การศึกษาความคงสภาพและการประเมินผลทางคลินิกของสารละลายคลอรัลไฮเดรตรูปแบบสวนทวารหนักสำหรับเด็กที่ตรวจการได้ยินระดับก้านสมอง: การศึกษานำร่อง
Stability and Clinical Assessment of Chloral Hydrate Rectal Solution for Pediatric Undergoing Auditory Brainstem Response Testing: A Pilot Study

นิพนธ์ต้นฉบับ

Original Article

จุฑาภรณ์ ศิริเพิ่มพูล[1]* และ วัชรพงษ์ แจ่มสว่าง[2]

[1] กลุ่มงานเภสัชกรรม โรงพยาบาลมหาวิทยาลัยบูรพา คณะแพทยศาสตร์ มหาวิทยาลัยบูรพา อ.เมือง จ.ชลบุรี 20131
[2] คณะเภสัชศาสตร์ มหาวิทยาลัยบูรพา อ.เมือง จ.ชลบุรี 20131

* Corresponding author: chutaporn.si@go.buu.ac.th

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Chutaporn Siripermpool[1]* and Watcharaphong Chaemsawang[2]

[1] Department of Pharmacy, Burapha University Hospital, Faculty of Medicine, Burapha University, Mueang, Chonburi, Thailand 20131
[2] Faculty of Pharmaceutical Science, Burapha University, Mueang, Chonburi, Thailand 20131

* Corresponding author: chutaporn.si@go.buu.ac.th

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บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความคงสภาพของสารละลายคลอรัลไฮเดรตรูปแบบสวนทวารหนักความเข้มข้นร้อยละ 10 โดยน้ำหนักต่อปริมาตร ภายใต้สภาวะการเก็บรักษาที่แตกต่างกันและประเมินประสิทธิผลในการสงบประสาทเด็กที่ตรวจการได้ยินในระดับก้านสมอง **วิธีการศึกษา:** ศึกษาความคงสภาพทางกายภาพ เคมี และจุลชีววิทยา ของยาเตรียมเฉพาะคราวคลอรัลไฮเดรตรูปแบบสวนทวารหนักความเข้มข้นร้อยละ 10 โดยน้ำหนักต่อปริมาตร ที่เก็บในภาชนะบรรจุขวดแก้วกันแสงภายใต้สภาวะการเก็บรักษาต่าง ๆ (ในตู้เย็นอุณหภูมิ 5 ± 2 องศาเซลเซียส และอุณหภูมิห้อง 25 ± 2 องศาเซลเซียส) โดยประเมินความคงสภาพของตัวอย่างในวันที่ 0, 15, 30, 45, 60 และ 90 ของการศึกษา รวมทั้งประเมินอัตราความสำเร็จในการสงบประสาทเด็ก 10 คนที่ตรวจการได้ยินในระดับก้านสมอง **ผลการศึกษา:** สารละลายคลอรัลไฮเดรตรูปแบบสวนทวารหนักที่เก็บที่ 5 ± 2 องศาเซลเซียส มีตัวยาสำคัญอยู่ในช่วงค่ามาตรฐาน คือร้อยละ 95 ถึง 110 นาน 90 วัน แต่ที่เก็บที่อุณหภูมิห้องมีระดับตัวยาสำคัญอยู่ในช่วงค่ามาตรฐานนาน 15 วัน ไม่พบเชื้อจุลชีพในสารละลายคลอรัลไฮเดรตที่เก็บภายใต้สภาวะที่แตกต่างกัน อัตราความสำเร็จในการสงบประสาทเด็กที่ตรวจการได้ยินระดับก้านสมองเท่ากับร้อยละ 100 **สรุป:** สารละลายคลอรัลไฮเดรตรูปแบบสวนทวารหนักความเข้มข้นร้อยละ 10 โดยน้ำหนักต่อปริมาตรมีความคงสภาพ 90 วัน ในภาชนะขวดแก้วปิดสนิทกันแสง ภายใต้สภาวะการเก็บรักษาในตู้เย็นที่อุณหูมิ 5 ± 2 องศาเซลเซียส และมีอัตราความสำเร็จในการสงบประสาทเด็กที่ตรวจการได้ยินระดับก้านสมองเท่ากับร้อยละ 100 โดยไม่พบอาการไม่พึงประสงค์

