

## Efficacy of Chloral Hydrate-Hydroxyzine and Chloral Hydrate-Midazolam in Pediatric Magnetic Resonance Imaging Sedation

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### Abstract

#### Objective

Magnetic resonance imaging (MRI) is a useful diagnostic tool for the evaluation of congenital or acquired brain lesions. But, in all of less than 8-year-old children, pharmacological agents and procedural sedation should be used to induce motionless conditions for imaging studies. The purpose of this study was to compare the efficacy and safety of combination of chloral hydrate-hydroxyzine (CH+H) and chloral hydrate-midazolam (CH+M) in pediatric MRI sedation.

#### Materials & Methods

In a parallel single-blinded randomized clinical trial, sixty 1-7-year-old children who underwent brain MRI, were randomly assigned to receive chloral hydrate in a minimum dosage of 40 mg/kg in combination with either 2 mg/kg of hydroxyzine or 0.5 mg/kg of midazolam. The primary outcomes were efficacy of adequate sedation (Ramsay sedation score of five) and completion of MRI examination. The secondary outcome was clinical side-effects.

#### Results

Twenty-eight girls (46.7%) and 32 boys (53.3%) with the mean age of  $2.72 \pm 1.58$  years were studied. Adequate sedation and completion of MRI were achieved in 76.7% of CH+H group. Mild and transient clinical side-effects, such as vomiting of one child in each group and agitation in 2 (6.6 %) children of CH+M group, were also seen. The adverse events were more frequent in CH+M group.

#### Conclusion

Combinations of chloral hydrate-hydroxyzine and chloral hydrate-midazolam were effective in pediatric MRI sedation; however, chloral hydrate-hydroxyzine was safer.

**Keywords:** Sedation; Children; MRI; Hydroxyzine; chloral hydrate, Midazolam.

### Introduction

Magnetic resonance imaging (MRI) is a useful diagnostic tool for evaluation of congenital or acquired brain lesions, dysmyelination or demyelination, gliosis, primary and metastatic brain tumors, cerebral edema, and acute stroke. But, in all of less than 8-year-old children, pharmacological agents and procedural sedation should be used to induce motionless conditions for imaging studies (1), for which different sedation regimens may be used in radiology departments (2,3).

Schulte-Uentrop and Goepfert (4) in their research concluded that dexmedetomidine may be convenient for MRI sedation of children without cardiac risk. But, the drug is expensive and hardly available in many developing countries such as Iran.

Chloral hydrate (CH) is a non-opiate, non-benzodiazepine sedative-hypnotic drug, which has been used for pediatric sedation in a dosage of 40-100 mg/kg for many years (3,5). But, it was not effective in some children, even at maximum dosage, and there are concerns about its long acting duration, obstruction of airway, respiratory depression with intra- and post-procedural oxygen desaturation, sedative effects consistency, and its potential for carcinogenicity, especially at high doses (5-7).

Chloral hydrate at a dose of 40 mg/kg is safer and its combination with antihistamines might decrease chloral hydrate dosage (7,8).

Combination of chloral hydrate and hydroxyzine has been used for sedation of children in dental procedures, and it can decrease the required dosage of chloral hydrate and also cause improvement in safer sleeping of patient and decrease the risk of chloral hydrate related nausea and vomiting (9).

Midazolam is a water-soluble benzodiazepine, which can be used in different routes (oral, intravenous, intramuscular, rectal, sublingual, aerosolized buccal, and intranasal) for sedation induction in children (10,11).

Oral midazolam is a non-parenteral route, which does not cause pain of injection and is used at dosages of 0.5-1 mg/kg in pediatric sedation induction (12).

The purpose of this study was to compare the efficacy and safety of chloral hydrate at minimum dosage in combination with hydroxyzine or midazolam in pediatric MRI sedation induction.

## Materials & Methods

We followed a randomized single-blind study on children who underwent sedation for elective MRI at the Radiology Department of a tertiary-care hospital (Shahid Sadoughi Hospital) in Yazd, Iran from November 2012 to March 2013.

An Informed consent was taken from patients' parents before the administration of the drugs, and the study was approved by the Ethics Committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

The sample size was calculated to be 30 children in each group to detect a 20% difference in efficacy between the two groups with type one error (alpha) of 0.05 and 80%

power. Eligible participants included children aged 1-7 years, who were in American Society of Anesthesiology (ASA) class 1 (a normally healthy patient) or 2 (a patient with mild systemic disease: mild asthma, controlled diabetes mellitus, etc.) (13).

