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ORIGINAL ARTICLE

Chloral Hydrate, Chloral Hydrate - Promethazine and Chloral Hydrate -Hydroxyzine Efficacy in Electroencephalography Sedation

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Abstract
Objective To compare efficacy and safety of chloral hydrate (CH), chloral hydrate and promethazine (CH + P) and chloral hydrate and hydroxyzine (CH + H) in electroencephalography (EEG) sedation.
Methods In a parallel single-blinded randomized clinical trial, ninety 1–7 y-old uncooperative kids who were referred to Pediatric Neurology Clinic of Shahid Sadoughi University, Yazd, Iran from April through August 2012, were randomly assigned to receive 40 mg/kg of chloral hydrate or 40 mg/kg of chloral hydrate and 1 mg/kg of promethazine or 40 mg/kg of chloral hydrate and 2 mg/kg of hydroxyzine. The primary endpoint was efficacy in sufficient sedation (obtaining four Ramsay sedation score) and successful completion of EEG. Secondary endpoint was clinical adverse events.
Results Thirty nine girls (43.3 %) and 51 boys (56.7 %) with mean age of 3.34±1.47 y were assessed. Sufficient sedation and completion of EEG were achieved in 70 % (N=21) of chloral hydrate group, in 83.3 % (N=25) of CH + H group and in 96.7 % (N=29) of CH + P group (p=0.02). Mild clinical adverse events including vomiting [16.7 % (N=5) in CH, 6.7 % (N=2) in CH + P, 6.7 % (N=2) in CH + H], agitation in 3.3 % of CH + P (N=1) group and mild transient hypotension in 3.3 % of CH + H (N=1) group occurred. Safety of these three sedation regimens was not statistically significant different (p=0.14).
Conclusions Combination of chloral hydrate—antihistamines can be used as the most effective and safe sedation regimen in drug induced sleep electroencephalography of kids.

Keywords Chloral hydrate · Promethazine · Hydroxyzine · Sedation · Electroencephalography

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Introduction

Up to 5 % of general population experiences one nonfebrile seizure during their lifetime and electroencephalography (EEG) is indicated in patients with first unprovoked seizure [1].

During EEG recording, the patient should be immobile and in almost no case, sedation is really necessary. But in not naturally sleeping, uncooperative children, sleep should be induced by sedation regimens [2].

Many sedative drugs have been used in children EEG sedation and the drugs must be of no or minimal effect on the background and epileptic discharges of the EEG [2–4]. Midazolam may induce scalp EEG signal changes and widespread augmentation of sigma-oscillations [5]. Dexmedetomidine sedation elicits the EEG pattern similar to Stage II of sleep with modest increases in theta, alpha, and beta activity and it has no effect on EEG epileptiform activity in children [6]. But, dexmedetomidine is expensive and hardly available in many developing countries such as Iran.

One of the most frequently administered sedative drugs in children is chloral hydrate (CH) that can be used in dosage of 40–100 mg/kg [7]. But, it has not been effective in some of the children, even in maximum dose and its long action duration

is concerning, airway obstruction and suppression of respiratory effort with intra and post procedural oxygen desaturation, consistency in sedation effects and its carcinogenicity potentiality, especially at high doses [7–9], and it may also be accompanied by post-discharge side effects in doses of 70–100 mg/kg [10].

Melatonin as a useful oral natural-sleep agent can modulate the circadian rhythm of sleep; it does not change the quality of recording EEG in epileptic children [11] and after chloral hydrate, melatonin is next commonly used drug for sedation for EEG.

Chloral hydrate in dosage of 40 mg/kg is safer and its combination with antihistamines might decrease chloral hydrate dosage [8, 12]. Combination of chloral hydrate and hydroxyzine has been used for sedation of children in dental procedures and it can decrease dosage need of chloral hydrate and also cause improvement in safer sleeping of the patient and decrease the risk of chloral hydrate related nausea and vomiting [12].

Promethazine is an inexpensive and easily feasible antiemetic and antisialagogue agent which nowadays is primarily used as a sedative agent [13, 14].

