RESEARCH ARTICLE

Clinical and Stability Assessment of Chloral Hydrate Syrup for Sedation in Pediatrics

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ABSTRACT

To develop a stable chloral hydrate (CH) syrup and to test its clinical efficacy in inducing painless sedation during diagnostic imaging examinations in children under 4 years of age. For the physico-chemical tests, the vials were stored at + 5 and + 25°C and the analysis was carried out for 60 days. The microbiological tests were performed in 4 days of analysis. The prospective clinical study was conducted in 33 infants and children after receiving CH syrup orally for sedation prior to magnetic resonance imaging (MRI). After two months of storage, the average concentrations in all tests were greater than 95% of the initial chloral hydrate concentration. No microbiological growth was noted after 60 days of storage. The clinical use of syrup in children resulted in effective sedation in 100% of children and rare side effects. Compared to midazolam, chloral hydrate is more effective for sedating children under 5 years of age and is significantly less expensive. The prescription of 5% CH syrup for sedation prior to imaging diagnosis has well-established efficacy. However, the safe use of chloral hydrate in infants and children under 5 years of age should be in accordance with international recommendations.

Keywords: Chloral hydrate, Magnetic resonance imaging, Midazolam, Sedation, Syrup.

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INTRODUCTION

Sedation is often required in children undergoing painless diagnostic imaging, including magnetic resonance imaging (MRI), computed tomography (CT), and echocardiography, in an effort to reduce anxiety and facilitate a successful diagnostic study with no motionally degraded imaging results. A rapidly acting, short-lived drug with predictable effects that is easy to administer and well tolerated would be the ideal sedative agent for this indication. Both chloral hydrate (CH) and midazolam are widely used for this pediatric sedation.

CH, one of the oldest hypnotics of synthesis (Figure 1), has been used in children since 1894 and still has a sedative interest in premedication in specialized tests or in child dentistry and neonatal resuscitation[1,2] including brain neuroimaging and electroencephalography (EEG). The CH had a reputation for being a safe and easy use product, despite many publications on its side effects dating back a hundred years. CH has a bitter taste and is known to cause vomiting[1,3] including brain neuroimaging and (EEG). A recent evaluation has questioned the benefit/risk ratio related to its use.[4] Specifically, the suspicion of a mutagenic and carcinogenic power led to severe restrictions of its use to children and its withdrawal from the composition of certain products with the purpose of external analgesia.

CH is an orally or rectally administered hypnotic, and it is especially useful to children and elderly people who do not tolerate barbiturates.[5] Its use is restricted to children between 2 and 60 months, in case of need for total and prolonged immobilization (at least half an hour) essential to the realization of diagnostic investigations like respiratory functional exploration (EFR) without getting the respiratory system depressed, the extended imaging by MRI and the CT scan.[6-8]

In pharmacokinetic terms, the CH is quickly absorbed in the gastrointestinal tract (GIT). An efficient plasma rate is reached in half an hour. The CH is metabolized into trichlorethanol by the liver alcohol dehydrogenase (Figure 2)[9] to a lesser degree, metabolized to dichloroacetic acid (DCA). Its plasma half-life is about 8 hours. Trichlorethanol is the active metabolite with a hypnotic effect; the urinary tract eliminates it after glucuronidation. Oral bioavailability is about 60% and plasma protein binding is about 35%. The 20 to 40% of the trichloroethane is oxidized into trichloracetic acid. Trichloroethane is found in the cerebrospinal fluid, the placenta, and the fetus and in very small concentrations in breast milk[1,10]

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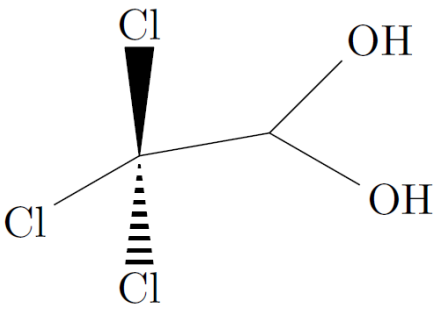


Figure 1: Chemical structure of chloral hydrate

including brain neuroimaging and electroencephalography (EEG. The half-life of the trichloroethane elimination is increased prematurely, hence a risk of accumulation of the toxic metabolite.[2] Depending on the route used, its time of action is variable, for intravenous route ranges from 3 to 5 minutes and 10 to 20 minutes for the oral route.[8,11] with patient demographics, sedation dose, comorbidities, time to discharge, and side effects of sedation noted. Results 400 and 11 infants (median [range] postmenstrual age per weight at scan 42 [31 + 4–60] weeks per 3500 g [1060–9900 g].