คำสำคัญ: การตรวจการได้ยินระดับก้านสมอง; คลอรัลไฮเดรต; โรคเด็ก; การบริหารยาทางทวารหนัก; การสงบประสาท; การศึกษาความคงสภาพ

Abstract

Objective: To assess the stability of a 10% w/v chloral hydrate rectal solution under different storage conditions and evaluate its effectiveness in sedating children undergoing auditory brainstem response (ABR) testing. **Method:** The 10% w/v chloral hydrate rectal solution was prepared through extemporaneous compounding and stored in light-resistant glass containers under various conditions: refrigerated (5 ± 2 °C) and room temperature (25 ± 2 °C). The stability of the samples was assessed on days 0, 15, 30, 45, 60, and 90 for physicochemical and microbiological properties. Sedation success rates in 10 children undergoing ABR testing was also examined. **Results:** The refrigerated (5 ± 2 °C) chloral hydrate rectal solution remained stable within the 95.0% to 110.0% standard range for 90 days. In contrast, samples stored at room temperature remained stable for 15 days. Microbiological tests yielded negative results under all conditions indicating the influence of storage conditions on chloral hydrate content. Clinical studies demonstrated a 100% success rate in children undergoing ABR testing. **Conclusion:** The 10% w/v chloral hydrate rectal solution remained stable for at least 90 days when refrigerated (5 ± 2 °C) in a tightly sealed, light-resistant glass container. Rectal administration of the chloral hydrate rectal solution to children undergoing ABR testing resulted in a 100% success rate without any side effects.

Keywords: auditory brainstem response testing; chloral hydrate; pediatric; rectal administration; sedation; stability test

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Introduction

Chloral hydrate ($C_2H_3Cl_3O_2$) exhibits a colorless crystalline solid with a pungent odor. It has a melting point of 57 – 58 °C and a boiling point of 97 – 98 °C. This compound dissolves well in water and ethanol, with a density of 1.48 g/cm³. In solution, it may exhibit a slightly acidic pH, which can affect its chemical behavior.[1]

Chloral hydrate is a sedative medicine used for a decade in non-painful sedation in children, requiring patient cooperation during procedures such as electroencephalography, dentistry, computed tomography (CT) scan, ophthalmic procedures, and auditory brainstem response (ABR) examination.[2-7] In Thailand, no commercial pharmaceutical product containing chloral hydrate is currently available on the market. Therefore, hospital pharmacists must prepare it extemporaneously to meet individual needs and achieve suitable medication that meets clinical treatment standards.[8]

Extemporaneous compounding formulations consist of active pharmaceutical ingredients and excipients. The active pharmaceutical ingredient is a major component that provides pharmacological activity in the treatment, prevention, diagnosis of disease, or affect any function of the body. Meanwhile, excipients serve as the vehicles and diluents for the pharmaceutical ingredient.[9,10]

Chloral hydrate has an extremely unpleasant taste and pungent odor, causing rejection of the drug during oral administration. The most common adverse effect of oral chloral hydrate administration is gastrointestinal tract irritation, leading to vomiting.[11-13] Despite the development of formulation using flavored syrup and sweetening agents to mask the taste, it remains ineffective and leads to children being uncooperative with administration. Considering this problem, chloral hydrate rectal solution is compounded to ease the administration in children.