Exclusion criteria consisted of presence of gastritis or any other serious systemic diseases, severe systemic reaction, head injury, and receiving a sedative hypnotic agent within the past 48 hours.

The trial used computer generated equal simple randomization by random numbers, and allocation ratio was 1:1 for the two groups.

Randomization and blinding were performed by an investigator with no clinical involvement in the trial. Data collectors, outcome assessors, and data analysts were all kept blinded to the allocation. But, patients and an MRI nurse allocated to the intervention group, were aware of the allocated arm. A pharmacist prepared the drugs, which were given in a suspension of 1 cc/kg.

The drug combination was delivered by MRI nurses who had certificates in pediatric advanced life support and basic life support, when the participants entered the preparation room. Primary and secondary outcomes were assessed by a pediatric resident who was not informed of the group assignment of drug combination.

The children were randomly assigned to two groups to receive either 40 mg/kg of chloral hydrate and 2 mg/kg of hydroxyzine (Group I) or 40 mg/kg of chloral hydrate and 0.5 mg/kg of midazolam (Group II).

Ramsay sedation scale was used for assessment of the sedation level (14), and it was measured every 10 minutes. The Ramsay sedation scale of five was considered as adequately deep sedation.

The primary outcomes were efficacy in adequate deep sedation and completion of MRI examination.

The secondary outcomes included clinical side-effects, serious adverse events (hypotension, hypoxia and cyanosis, severe vomiting, intractable irritability and agitation, apnea, laryngospasm, and bradycardia), time from administration of the drug combination to adequate sedation, caregiver's satisfaction on a likert scale of 1-5 (1= completely unsatisfied; 2= partially unsatisfied; 3= partially satisfied; 4= satisfied; and 5=completely satisfied), and total stay time in MRI center.

Respiratory depression requiring assisted ventilation,

oxygen saturation of less than 90%, or a 25% or greater decrease in pre sedation mean arterial blood pressure were considered as serious side-effects.

Failure to achieve adequate sedation (patient's wakening or movement, interfering with completion of MRI examination, inadequate sedation, and need for administration of other sedatives) and procedure abortion due to serious adverse events, were considered as failure of sedation regimen.

The developmental status of the patient was assessed by a pediatric neurologist based on Denver II Developmental screening test (15).

The strength of the MRI machine of our hospital was 1.5 Tesla, and it had been manufactured by Siemens in 2010. Non-contrast brain MRI of these children was interpreted by a pediatric neurologist and a radiologist using a three-point scale: 1- good quality and no motion, 2= reportable and minor movement, and 3= non reportable and major movement.

The data were analyzed using SPSS statistical software (version 17). Chi-square and Fisher's exact tests were used for data analysis of qualitative variables, and mean values were compared by independent t-test.

Kaplan-Meier survival analysis was used to calculate probability of adequate sedation during the observation period. The differences were considered significant at  $p < 0.05$ .

This study was registered in Iranian clinical trials with registration number IRCT201302092639N10.

## Results

The design and conduct of this trial was straightforward, and we did not have any losses to follow-up or exclusions. Twenty-eight girls (46.7%) and 32 boys (53.3%) with the mean age of  $2.72 \pm 1.58$  years were evaluated.

No statistically significant differences were observed between the two groups in terms of mean of age, mean of weight, sex distribution, developmental status, and age group of children in two groups (Table 1).

Adequate deep sedation (Ramsay sedation score of five) and completion of MRI examination was achieved in 23 (76.7%) children in chloral hydrate-hydroxyzine group [95% confidence interval (CI): 0.61-0.92] and in 22 (73.7%) children in chloral hydrate-midazolam group (95% CI: 0.58-0.89), and the statistical analysis

showed that the efficacy of both drugs combination in the sedation induction was not statistically different ( $p=0.76$ ).

Also, the quality of MRI was not significantly different between the two groups (Table 1).

Table 2 shows comparison of the mean of acquired Ramsay sedation score, time between drugs taking and reaching the Ramsey score of five, caregiver's satisfaction scale, and total stay time in radiology department which indicates that in chloral hydrate-hydroxyzine group, parents waited less in the radiology department.

Comparison of completion of MRI examination in both groups based on developmental status and age group is shown in Table 3, which indicates that the efficacy of both drugs combination in sedation induction was not statistically different in children with and without developmental delay, in infants (less than two years old), and also in children.

Probability of being adequately sedated vs. time after taking the drugs is shown in Kaplan-Meier plots in figure 1, which indicates that Ramsay sedation score of five was obtained in all children who achieved adequate sedation 40 minutes after taking the drugs combination.