CH can be used when general anesthesia is not feasible. The recommended dosage is 20 to 75 mg/kg in a single dose and should never exceed a total dose of 75 mg/kg or 1 g. The repetition of administrations should be limited to the maximum. The administration may be either oral or *via* intra-rectal slow injection. Several pathological situations represent a contraindication to the use of the CH, namely fever, the risk of central sleep apnea or device, intracranial hypertension, and respiratory, renal, heart, and liver failure,[1,2,5] including brain neuroimaging and EEG.

No pharmaceutical specialty containing the CH has authorization in the Moroccan market. The purpose of this research is to assess the stability of a hospital formula and to study the clinical and economic interest of the use of CH syrup in comparison with midazolam medication in infant sedation. In this focus, we will look at the new recommendations on the use of the CH in pediatrics and the benefits/risk of hospital preparation.

MATERIAL AND METHODS

Chemicals and Reagents

CH ($C_2H_3Cl_3O_2$, USP grade) was purchased from Solvachim Sarl (Morocco). Sucrose ($C1_2H_{22}O_{11}$, USP grade), sodium hydroxide and sulfuric acid solutions were procured from Sigma-Aldrich GmbH (Germany).

The culture media utilized for the microbiological analysis were casein-soya-agar and sabouraud-dextrose-agar (LiofilChem, Italy). These mediums were performed according to the instructions of the manufacturer..

Phenolphthalein indicator 1% was purchased from Solvachim S.A. (Morocco). Orange essence was provided by the Moroccan company Somaprol. Throughout the study, we used distilled and filtered water.

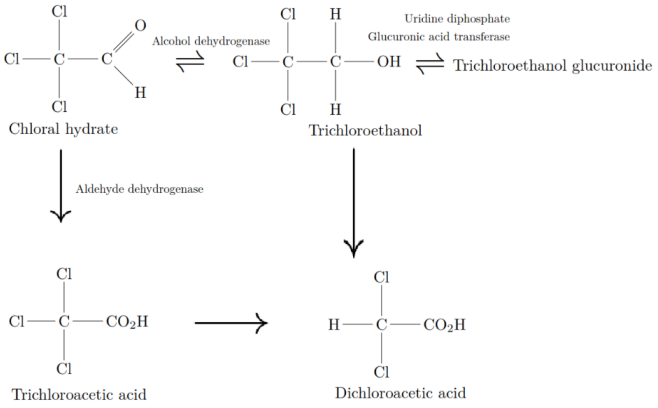


Figure 2: Chloral hydrate metabolism [9]to a lesser degree, metabolized to dichloroacetic acid (DCA).

Table 1: General formula of 5% w/v chloral hydrate syrup

Ingredients	*Quantity*
Chloral hydrate	5 g
Distilled water	7 mL
Essence of orange	1 drop
Simple syrup	q.s 100 mL

Preparation of 5% CH Syrup

The general formula of the syrup of CH is dosed at 5% w/v of CH. It contains the essence of orange, distilled water, and simple syrup in accordance with the formula in Table 1. The simple syrup was prepared with hot sucrose at 65% w/v.

Several batches of syrup based on 5% CH were prepared to carry out the physicochemical, microbiological and clinical tests. The preparation is carried out under a laminar flow host (NÜVE MN090, Turkey). The required quantity of CH was solubilized with distilled water, and completed with simple filtered syrup. In the end, we add a few drops of the essence of orange as a flavoring agent. The batches were stored in light-resistant glass containers of both 60 and 200 mL, with child-resistant caps, to simulate multi-dose dispensing forms. Two batches divided into 60 mL bottles and two other batches in 200 mL bottles were prepared for the microbiological and physicochemical tests, respectively. Four batches were prepared and dispensed in 60 mL glass bottles during the clinical study. The CH content of each batch was quantitatively analyzed before distribution to the hospital department.

Physicochemical Stability Evaluation

We prepared two batches of 5% CH syrup. Each lot was divided into 6 glass bottles resistant to light of 200 mL and stored under room conditions (+25 ± 2°C) with an air-conditioned room and refrigerated conditions (+5 ± 2°C). Temperature monitoring under both conditions was performed daily with a digital thermo-hygrometer, which records temperature values. We labeled all the samples and kept them for 60 days.