The formulation of rectal solution includes an active pharmaceutical ingredient dissolved in a vehicle containing sterile water, preservatives (paraben concentration), and polyethylene glycol (PEG) 400. PEG 400 serves as both a solvent and drug carrier, facilitating the dissolution of active pharmaceutical ingredients and ensuring a homogeneous mixture. It enhances the solubility and bioavailability of poorly water-soluble drugs, beneficial for rectal solutions aiming for rapid absorption and efficacy. Additionally, PEG 400 plays a crucial role in formulating effective and patient-friendly rectal solutions. It modifies solution viscosity, enhances drug stability, and aids drug absorption through the rectal mucosa.[14]

There are many stability studies on chloral hydrate extemporaneous syrup preparation, with success rate in painless sedation ranging from 56.10% to 100%.[15-17] However, few stability studies exist on chloral hydrate solutions for rectal use.[18,19] This study aimed to evaluate the physicochemical and microbiological stability of 10% w/v chloral hydrate rectal solution under room temperature and refrigerated conditions and assess the sedation success rate in children during ABR examination.

Materials and Methods

Chemicals and reagents

Chloral hydrate (lot number: 20230302, Forbest Chemical Company Limited, Bangkok, Thailand) was used as the pharmaceutical active ingredient. PEG 400 (lot number: X22547, S. Tong Chemicals Company Limited, Nonthaburi, Thailand) was used as a co-solvent. Paraben concentrate containing methylparaben (lot number: IK2311) and propylparaben (lot number: IJ1011) in propylene glycol (lot number: CB15N5BR41, S. Tong Chemicals Company Limited, Nonthaburi, Thailand) was used as a preservative. Sterile water (lot number: 123330, A .N .B Laboratories, Bangkok, Thailand) was also used. Acetonitrile high-performance liquid chromatography (HPLC) grade (Honeywell, USA) was used as the mobile phase.

Preparation of 10% w/v chloral hydrate rectal solution

The extemporaneous preparation of 10% w/v chloral hydrate rectal solution was prepared by using the formulation modified from Breimer et al. (Table 1). Chloral hydrate was weighed using an automatic balance (Model TB-214, Denver Instrument, Germany) to 10 g and dissolved in 60 mL of sterile water at room temperature (25 ± 2 °C). A 1 mL of paraben concentration (containing 10 g of methylparaben and 2 g of propylparaben in propylene glycol per 100 mL) was added and stirred thoroughly. PEG 400 was gradually added until it reached a volume of 100 mL, ensuring constant stirring. A total volume of 720 mL of chloral hydrate rectal solution was prepared. Two batches of samples were labeled and divided into three separate containers, with each batch containing 60 mL. The samples were stored in light-resistant glass containers under room temperature (25 ± 2 °C) and refrigeration (5 ± 2 °C) for stability testing.

Table 1 Formula of 10% w/v chloral hydrate solution.

Ingredients	Quantity	Function
Chloral hydrate (g)	10.00	Pharmaceutical active ingredient
Sterile water (mL)	60.00	Solvent
Paraben concentrate (mL)	1.00	Preservative
Polyethylene glycol (PEG 400) q.s (mL)	100.00	Vehicle

Stability evaluation

1. Physical stability test

Two batches of 10% w/v chloral hydrate rectal solution were prepared based on the master formulation shown in Table 1. Each batch was divided into three 60 mL glass bottles resistant to light and stored under room temperature (25 ± 2 °C) and refrigerated conditions (5 ± 2 °C). Daily

temperature recordings were made using a digital thermometer under both conditions, with all samples labeled and stored for 90 days. To evaluate physical stability, 10 mL of samples were collected from each batch on days 0, 15, 30, 45, 60, and 90, adhering to the specified temperature conditions. Physical stability at each time point was characterized by assessing organoleptic properties to determine the absence of visible particulate matter, color changes, or odor alterations. The pH of each sample was measured in triplicate using a pH meter (Thermo Fisher) at 25 °C in a water bath.

2. Chemical stability test

The chloral hydrate content was determined using the HPLC method with the HPLC equipment (Shimadzu, LC20AD). Chloral hydrate was detected at a wavelength of 220 nm. The mobile phase consisted of a mixture of 0.02 M monopotassium phosphate pH 8.0 and acetonitrile at a ratio of 80:20. The injection volume was 100 µL with a C18 column 150 x 4.6 mm, with 5 µm packing and flow rate at 1 mL/min. For the HPLC analysis of the chloral hydrate rectal solution, 10 µL of the chloral hydrate rectal solution (100 mg/mL) was withdrawn from a 60 mL light resistance glass bottle. The sample was diluted with mobile phase to a final volume of 10 mL. The time at chloral hydrate content did not remain in 95% to 110% of the standard range, which indicated significant instability.