No serious adverse events were seen in the two groups.

Mild and transient clinical side-effects were seen, such as vomiting in one child in each group and agitation in 2 (6.6%) children of CH+M group. The adverse events were more frequent in CH+M group ( $p=0.04$ ).

## Discussion

Various drugs have been used for pediatric MRI sedation. The Results of this randomized clinical trial showed that combination of chloral hydrate at minimum dosage and hydroxyzine or midazolam were equally effective in children who underwent MRI.

In another Iranian study, adequate sedation and completion of CT scan examination were achieved in 76.7% of children who aged 1-10 years and received 100 mg/kg chloral hydrate orally (16).

In Mason et al.'s study, efficacy of oral chloral hydrate at a dosage of 50 mg/kg and oral pentobarbital were equal in MRI sedation of younger than 1-year-old infants; however, side-effects frequency was significantly lower in pentobarbital group (17).

However, Schulte-Uentrop and Goepfert concluded

that in sedation induction for MRI, chloral hydrate, pentobarbital, and midazolam are not proper and dexmedetomidine may be a more effective drug in sedation induction in children without cardiac risk, and if anesthesiologists or pediatric intensivists are present, propofol can be used and general anesthesia is a preferred technique in preterm or small children (4).

In a study in Iowa, USA, a combination of 25 mg/kg chloral hydrate, 1 mg/kg hydroxyzine, and 1 mg/kg meperidine was more effective than 0.65 mg/kg of oral midazolam in sedation for dental procedures (18).

In a study in Miami, USA, efficacy of chloral hydrate, combination of chloral hydrate and diphenhydramine, chloral hydrate-hydroxyzine hydrochloride combination and midazolam alone were compared in case of sedation induction for echocardiography. In chloral hydrate group, children fell asleep the most quickly and chloral hydrate and diphenhydramine group had the most prolonged sedations (19).

In a study in Mexico City, combination of 70 mg/kg chloral hydrate and 2 mg/kg hydroxyzine in comparison with 70 mg/kg chloral hydrate alone caused a significantly more decrease in crying and movement within 45-60 minutes after a rubber dam insertion. But, in both groups, overall behavior was not different during the dental procedures (20).

In a study in Mexico, a combination of 0.50 mg/kg midazolam and 1.5 mg/kg hydroxyzine or 50 mg/kg chloral hydrate and 1.5 mg/kg hydroxyzine were more effective than 2 mg/kg hydroxyzine alone in sedation induction for dental procedures (21).

In the present study, the efficacy of both combination of the drugs in sedation induction were not statistically different in infants (less than two years old) and also in children. But, in a Korean study, chloral hydrate was more effective in MRI sedation of younger than 18-month-old children (22).

In our study, the efficacy of both combinations of the drugs in sedation induction for MRI was not statistically different in children with and without developmental delay, which is in agreement with a study in the USA (23). Possible explanations for these discrepancies include differences in age, drugs combination and dosage, race, sample size, type of procedure, etc.

In the present study, both sedation regimens were safe and no serious clinical adverse events were seen in the two groups. But, in Fávero et al.'s study, respiratory complications occurred in two of 41 children who received 50 mg/kg of chloral hydrate (24) and in Heistein et al.'s study in Texas, serious side-effects such as apnea occurred in 0.3%, airway obstruction in 1.4%, hypoxia in 5.9%, hypercapnia in 6.6%, and hypotension in 0.4%

**Table 1.** Comparison of Some Characteristics of Children between the Two Groups

Data		Group	Chloral hydrate and hydroxyzine	Chloral hydrate and midazolam	p=
Age in year (mean±SD)			2.93±1.56	2.51±1.59	0.3
Weight in kg (mean±SD)			12.68±4.11	12.45±3.24	0.3
Sex	Female		13	15	0.6
	Male		17	15	
Developmental status	Normal		14	17	0.4
	Delay		16	13	
Age group	< 2 years		10	14	0.2
	≥ 2 years		20	16	
MRI quality	No motion		18	19	0.5
	Minor movement		4	2	
	Major movement		1	1	

of children who were sedated with chloral hydrate for echocardiography (25).

In this research, achieving sleep in majority of children who were adequately sedated with the two sedation regimens appeared up to 40 minutes after administration of the drugs combination, therefore, administration of these sedative drugs in 40 minutes before the procedure could be more effective.