To test the chemical and physical stability, 30 mL of each multi-dose container of CH syrup was taken on days 0, 7, 14, 21, 28 and 60, respecting the temperature conditions mentioned.

According to the USP method, physical stability was checked at each time point via both visual inspection and specific gravity measurement, using a calibrated 25 mL pycnometer (Brand GmbH, Germany).

The CH content of the samples was monitored to assess chemical stability. The content of CH was determined titrimetrically with 1.0 N sodium hydroxide in accordance with the USP 41 Standard.[12]

The pH was determined by thermostating the samples at 25°C in a water bath (GFL1083, Germany). A glass electrode pH meter was used to measure pH (Bante 920, Bante Instruments L. China). The pH meter was calibrated before each use with a buffer solution of pH 4.0, 7.0, and 9.0.

The chemical stability of the formulation was defined by the presence of at least 95% and no more than 110% of the labeled CH content in the samples and also by no lower than 2.05 pH value. Repeatability was determined from six titrations of 5% CH syrup and the relative standard deviation obtained was below 1%. For each package, the results obtained are the average of three bottle determinations.

Microbiological Stability Evaluation

According to the European Pharmacopeia monograph, a microbiological evaluation was performed on the samples to determine if they met the microbiological characteristics of non-sterile pharmaceuticals.[13,14] For non-sterile pharmaceutical products, the criteria for acceptance are focused on the total aerobic microbial count (TAMC) and the total Yeast/mold combined count (TYMC), with an average of three replicate counts. Specifications were set as total aerobic microbial count below 10^2 CFU/mL, total combined yeasts/molds count below 10^1 CFU/mL and absence of *Escherichia coli*. All microbiological tests were carried on the central laboratory of bacteriology of Ibn Sina university hospital.

The study is done in 4 days of analysis: d_0, d_{15}, d_{30} and d_{60}. At day 0, 12 containers of 60 mL of syrup were prepared from 2 batches. Each batch is composed of 3 bottles of syrup at 25 ± 2°C and 3 others at 5 ± 2°C. One bottle of simple syrup without chloral hydrate is stored under each temperature condition.

A dilution of 10^{-1} of the syrup in peptone water at pH 7.0 was prepared in each day of analysis. Plate-count with surface spread method was used for the enumeration of micro-organisms.[15-18] This method was previously validated by a growth promotion test to ensure that one of the products present in the syrup did not inhibit the sprouts. A volume of 10 µL, of each dilution was taken and spread over 3 Petri dishes of casein soya bean digest agar and incubated at 30–35°C for 5 days. Three other plates of sabouraud-dextrose agar were incubated at 20–25°C for 5 days.

Pharmacoeconomic Evaluation

The direct cost of hospital preparation of 5% w/v CH syrup at 50 mg/kg was calculated and compared to midazolam 5 mg/5 mL injectable administered rectally.

Clinical Study Protocol

A 4-month prospective observational study of 33 infants and children aged from 8 to 48 months (19.97 ± 11.67 months) was performed. Each patient received 50 mg/kg of 5% oral CH syrup for sedation prior to MRI. Only children under 48 months of age and weighing 25 kg or less were included in the study. After receiving CH syrup, the time of drug administration, time required to obtain sedation or the latency time, necessity for taking a second dose, sedation time and retrieval time were recorded. If 30 minutes after the initial dose, sedation was not achieved, the child received a second dose of 25 mg/kg of syrup.

Sedation time is defined as the time from receipt of 50 mg/kg of CH syrup until the time sedation is initiated. The length of sedation as defined as the time from the start of sedation to the patient's awakening. Recovery time also was defined as the time from receipt of the initial dose of study drug to complete recovery. A successful sedation was judged if the MRI tests were concluded with 95% or more of the images showing