The aim of present research was to compare effectiveness and safety of chloral hydrate alone in the minimum dosage, combination of chloral hydrate - promethazine (CH + P) and combination of chloral hydrate - hydroxyzine (CH + H) in children electroencephalography sedation.

Material and Methods

A parallel single-blinded randomized clinical trial was conducted on children who were referred to electroencephalography room of Pediatric Neurology Clinic of Shahid Sadoughi University, Yazd, Iran from April through August 2012.

To determine a 20 % difference in efficacy between the three groups, with type one error (alpha) of 0.05 and 80 % power based on a study done in the past in authors' department [4], sample size was estimated as 30 children in each group.

Eligible participants included children aged 1–7 y, those who were guided to electroencephalography room for recoding of EEG and those who did not naturally sleep and were uncooperative with EEG device. These children were in class 1 (healthy persons) or 2 (a patient with mild systemic disorders: mild asthma, controlled diabetes mellitus, *etc.*) of American Society of Anesthesiology [15].

Those with gastritis, severe systemic disorders, serious systemic reaction, head trauma and taking a sedative drug within 2 d, were excluded.

Simple randomization of the study was computer generated by random numbers and allocation ratio was 1:1 for the three groups.

A researcher who was not involved in the trial, did the randomisation and blinding. Data gatherers, endpoint assessors and data analysts were all allocation blinded. But, patients and allocated EEG staff to the intervention group were aware of the allocated arm. A pharmacist prepared the drugs and the drugs were given in a suspension of 1 cc/kg. For sedative identification prevention, medicine bottles were coded; code was known only to the EEG staff unit.

EEG staff delivered the drug and primary and secondary endpoints were assessed by the study general physician that had no information of the sedation regimens group assignment.

Ninety consecutive children who were referred for EEG and were uncooperative with the EEG setup and required sedation were randomly assigned to three groups to receive chloral hydrate in dosage of 40 mg/kg (Group I) or 40 mg/kg of chloral hydrate and 1 mg/kg of promethazine (Group II) or 40 mg/kg of chloral hydrate and 2 mg/kg of hydroxyzine (Group III).

The drugs were given orally in the three groups and before the patients entered the electroencephalography room.

Heart rate, respiratory rate, blood pressure, and saturation of oxygen during 60 min after sedative drug administration, were monitored continuously and all vital signs were measured every 15 min by the general physician of research.

Obtaining four Ramsay sedation score [16] was considered as sufficient sedation.

The primary endpoint was efficacy in sufficient sedation and successful EEG recording. Secondary endpoints were clinical adverse events, severe side effects (hypotension, hypoxia and cyanosis, serious vomiting, refractory irritability and agitation, apnea, laryngospasm, and bradycardia), time from drug taking to sufficient sedation, caretakers' satisfaction on a Likert scale (5 for completely satisfied, 4 for satisfied, 3 for partially satisfied, 2 for partially unsatisfied and 1 for completely unsatisfied) and total stay time in the EEG room.

Assisted ventilation, Respiratory depression, oxygen saturation of less than 90 %, or a 25 % or greater decrease in before sedative drug taking mean arterial blood pressure, were thought of as severe adverse events.

Not achieving sufficient sedation (child awakened or moved, interfered with EEG recording, inadequate sedation and need for other sedative drugs) and procedure failure due to severe side effects, were considered as abortion of sedation regimen.

A pediatric neurologist assessed the developmental status of the children by Denver Developmental screening test-II [4].

The data were analyzed using SPSS: 17 statistical software. Recorded data were assessed for normal distribution using the Shapiro Wilk test and qualitative variables data analysis was done by Chi-square test. Comparison of mean values was done by ANOVA test and as a significant result was obtained, the Tukey test was applied for post hoc pair wise comparisons.

Kaplan–Meier survival analysis was used to calculate probability of adequate sedation during the observation period. *P* values of less than 0.05 were taken as statistically significant.

Informed consent was taken from patients' parents before administration of the drugs and the Ethics Committee of Ali-ebn-Abitaleb School of Medicine, Islamic Azad University, Yazd Branch, Yazd, Iran has approved this clinical trial.