3. Microbiological stability test

Microbiological tests were conducted at the bacteriology laboratory of Burapha University Hospital. The analysis of the study was conducted on days 0, 15, 30, 45, 60, and 90. On day 0, all samples of 60 mL chloral hydrate rectal solution were prepared from two batches. In each batch, three bottles were stored at room temperature (25 ± 2 °C), and three others were kept under refrigerated conditions (5 ± 2 °C). A bottle of chloral hydrate-free rectal solution was kept under each temperature condition for negative control.

A 10-fold dilution of the chloral hydrate rectal solution in phosphate buffer solution at pH 7.2 was prepared on each day of analysis. Microorganisms were counted using the surface spread plate method. A volume of 0.1 mL of each solution was spread over soybean-casein digest agar Petri dishes and incubated at 30–35 °C for 3 days. Additionally, three Sabouraud dextrose agar plates were incubated at 20–25 °C for 5 days. According to the United States Pharmacopeia 44 NF 39 (USP 44-NF 39), microbiological examination of the samples for non-sterile pharmaceutical products included acceptance criteria focusing on total aerobic microbial count and total yeast/mold count, determined through an average of three replicate counts. Specifications include a total aerobic microbial count below 10^2 CFU/mL, a total combined yeast/mold count below 10^1 CFU /mL, and the absence of *Staphylococcus aureus*, Pseudomonas aeruginosa, and *Candida albicans*.

Clinical study protocol

The study was conducted based on the Helsinki Declaration and approved by the Institutional Review Board of Burapha University (approval number HS107/2565). A pilot study was performed between May and June 2023 at the Ear, Nose, and Throat (ENT) Outpatient Department of Burapha University Hospital, Chonburi, Thailand. Children aged 1 – 5 years old who were referred for ABR examination were included and received 10% w/v chloral hydrate rectal solution at a dose of 50 mg/kg body weight before ABR examination. Children with cardiovascular disease, liver or kidney disease, and those allergic to chloral hydrate were excluded.

Before the procedure, each child was evaluated by an ENT specialist who inquired about the medical history. Research nurses recorded the baseline characteristics of the children, such as sex, age, weight, height, and history of drug allergies, in a case record form. After explaining the protocol, parents signed the informed consent form to provide approval. The 10% w/v chloral hydrate solution was administered rectally at a dose of 50 mg/kg and could be supplemented if the children expelled the drug or did not fall asleep within 30 minutes after the first administration. However, the supplement dose should not exceed the maximum dose of 120 mg/kg or a total dose of 2 g. After administering the chloral hydrate rectal solution, sedation time was defined as the time from when the patient received the drug until sedation initiation. The duration of sedation was represented as the time from patient sedation until their awakening. Recovery time was recorded as the time from drug administration to full recovery. Successful sedation was defined as the patient completing the ABR testing record.

Statistical analysis

Continuous variables are presented as means with standard deviations (mean ± SD). Chloral hydrate content within the acceptable range of 95% to 110% was considered stable. A paired t-test assessed pH differences within the group between day 0 and day 90 of the study. Statistical significance was considered at P-value < 0.01. The sedation success rate and adverse effects were summarized as frequency with percentages. Statistical analysis was performed using Minitab® statistical software version 21 (Minitab Inc., State College, PA, USA).

Results and Discussions

Assay validation

The chromatogram of chloral hydrate is depicted in Figure 1. Chromatograms of chloral hydrate standard and chloral hydrate rectal solution were similar, with retention times of 4.996 and 4.990 minutes, respectively.

