriate size was inserted. All children underwent monitoring of heart rate, blood pressure and pulse oximetry during eye examination.

During eye examination a pediatric ophthalmologist evaluated the tumor progression or response to treatment. The average time for the eye examination was about 20- 30 minutes. After the examination, the children woke up and were transferred to recovery room. During stay in the recovery room, regular clinical examination included heart rate, respiratory rate and oxygen saturation were monitored every 15 minutes till the child is awake. Our subjects were discharged once they tolerated a feed and reached their baseline characteristics. Subsequently, children were given to the parents and then they were sent home. One of the nurses of anesthesia contacted with parents by telephone the day following sedation and asked them if the child remained well and had any complications of CH ingestion at home. Statistical analysis was performed using the SPSS 13 statistical software. Continuous variables were analyzed using the t-test. Categorical data were analyzed with a chi-square test or Fisher exact test as appropriate. P-value < 0.05 was considered significant.

Table 1- Absolute and relative contraindications of chloral hydrate for oral sedation

Absolute Contraindications
Cyanotic cardiac conditions
Significant airway abnormality
Previous adverse reaction to choral hydrate
Respiratory tract infection
Nasal obstruction
Stridor, tracheolaryngomalacia
Apnoea of prematurity, sleep apnoea
Micrognathia
Relative contraindications
Macroglossia
Adenoidal hypertrophy
Short and/or wide neck
Sickle cell disease
Opioid or other sedative medication
Facial haemangioma in the "beard" distribution of face/neck

Results

In our study 158 (95.7%) children were sedated by CH and sixty four (40.5%) of these patients were under one year of age and ninety four (59.5%) were older. Mean age was 1 year 4 months (range; 1 month to 10 years 8 months). Mean weight was 8.4±4.8 kg (2.4-20 kg). Successful sedation was achieved in 150/158 (94.9%) of our children. The success rate of sedation was higher in children below 1 year of age (63/64; 98.4%) compared to subjects older than 1 year (88/94; 93.6%) (P=0.01). Moreover, requirement of an augmentation dose of CH after the initial dose was lower in children below 1 year of age (2/64; 3.1%) compared to subjects older than 1 year (8/94; 8.5%) (P=0.001). The mean time interval between administration of initial and augmentation doses of CH was 20.8 minutes (15-60 minutes). One child failed to be sedated following augmentation dose of CH in children older than 1 year. The mean of time to sedation was 20.8±12.4 and 22.4±14.8 minutes in children below 1 year of age and older 1 years respectively (p=0.91). Parent's satisfaction in all children who ingested CH was 98.7%. The level of sedation after use of CH with dose of 25 mg/kg was moderate sedation in 148 cases (93.6%) and deep sedation in 10 cases (6.4%). 136/158

cases (86%) of our children were separated easily from parents at the time of transmission to the operating room. We observed no episodes of desaturation after administration of CH in all subjects. Complications were observed in 12/158 (7.5%) of our children (Table 2). We had no nausea and vomiting in our children after ingestion of CH and also, in postoperative period. Moreover, postoperative nausea and vomiting was decreased in 8 children (5%) compared to previous general anesthesia where CH was not used as a sedation agent. Emergent delirium after general anesthesia was rare (14/158, 8.8%) and most of our children were calm in the recovery room. Children with one of the complications remained under observation under a nurse of anesthesia for about 2 hours and then returned home without any further undesirable side effects being observed. We found no complications during 24 hours after general anesthesia and all of our children were well.

Table 2- Side effects of CH sedation

Side Effect	Number of children	Percentage
Deep sedation	8	5%
Hyperactivity	3	1.8%
Rash	1	0.6%

Discussion

We performed this study to evaluate the safety and efficacy of CH as a sedation agent before general anesthesia in children with retinal tumor, because literature is lacking in scale studies. We believed that sedation with a 5% concentration of CH at a dose of 25 mg/kg, and if needed, administration of an augmentation dose of CH is an effective method with a relative very low rate of unwanted side effects. Our overall rate of sedation success (94.9%) is consistent with those of previously published studies, where sedation success has ranged from 85% to 98.7% [2-10]. Moreover, in consistent with previous studies we observed a negative correlation between increasing of age and sedation success with CH [11-12]. CH is the most widely used sedative agent in children for many years, with the result that safe dosing regimens for CH are well documented [13]. It is shown that sedation included four levels as follow: minimal sedation, moderate sedation (conscious sedation), deep sedation and anesthesia [14]. In moderate sedation level, patients' being sleepy but purposeful response to verbal commands and patients airway remains patent and no intervention is needed. In deep sedation level, the patient is asleep, but with purposeful response to painful stimulation and may require assisted ventilation. In order to have a safe level of sedation we preferred to establish a moderate level of sedation that maintains a patent airway. We observed that administration of CH with a dose of 25 mg/kg could induce the moderate level of sedation in 93.6% of children. It was shown that CH sedation was successful in 100% for all children who underwent CT scan [15], whereas, another study found that with dose 56.9 mg/kg, 79% children were sedated effectively and after an augmentation dose of 18.5 mg/kg, the success rate rose to 95% [16]. We found no nausea and vomiting after ingestion of CH and also, in postoperative period. Moreover, postoperative nausea and vomiting was decreased in 8 children (5%) compared to previous general anesthesia that did not use CH as a sedation agent. We think that the use of CH may decrease the need for maintenance of anesthesia drugs and this item led to less postoperative nausea and vomiting. We found that emergent delirium after general anesthesia was rare and most of our children were clam in postoperative period. We think that the sedation effect of CH remains through hours after administration of it because of long half life of the metabolite of CH. It was believed that administration of repetitive dose of CH could maintain prolonged sedation in patients who underwent mechanical ventilation, but may arise a concern because of accumulation of active metabolites [17]. Overdose of CH may be dangerous, because of events such as central nervous system depression, cardiac arrhythmia, liver dysfunction and gastric irritation [18-19]. Previous experimental animal studies have shown that use of CH may induce potential carcinogenicity. This idea was based on the assumption that CH is a reactive metabolite of trichloroethylene, which is a carcinogenic agent in animal studies [20-21]. Laboratory animal studies have shown that the use of CH for mice induced liver adenomas and this effect was related to trichloracetic acid, one of the metabolite of CH. Also, it was reported that high doses of CH cause aneuploidy, a term denoting the number of chromosomes in cellular [22]. However, multiple human studies have failed to show an increase in cancer induced by administration of CH [22-25]. Consistent with these previous results of our results showed that CH was a safe drug and because we used CH with low dose in our children, we observed complications in 2.5% of patients and most of them without demanding medical treatment. In our study after administration of CH, vital signs and oxygen saturation were monitored and we had no episode of desaturation in all of our subjects. In conclusion, CH is a safe and effective sedative agent for children before general anesthesia provided it is used in a hospital setting with appropriately trainedstaff.

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