Table 2: Physicochemical results

Batch number	*Storage T (°C)*	*Parameters**	*Sampling day*					
			0	*7*	*14*	*21*	*28*	*60*
1	5	CH content (%)	98.25 ± 0.23	98.41 ± 0.45	97.72 ± 0.73	97.05 ± 0.51	96.85 ± 0.13	96.14 ± 0.32
		pH	4.234 ± 0.05	4.244 ± 0.04	4.221 ± 0.007	4.264 ± 0.06	4.154 ± 0.05	4.194 ± 0.010
		Specific gravity (mg/mL)	1.35 ± 0.02	1.35 ± 0.03	1.35 ± 0.04	1.35 ± 0.02	1.35 ± 0.02	1.35 ± 0.03
	25	CH content (%)	98.85 ± 0.13	98.78 ± 0.14	97.15 ± 0.45	96.85 ± 0.16	96.85 ± 0.17	96.85 ± 0.48
		pH	4.284 ± 0.05	4.270 ± 0.02	4.304 ± 0.04	4.251 ± 0.02	4.173 ± 0.05	4.174 ± 0.10
		Specific gravity (mg/ml)	1.35 ± 0.02	1.35 ± 0.03	1.35 ± 0.04	1.35 ± 0.05	1.35 ± 0.06	1.35 ± 0.07
2	5	CH content (%)	98.55 ± 0.23	98.12 ± 0.45	97.72 ± 0.73	97.05 ± 0.51	96.75 ± 0.13	96.74 ± 0.32
		pH	4.264 ± 0.05	4.214 ± 0.04	4.302 ± 0.007	4.208 ± 0.06	4.021 ± 0.05	4.190 ± 0.010
		Specific gravity (mg/mL)	1.35 ± 0.02	1.35 ± 0.03	1.35 ± 0.04	1.35 ± 0.02	1.35 ± 0.02	1.35 ± 0.03
	25	CH content (%)	98.85 ± 0.13	98.47 ± 0.14	97.45 ± 0.45	96.79 ± 0.16	96.39 ± 0.17	96.95 ± 0.48
		pH	4.384 ± 0.05	4.281 ± 0.02	4.344 ± 0.04	4.261 ± 0.02	4.203 ± 0.05	4.174 ± 0.10
		Specific gravity (mg/mL)	1.35 ± 0.02	1.35 ± 0.03	1.35 ± 0.04	1.35 ± 0.05	1.35 ± 0.06	1.35 ± 0.07

*(mean ± S.D., n=3). S.D. = Standard Deviation

Table 3: Chloral hydrate content for clinical batches

Batch n°	*1*	*2*	*3*	*4*
CH content* (%)	98.70 ± 0.28	97.25 ± 0.55	97.45 ± 0.65	98.10 ± 0.48

*(mean ± S.D., n=3). S.D. = Standard Deviation

Table 4: Microbiological tests results

Batch number	*Storage T°*	*Microbial test*	*Sampling day*			
			0	*15*	*30*	*60*
1	5°C	TAMC	(-)	(-)	(-)	(-)
		TYMC	(-)	(-)	(-)	(-)
	25°C	TAMC	(-)	(-)	(-)	(-)
		TYMC	(-)	(-)	(-)	(-)
2	5°C	TAMC	(-)	(-)	(-)	(-)
		TYMC	(-)	(-)	(-)	(-)
	25°C	TAMC	(-)	(-)	(-)	(-)
		TYMC	(-)	(-)	(-)	(-)

TAMC: Total Aerobic Microbial Count.
TYMC: total combined yeasts/moulds count.
(-): no growth.

little or no motion artifacts. We defined complete recovery as the capacity to keep up normal respiratory activity, and the capacity to stay seated for at least 10 seconds or more. In addition, each child remained in the unit for at least one hour after full recovery.

The evaluated parameters were compared to the literature data using a 1-sample t-test. Significance was considered when the level was less than 0.05. All tests were performed using Minitab[17] (Minitab LLC, USA).

RESULTS

Physicochemical and Microbiological Stability Studies

The results of the chemical and physical properties of the two batches of 5% CH syrup are presented in Table 2. After visual examination, no visible particles or changes of color and/or odor were found in any of the test samples. For clinical batches, the CH content is presented in Table 3. Results for microbiological tests for the two batches are presented in Table 4.

Clinical Observations

The results of the study in 33 children (8–48 months) requiring MRI and given orally CH syrup at 50 mg/kg are presented in Table 5.

The total duration of sedation was between 8 and 30 minutes, the average total duration of sedation was between 40 and 80 minutes, and the average total duration of recovery to normal activity or recovery time was between 80 and 150 minutes.

The results of the 1-sample t-test applied on both parameters: sleep latency time and sedation duration in comparison with reference literature values were shown in Table 6.

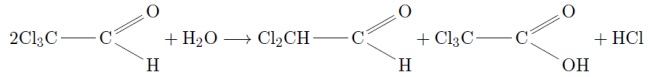
The comparison of the ratio of side effects by the use of the normal law approximation with respect to the common proportion from previous studies, after oral administration of CH, is presented in Table 7.