The registration number of the research in clinical trials of Iran is IRCT201204262639N8. Meanwhile, the researchers got no support from the drugs company.

Results

Four hundred fifty six children underwent EEG during the study period and amongst them, 90 consecutive uncooperative children with EEG setup including 39 girls (43.3 %) and 51 boys (56.7 %) with age of 3.34±1.47 y were investigated. No losses to follow-up or exclusions were seen.

After application of Shapiro Wilk test, the data had normal distribution.

Table 1 presents comparison of characteristics of children in different groups and shows that mean of age and mean of weight, sex distribution, developmental status and age group of children were not statistically significantly different in the three groups.

Sufficient sedation and successful EEG recording were achieved in 21 children (70 %) in chloral hydrate (95 % confidence interval: 0.54–0.86), in 29 children (96.7 %) in chloral hydrate-promethazine (95 % CI: 0.9–1) and in 25 children (83.3 %) in chloral hydrate-hydroxyzine (95 % CI: 0.67–0.97) groups, respectively. Statistical analysis showed that combination of CH + P or CH + H was more effective than sole chloral hydrate in sedation induction (p value=0.02).

All the children who were not sedated required re-sedation with other sedation regimens.

Probability of being adequately sedated *vs.* time after taking the drugs by Kaplan–Meier plots is shown in Fig. 1 and indicates that Ramsay sedation score of four was obtained in all children who achieved adequate sedation 40 min after taking the drugs.

Abnormal epileptiform discharges on EEG were seen in 63.4 % (N=19) of chloral hydrate group, in 66.7 % (N=20) of CH + H group and in 56.7 % (N=17) of CH + P group (p value=0.7) and yield of epileptic discharge detection was not statistically different in the three groups.

The only drug effect on background rhythm of EEG was generalized fast beta activity followed by slow delta activity in temporal regions. The occurrence of fast background rhythm was not statistically different in three groups [12 children (40 %) in chloral hydrae group, 11 children (36.7 %) in CH + H group and 10 children (33.3 %) in CH + P group; p value=0.86].

Table 2 compares means of some variables and shows that CH + H group sooner obtained four Ramsay sedation score than CH + P and alone chloral hydrate groups. In groups of chloral hydrate and antihistamine combination (hydroxyzine or promethazine), as compared to sole chloral hydrate group, EEG recording completion was done in shorter time after the drug taking and the parents were more satisfied by waiting less in the EEG unit. The table shows that the effect of CH + H is more than CH + P. In CH + H group, Ramsay sedation score of four was sooner obtained, recording of EEG was completed in shortest time after taking the drug and the parents waited less in the EEG unit and were more satisfied.

None of children had autistic feature. But, 48 children in all three groups were mentally retarded and adequate sedation was achieved in 39 children (81 %). Comparison of success in EEG recording in three groups based on the developmental status is shown in Table 3 which indicates that efficacy of three sedation regimens was not significantly different in children with and without developmental delay.

No life-threatening and severe side effects were witnessed in the three groups.

Clinical side effects such as vomiting [16.7 % (N=5) in CH, 6.7 % (N=2) in CH + P, 6.7 % (N=2) in CH + H], agitation in 3.3 % of CH + P (N=1) group and mild transient

Table 1 Comparison of some characteristics of children in the three groups

Data		Chloral hydrate	Chloral hydrate and promethazine	Chloral hydrate and hydroxyzine	P value
Age in years (mean ± SD)[a]		3.29±1.64	3.63±1.41	3.11±1.36	0.4
Weight in kg (mean ± SD)[a]		13.01±4.01	13.38±3.01	12.43±3.33	0.5
Sex[b]	Female (%)	13 (43.3)	15 (50)	11 (36.6)	0.6
	Male (%)	17 (56.7)	15 (50)	19 (63.4)	
Developmental status[b]	Normal (%)	15 (50)	16 (53.3)	11 (36.6)	0.4
	Delay (%)	15 (50)	14 (46.7)	19 (63.4)	
Age group[b]	<2 y (%)	8 (26.7)	6 (20)	5 (16.7)	0.6
	≥2 y (%)	22 (73.3)	24 (80)	25 (83.3)	