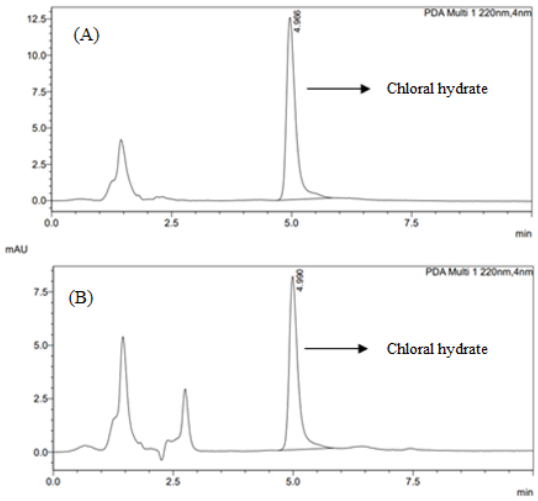

Figure 1 Chromatograms of (A) chloral hydrate standard and (B) chloral hydrate rectal solution.

Physicochemical stability studies

The physicochemical properties of the two batches of 10% w/v chloral hydrate rectal solution are presented in Table 2. After the organoleptic examination on each sampling day and throughout the study, the rectal solution samples stored at 5 ± 2 °C showed no particles, color changes, or odor changes. However, regardless of the room temperature condition, samples stored at 25 ± 2 °C exhibited an acidic odor. The pH of samples stored at 5 ± 2 °C changed slightly, remaining within the range of 4 .90 and 5 .79, while the pH of samples stored at 25 ± 2 °C decreased significantly from 5 .82 (day 0) to 3 .21 (day 90) (Figure 2). The acidic pH was caused by an oxidation-reduction process leading to hydrochloric (HCl) formation in aqueous solution.[20] This result indicated that the storage temperature condition affects the pH of the rectal solution. The previous study reported that 5% w/v chloral hydrate rectal solution stored in a glass container at room temperature (25 °C) demonstrated a significant decrease in pH by day 30 of the study.[19] Moreover, McQuillan et al. reported that formic acid and chloroform were degradation products resulting from the hydrolysis mechanism of chloral hydrate. The degradation reaction was initiated at pH 5, and significant decomposition occurred at pH 7 and above.[21] This is consistent with our study, in which the pH gradually decreased slightly in refrigeration storage conditions and significantly decreased in room temperature conditions.

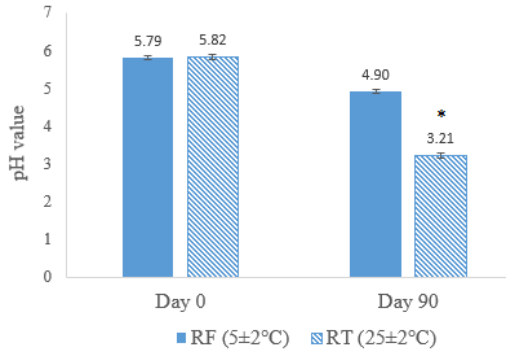

Figure 2 pH value under refrigeration (RF) and room temperature (RT) condition in day 0 and day 90; asterisks (*) indicate significant difference (P-value < 0.01) between day 0 and day 90.

Figure 3 displays the chloral hydrate content at each sampling day. The results indicated that the chloral hydrate content of samples stored at 25 ± 2 °C tended to increase, exceeding 110% from day 30 of the examination. Meanwhile, the samples stored at 5 ± 2 °C exhibited an increasing trend but remained within 110% throughout the 90 days of the study. The amount of chloral hydrate content increased due to water evaporation in samples kept at room temperature (25 ± 2 °C) after 30 days of storage, while the drug content remained unchanged in samples stored under refrigerated conditions (5 ± 2 °C) throughout the study. This indicates that temperature is an important factor affecting pH and drug content, with higher temperatures making it easier

for the water to evaporate. Moreover, 10% w/v chloral hydrate rectal solution was prepared in multiple doses; the frequent opening during the examination or administration could increase water evaporation, leading to the amount of chloral hydrate exceeding 110%, aligning with the previous report by Fierro et al.[22] Manojlovikj et al reported the stability study of 10% w/v rectal emulsion of chloral hydrate, where the average drug content remained within the acceptable range when stored in light resistance plastic bottle under room temperature (25 °C) for at least 90 days.[18] Naohiro et al reported the amount of chloral hydrate remained within the acceptable range for at least 90 days when stored in glass or polypropylene plastic bottles protected from light at refrigerated conditions.[19] The previous study indicated that neither type of container affected drug content.