Pharmaco-economic Evaluation

The hospital preparation of the 5% CH syrup in a 100 mL glass bottle costs $ 1.90. The direct cost of preparation of sedation is $ 0.40 for each child of 20 kg against $ 1.28 for a child of the same weight by midazolam 5 mg/5 mL.

DISCUSSION

The results of physicochemical studies show that specific gravity after 2 months of storage was under 1.30 mg/mL. This complies with USP specifications.[12] The pH did not change significantly either, because it stayed within the range of 4.154 and 4.384 under room and refrigeration temperatures. The slight acid pH can be explained by the formation of HCL in aqueous solution by an oxidation-reduction process (Eq. 1).[19,20]



Eq. 1

Quantitative examinations of CH in different storage conditions indicated that the average content of the active substance (97.48 ± 0.89 % for batch n°1 and 97.49 ± 0.83% for batch n°2) was within the acceptable concentration. The average concentrations in all test samples after 2 months of storage were higher than 95% of the initial CH concentration, indicating no significant loss of CH. No increase in CH concentration was also observed, indicating a lack of evaporation of the vehicle in multi-dose vials for 2 months of storage and after 6 times for sampling during stability testing. So, opening the multi-dose vials frequently to take successive doses did not affect the concentration of chloral hydrate or the characteristics of the syrup. These findings suggest that there was no chemical degradation after stability evaluation. This is consistent with a previous work showing that the 10% aqueous CH solution and syrup were not significantly changed after 3 months of storage at room temperature or at 60°C[21,22] In addition, according to several hospital forms, chloral hydrate solutions, as extemporaneous preparations with concentrations of 5-10% chloral hydrate, expired between 15 and 30 days at most. Short expiration date may likely be a safety issue as these formulations may not be supported by studies to document stability.[1,23]

For microbiological stability (Table 4), all samples in both batches were negative. This proves that the product conforms with European pharmacopeia 8th specifications after two months of storage.[14,18,24] Several studies have shown that extemporaneous CH preparation remains stable over a minimum of 180 days if kept in light-resistant glass multi-dose vials at 2–8°C[25–27]

All these aspects support that 5% CH syrup is stable in the refrigerator and at room temperature chemically, physically and microbiologically for at least 60 days.

The evaluation of the clinical data (Table 5) after oral administration of 50 mg/kg of CH syrup, showed that 30.3% of patients were less than 1 year old, 81.8% were less than 2

Table 5: Clinical study results of CH syrup

Patient number	*Age (months)*	*Gender*	*Weight (Kg)*	*Repeated dose*	*Latency time (min)*	*Sedation duration (min)*	*Recovery time (min)*	*Side effects (SE)*	*Test success*
1	23	M	14	No	15	60	90	Vomiting	+
2	36	M	20	No	15	50	80	-	+
3	24	M	12	No	10	55	80	-	+
4	22	F	13	No	10	60	105	Vomiting	+
5	10	F	8	No	15	70	115	-	+
6	15	M	10	No	10	60	110	-	+
7	48	M	22	Yes	30	40	150	-	+
8	8	F	10	No	8	80	110	-	+
9	15	F	9	No	10	60	115	-	+
10	18	M	12	No	15	55	95	-	+
11	42	F	25	No	20	45	90	Vomiting	+
12	11	M	12	No	10	50	100	-	+
13	9	M	10	No	10	70	120	-	+
14	18	F	15	No	15	60	120	-	+
15	10	F	14	No	10	70	90	-	+
16	14	M	15	No	10	60	100	-	+
17	8	M	10	No	10	75	120	-	+
18	24	M	14	No	15	50	85	-	+
19	11	F	11	No	10	60	95	-	+
20	15	M	12	No	15	60	105	-	+
21	23	M	14	No	15	60	105	Vomiting	+
22	36	M	20	No	15	50	90	-	+
23	24	M	12	No	10	55	80	-	+
24	22	F	13	No	10	60	105	Vomiting	+
25	10	F	8	No	15	70	100	-	+
26	15	M	10	No	10	60	110	-	+
27	45	M	22	Yes	30	40	130	-	+
28	8	F	10	No	8	80	120	-	+
29	15	F	9	No	10	60	115	-	+
30	18	M	12	No	15	55	105	-	+
31	42	F	25	No	20	45	80	Vomiting	+
32	11	M	12	No	10	50	90	-	+
33	9	M	10	No	10	70	120	-	+