**In conclusion,** results of the present study showed that a combination of chloral hydrate at minimum dosage and hydroxyzine or midazolam are equally effective in pediatric MRI sedation. But, a combination of chloral hydrate and hydroxyzine is safer.

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### Author Contribution

Dr. Razieh Fallah: Writing the manuscript and Data analysis

Dr. Nafiseh Fadavi: Gathering the data

Dr. Shekofah Behdad : Gathering the data

Dr.Mahmoud Fallah Tafti : Editing the manuscript

**Table2.** Comparison of Mean of Sedation Parameter Variables between the Two Groups

Data	Group	Chloral hydrate and hydroxyzine	Chloral hydrate and midazolam	p-value
Acquired Ramsay sedation score		5.07± 1.23	4.71± 1.62	0.3
Time between drugs taking and reaching Ramsey score of five (in minute)		18.91± 8.15	22.27± 9.22	0.2
Time after taking the drug to completing MRI examination (in minute)		33.95± 12.06	39.18± 11.21	0.1
Caregiver's satisfaction scale		3.81±1.27	3.37± 1.41	0.2
Total stay time in radiology department (in minute)		69.1± 22.49	81.81± 23.24	0.03

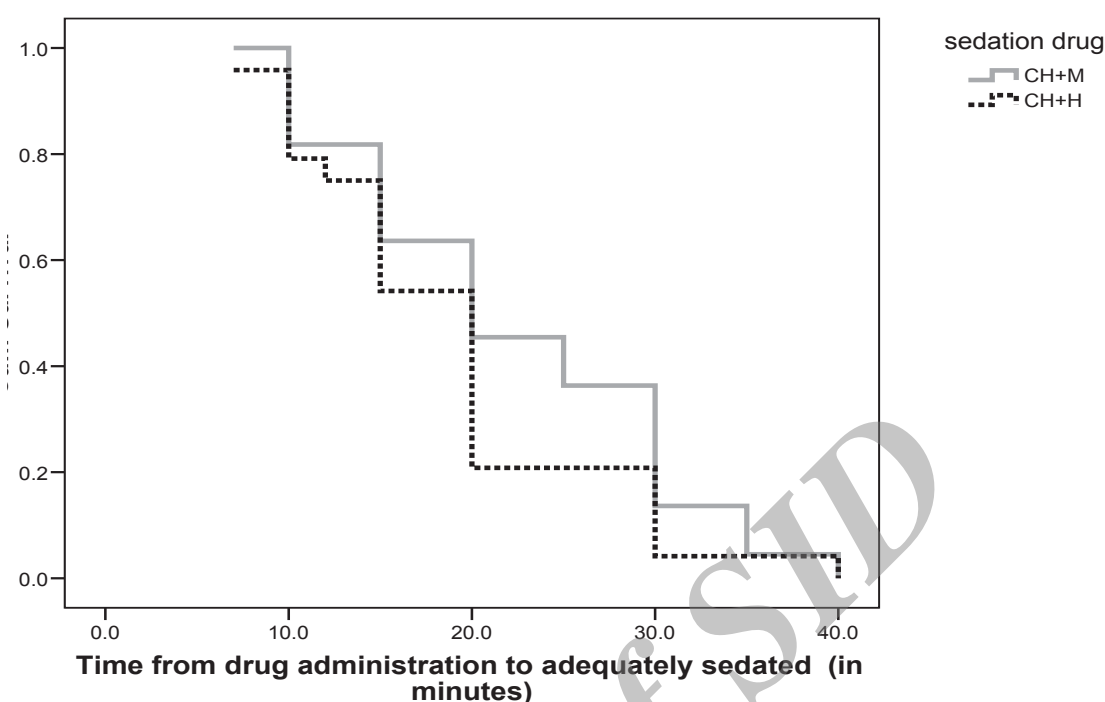
**Table 3.** Comparison of Success in Completing MRI Examination in Both Groups Based On Developmental Status and Age Group

Data	Success in completing MRI		Yes	No	P-value
Developmental status	Normal	CH+H	10	4	0.6
		CH+M	12	5	
	Delay	CH+H	13	3	0.6
		CH+M	10	3	
Age group	<2 years	CH+H	8	2	0.5
		CH+M	11	4	
	≥ 2 years	CH+H	15	5	0.6
		CH+M	11	4	

\* CH+H: Chloral hydrate and hydroxyzine

\*\* CH+M: Chloral hydrate and midazolam





**Fig 1.** Probability of being adequately sedated vs. time after taking the drugs by Kaplan-Meier plots

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