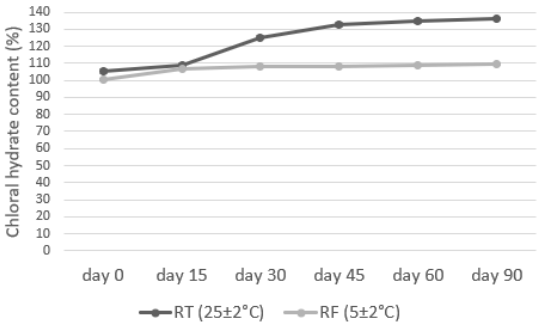

Figure 3 Chloral hydrate contents under refrigeration (RF) and room temperature (RT) condition.

The stability test using HPLC methods demonstrated a high drug content at room temperature conditions, which was inconsistent with the pH results. Chloral hydrate and its degradation product have similar structures and lack chromophore (Figure 4). Therefore, HPLC methods cannot detect chloral hydrate through its degradation product. The degradation product, possessing high water solubility, may have the same retention time as the drug, resulting in a higher Area Under Curve. Although analytical methods have been developed, chloral hydrate cannot be separated from its degradation product due to the similar molecular size and structure.

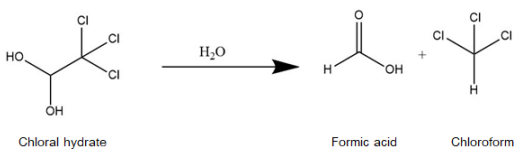

Figure 4 Hydrolysis mechanism of chloral hydrate in aqueous solution.

Microbiological stability test

The results of the microbiological tests are presented in Table 4. All samples and negative control from two batches stored at 5 ± 2 and 25 ± 2 °C tested negative for the total aerobic microbial count, total yeast or mold count, *S. aureus*, P. aeruginosa, and *C. albicans* throughout the examination. This indicates that there is no contamination in the culture medium and the conditions may not be suitable for bacterial growth. The paraben concentrate used as a preservative effectively inhibited the growth of aerobic bacteria, yeast, and mold. Moreover, PEG 400 can enhance the preservative action of parabens by providing additional antimicrobial activity, thus improving the microbial stability of the rectal solution. Several studies have demonstrated that high concentrations of PEG 400 can inhibit the growth of microorganisms such as bacteria and fungi, ensuring sterility and safety during storage and use.[14, 23-25] Our study found that 40% v/v concentration of PEG 400 in rectal solutions effectively inhibits microbial growth, ensuring solution stability. All these data support that 10% w/v chloral hydrate rectal solution is stable in a light-resistant glass container stored under refrigerated conditions (5 ± 2 °C) for at least 90 days.

Clinical study

After the stability test was conducted, a clinical test was done in 10 children referred for ABR examination and meting the eligibility (Table 5). The participants consisted of four female and six male children with an average age of 1.75 ± 0.81 years and an average body weight of 14.70 ± 2.71 kg. The mean dose of chloral hydrate was 1.27 ± 0 .47 g. The onset of sedation ranged from 26 to 120 minutes (mean 85.00 ± 32.20 minutes), the duration of sedation ranged from 28 to 55 minutes (mean 38 .80 ± 12 .43 minutes), and the recovery time ranged from 76 to 160 minutes (mean 129.20 ± 30.34 minutes). Sedation was effective at the first dose in three children (30%), with the sedation success rate of chloral hydrate rectal solution being 100% without side effects.

Chloral hydrate administered rectally takes effect within 30 to 60 minutes, with the variation depending on age, weight, and health status. Nie et al found that rectal administration of chloral hydrate in children with a mean age of 16.05 months had a mean onset time of 16.41 minutes. Moreover, their study demonstrated that the onset of

Table 2 Physicochemical properties of 10% w/v chloral hydrate rectal solution (N = 3).