(M): male; (F): female; (-): no SE was observed; (+): successful sedation

Table 6: Sample t-test results

Parameter	*Mean of the sample* (n=33)*	*Reference values*	*C.I. at 95%*	*t value*	*p-value (α=0.05)*
Sleep latency time	*13.36 ± 5.33 min*	*20 min*	*[11.47; 15.25]*	*-7.15*	*≤ 0.01*
Sedation duration	*58.94 ± 10.21 min*	*60 min*	*[53.18; 78.33)]*	*-0.60*	*0.555*

*(mean ± S.D., n=3); S.D. = Standard Deviation; C.I.= confidence interval

Table 7: Side-effects proportion comparison results

SE	*Ratio of the sample*	*Reference ratio*	*Lower bound of C.I. at 95%*	*z value*	*p-value (α=0.05)*
Vomiting	0.18	0.15	0.071	0.51	0.304

C.I.= confidence interval

years old, and 18.2% were between 2 and 4 years. The average weight is 13.48 ± 4.7 kg, and 81.81% of the children weighed 15 kg or less.

Sedation by the CH syrup is effective in 90% of patients aged under 5 years old.[28] In our study, sedation was effective after the first dose in 94% of patients. Literature data in infants

and children indicate that sleep latency time is about 20 ± 10 minutes and patients wake up after 60 ± 32 minutes.[29-32] The 1-sample t-test applied on the time to achieve sedation showed that the average results obtained are significantly lower from the reference value ($p < 0.05$). This can be explained by the weight and average age of our sample which is less elevated than the panel used in previous studies. This is confirmed by the fact that the two children who required the use of a second dose after 30 minutes of administration of the first dose were 48 and 45 months and weighing more than 20 kg. For the duration of sedation, the results obtained do not differ significantly from the reference value ($p > 0.05$).

For microbiological stability (Table 4), all samples in both batches were negative. This proves that the product conforms with European pharmacopeia 8th specifications after two months of storage[14,18,24] Several studies have shown that extemporaneous CH preparation remains stable over a minimum of 180 days if kept in light-resistant glass multi-dose vials at 2–8°C[25–27] the prevalence of Gram positive bacteria including *Staphylococcus spp*. and *Bacillus spp*. were significant in both types of samples (the former in 24 syrups and 11 suspension samples, and the later species in 7 syrup and 4 suspension samples.

All these aspects support that 5% CH syrup is stable in the refrigerator and at room temperature chemically, physically and microbiologically for at least 60 days.

The evaluation of the clinical data (Table 5) after oral administration of 50 mg/kg of CH syrup, showed that 30.3% of patients were less than 1 year old, 81.8% were less than 2 years old, and 18.2% were between 2 and 4 years. The average weight is 13.48 ± 4.7 kg, and 81.81% of the children weighed 15 kg or less.

Sedation by the CH syrup is effective in 90% of patients aged under 5 years old[28] effectiveness and safety of chloral hydrate administered by radiologists for the sedation of children who require MRI procedures. Materials and methods: we retrospectively reviewed the clinical charts for all patients ages 0–10 years old who underwent sedation with chloral hydrate for MRI from January 2000 to December 2010. Demographic factors, dose information, indication for MRI, therapeutic failures and adverse reactions to the drug were reviewed. results: 1703 children (946 males, 757 females). In our study, sedation was effective after the first dose in 94% of patients. Literature data in infants and children indicate that sleep latency time is about 20 ± 10 minutes and patients wake up after 60 ± 32 minutes[29–32] pain and amount of sedative and analgesic drugs use in opium addicted critically ill patients. In a prospective, randomized, controlled trial from September 2011 to June 2012, this study has been conducted in Kerman, Iran. We randomly assigned 37 addicted mechanically ventilated patients who admitted to ICU in two groups; while in intervention group (group I. The 1-sample t-test applied on the time to achieve sedation showed that the average results obtained are significantly lower from the reference value ($p < 0.05$). This can be explained by the weight and average age of our sample which is less elevated than the panel used in previous studies. This is confirmed by the fact that the two children who required the use of a second dose after 30 minutes of administration of the first dose were 48 and 45 months and weighing more than 20 kg. For the duration of sedation, the results obtained do not differ significantly from the reference value ($p > 0.05$).