Batch number	Storage Temp (°C)	Parameters*	Sampling day					
			0	15	30	45	60	90
1	5 ± 2	Chloral hydrate content (%), mean ± SD	100.48 ± 0.27	106.98 ± 0.19	108.43 ± 0.81	108.27 ± 1.07	108.98 ± 0.83	109.94 ± 0.05
		Appearance	Clear	Clear	Clear	Clear	Clear	Clear
		pH	5.82 ± 0.03	5.76 ± 0.06	5.71 ± 0.04	5.62 ± 0.04	5.16 ± 0.12	4.91 ± 0.06
		Odor	A bit pungent	No change	No change	No change	No change	No change
	25 ± 2	Chloral hydrate content (%), mean ± SD	100.96 ± 1.57	109.75 ± 0.26	124.66 ± 1.03	133.52 ± 0.21	135.52 ± 0.98	136.26 ± 0.70
		Appearance	Clear	Clear	Clear	Clear	Clear	Clear
		pH	5.81 ± 0.02	5.71 ± 0.03	4.82 ± 0.03	4.39 ± 0.09	3.98 ± 0.08	3.22 ± 0.06
		Odor	A bit pungent	No change	No change	No change	No change	Acidic
2	5 ± 2	Chloral hydrate content (%), mean ± SD	100.48±0.27	106.98 ± 0.19	108.43 ± 0.81	108.23 ± 1.07	108.98 ± 0.83	109.60 ± 0.63
		Appearance	Clear	Clear	Clear	Clear	Clear	Clear
		pH	5.75 ± 0.06	5.79 ± 0.03	5.68 ± 0.09	5.56 ± 0.04	5.17 ± 0.05	4.88 ± 0.05
		Odor	A bit pungent	No change	No change	No change	No change	No change
	25 ± 2	Chloral hydrate content (%), mean ± SD	99.95 ± 0.92	108.08 ± 1.62	125.66 ± 0.88	131.84 ± 1.38	133.85 ± 1.71	135.92 ± 0.82
		Appearance	Clear	Clear	Clear	Clear	Clear	Clear
		pH	5.82 ± 0.09	5.74 ± 0.03	4.84 ± 0.04	4.38 ± 0.06	4.12 ± 0.03	3.19 ± 0.04
		Odor	A bit pungent	No change	No change	No change	No change	Acidic

Table 3 Chloral hydrate content for clinical batches (N = 3).

	Batch number		
	1	2	3
Chloral hydrate content (%), mean ± SD	106.98 ± 0.19	108.43 ± 0.81	108.98 ± 0.83

Table 4 Microbiological test results (N = 3). ใส่ N = 3 ได้ไหม

Batch number	Storage Temp (°C)	Microbial test	Sampling day					
			0	15	30	45	60	90
1	5 ± 2	Total aerobic microbial count	(-)	(-)	(-)	(-)	(-)	(-)
		S. aureus	(-)	(-)	(-)	(-)	(-)	(-)
		P. aeruginosa	(-)	(-)	(-)	(-)	(-)	(-)
		Total yeasts/molds count	(-)	(-)	(-)	(-)	(-)	(-)
		C. albicans	(-)	(-)	(-)	(-)	(-)	(-)
	25 ± 2	Total aerobic microbial count	(-)	(-)	(-)	(-)	(-)	(-)
		S. aureus	(-)	(-)	(-)	(-)	(-)	(-)
		P. aeruginosa	(-)	(-)	(-)	(-)	(-)	(-)
		Total yeasts/molds count	(-)	(-)	(-)	(-)	(-)	(-)
		C. albicans	(-)	(-)	(-)	(-)	(-)	(-)
2	5 ± 2	Total aerobic microbial count	(-)	(-)	(-)	(-)	(-)	(-)
		S. aureus	(-)	(-)	(-)	(-)	(-)	(-)
		P. aeruginosa	(-)	(-)	(-)	(-)	(-)	(-)
		Total yeasts/molds count	(-)	(-)	(-)	(-)	(-)	(-)
		C. albicans	(-)	(-)	(-)	(-)	(-)	(-)
	25 ± 2	Total aerobic microbial count	(-)	(-)	(-)	(-)	(-)	(-)
		S. aureus	(-)	(-)	(-)	(-)	(-)	(-)
		P. aeruginosa	(-)	(-)	(-)	(-)	(-)	(-)
		Total yeasts/molds count	(-)	(-)	(-)	(-)	(-)	(-)
		C. albicans	(-)	(-)	(-)	(-)	(-)	(-)

Note: (-) = no growth.