For side effects cases, it is found that the proportion of vomiting observed is not significantly different ($p > 0.05$) from the cases obtained in the other studies (of the order of 15%)[28,33] effectiveness and safety of chloral hydrate administered by radiologists for the sedation of children who require MRI procedures. Materials and methods: We retrospectively reviewed the clinical charts for all patients ages 0–10 years old who underwent sedation with chloral hydrate for MRI from January 2000 to December 2010. Demographic factors, dose information, indication for MRI, therapeutic failures and adverse reactions to the drug were reviewed. Results: 1703 children (946 males, 757 females. Regarding the impact of age and weight on the need for a second dose, 50% of patients older than 3 years (2 patients) needed a second dose after 15 minutes. This can be explained by the insufficiency of the prescribed dose.

sedation in pediatrics is often achieved with CH and midazolam. Midazolam is a more recent and costly benzodiazepine that has interesting pharmacodynamic properties and can be administered intravenously, orally, intramuscularly, intranasally, sublingually and rectally[34–36] randomized, double-blind study conducted between July 2005 and October 2006, at the pediatric day care unit (DCU). According to the United Kingdom's National Institute for Health and Care Excellence (NICE), using CH or midazolam is a safe sedative for pediatric procedures, assuming suitability for sedation has been evaluated, monitoring of the effects by appropriately trained staff, and the ready availability of resuscitative equipment.[37]

In addition, the sedation with midazolam administered rectally requires a dose of 0.5 mg/kg for children between 6 months and 5 years that is 10 mg for a child of 20 kg. The unit price for the purchase of a bulb of injectable midazolam 5 mg/5 mL by the hospital is $ 0.80, while the direct cost of the sedation for a child of 20 kg is $ 1.30. In comparison with 5% CH syrup, sedation costs only $ 0.40.

Furthermore, the average latency time by midazolam is 117 ± 5 minute and sedation duration is about 45 ± 12 minutes.[34,38] Compared with midazolam, CH has shown more profound and long-lasting sedation[39] In clinical use, other studies reported that chloral hydrate was more effective than midazolam in facilitating the completion of painless imaging studies, although it has a longer onset and duration, and reported minimal adverse events[30,40] Moreover, the reports on midazolam were not always positive despite his rapid action onset and short duration of action which does not encourage the health care provider shift from the old CH to the new midazolam as a sedative agent.[34,41] CH syrup remains

consequently cheaper and even more effective than the rectal midazolam, given its short latency time to cause sedation of children.

Otherwise, both chloral hydrate and midazolam have a wide margin of safety when used in limited dosage.[8,33,42] Administration of CH at repeated doses is not recommended because of the risk of accumulation of metabolites causing renal toxicity and metabolic acidosis resulting from their interferences with the binding of bilirubin to albumin.[31] In newborns, the half-life of the trichlorethanol, the active metabolite of CH, increases. Short-Term sedation with a single dose of 20 to 75 mg/kg is considered relatively safe, but its repeated administration carries a risk of serious toxicity[8,9,43] with patient demographics, sedation dose, comorbidities, time to discharge, and side effects of sedation noted. Results Four hundred and eleven infants (median [range] postmenstrual age per weight at scan 42 [31 + 4–60] weeks per 3500 g [1060–9900 g].

Actually, in the absence of appropriate alternatives, CH is essential for performing a medical examination in children in good condition. This is the case when the conduct of a medical examination in good condition is essential to the diagnosis and the medical care of children in serious pathologies. Within this framework, the national agency for medicament safety and health products in France (ANSM) estimates that CH risk-benefit balance remains positive if its use is limited to sedation in MRI, in children aged from 6 months to 4 years, with a maximum single dose of 75 mg/kg[44]

CONCLUSION

The results of the tests carried out on the CH syrup confirmed the physicochemical and microbiological stability of the hospital preparation. Clinical observation validated the efficacy of syrup at 50 mg/kg for children under 48 months of age for sedation during MRI tests. The results of our study align with the results of the literature and the new recommendations that confirm the superiority of the effectiveness of CH syrup and its better tolerance compared to the use of midazolam for painless sedation. The 5% syrup is also cheaper than midazolam administered rectally but should strictly follow the recommendations of international agencies to avoid the occurrence of serious side effects and maximize its effectiveness in children.

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CONFLICT OF INTEREST

No conflict of interest is associated with this work.

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