Table 5 Clinical study results of chloral hydrate rectal solution.

Patient No.	Sex	Age (years)	Weight (Kg)	Dose of chloral hydrate (mg)	Onset of sedation (min)	Duration of sedation (min)	Recovery time (min)	Side effects	Test success
1	M	3.02	20.00	2,000	118	40	160	-	+
2	F	3.00	15.00	1,500	94	50	149	-	+
3	M	2.09	14.00	1,400	93	55	155	-	+
4	F	2.07	9.00	450	48	23	76	-	+
5	M	4.03	15.00	1,500	120	32	155	-	+
6	M	3.07	16.00	1,600	81	22	110	-	+
7	M	2.03	14.00	1,400	88	36	129	-	+
8	F	4.03	14.00	1,400	122	28	153	-	+
9	M	2.11	16.00	800	60	50	117	-	+
10	F	2.04	14.00	700	26	52	88	-	+

Note: F :Female; M :Male; (-); no side effect was observed; (+); successful sedation.

sedation in children under 12 months (13.65 ± 6.16 minutes) was shorter than in children over 12 months (18.54 ± 9.99 minutes).[6] This corresponds to our study which found that younger children had a shorter onset of sedation than older children. In pediatric painless sedation procedures, the duration of sedation varies based on factors such as dosage and the children's physiological characteristics. Our study revealed that the duration of sedation (38.80 ± 12.43 minutes) is sufficient for ABR testing, which usually takes time for about 30 minutes.

The recovery time after chloral hydrate sedation was found to vary widely among children. The sedative effects were revealed to wear off within several hours, while the complete recovery of cognitive and motor functions could take longer. Residual drowsiness or dizziness could be observed in children for some time after the procedure. In our study, children receiving chloral hydrate rectal solution did not experience prolonged sedation.

The chloral hydrate dose was initially maintained at the minimum effective level for sedation and increased if the child did not achieve sedation. The maximum dose was not administered initially to prevent the risk of accumulating doses leading to prolonged sedation. The sedative effects were typically maintained for a sufficient duration to facilitate procedures.

The literature reported various success rates of chloral hydrate rectal administration in painless sedation, ranging from 65.70% to 98.71%.[2,6,7,26,27] The various procedural time affected the success rate. It was found that the procedures which take a short time will result in a high success rate. Moreover, the success rate depends on the dose of chloral hydrate and the age of children; administering a higher dose of chloral hydrate at a low age of children leads to a high success rate. Conversely, a high dose of chloral hydrate can cause more side effects compared to a low dose.

Conclusion

This study on a new formulation of 10% w/v chloral hydrate rectal solution established its physicochemical and microbiological stability for at least 90 days under storage at refrigerated condition (5 ± 2 °C) in a tightly sealed and light-resistant glass container. Therefore, the hospital pharmacy can set the expiration date of this preparation to 90 days under 5 ± 2 °C. This pilot study demonstrated that administering 10% w/v chloral hydrate rectal solution prior to ABR examination in children achieved a high efficacy with a 100% success rate without side effects. In the future, it can be applied to sedate children undergoing painless procedures. However, 10% w/v chloral hydrate rectal solution should be administered under specialized supervision to ensure safety.

The study is limited by the lack of investigation into pharmacokinetics and a short study duration. Future research should include a broader age range of participants, an extended timeframe, and the exploration of the pharmacokinetics of chloral hydrate rectal solution, which could be beneficial for other painless procedures in children.

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