[a] Statistical test used ANOVA

[b] Statistical test used Chi-square test

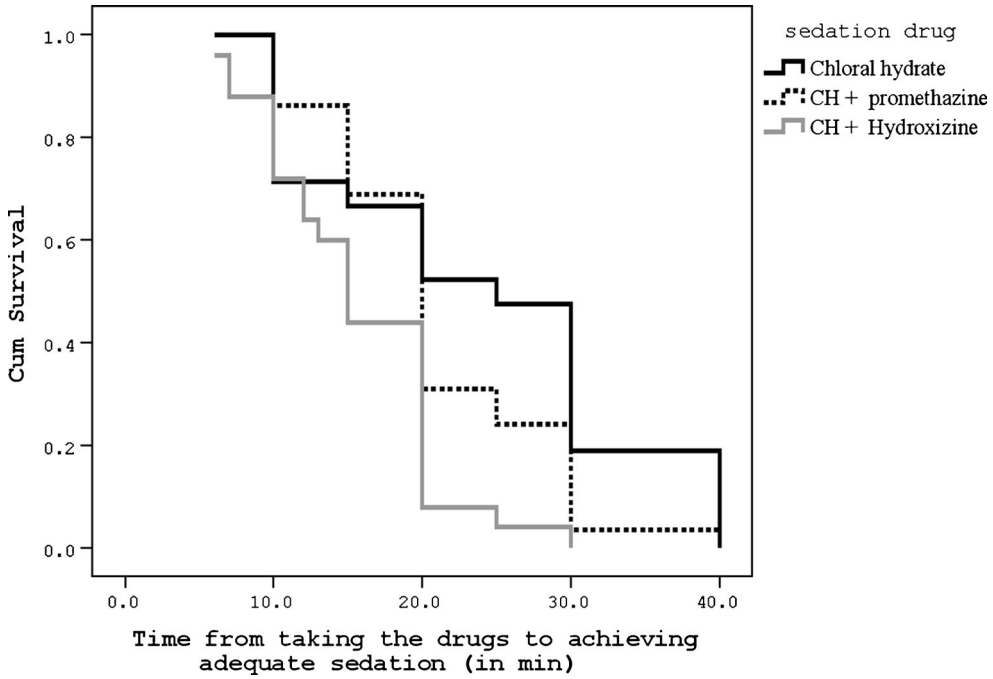

Fig. 1 Probability of being adequately sedated *vs.* time after taking of the drugs by Kaplan–Meier plots

hypotension in 3.3 % of CH + H ($N=1$) group were seen. Safety of these three sedation regimens was not different significantly ($p=0.14$).

Discussion

Many sedation regimens have been used for children sedation induction in different procedures. In this randomized clinical trial, adequate sedation and completion of EEG were achieved in 70 % of chloral hydrate group, in 83.3 % of chloral hydrate-hydroxyzine group and in 96.7 % of chloral hydrate-promethazine group and the result showed that a combination of 40 mg/kg chloral hydrate and antihistamines was more effective than sole chloral hydrate in sleep induction for EEG recording in children. On the other hand, yield of epileptic discharge detection and effect on EEG background were not different in these three sedation regimens which is in agreement to Britton et al. study, that yield of sleep-specific epileptic abnormalities detection was not statistically different

Table 2 Comparison of mean of some variables in the three groups

Groups / Data	Chloral hydrate	Chloral hydrate and promethazine	Chloral hydrate and hydroxyzine		P value
Acquired Ramsay sedation score	4.53±1.63	5.03±1.09	4.81±1.42		0.4
Time from drug taking to achieving adequate sedation (in min)	23.81±11.28	20.86±7.44	15.68±6.01	CH, CH + P	0.22
				CH, CH + H	0.001
				CH + P, CH + H	0.02
Time after taking the drug to completing EEG recording (in min)	39.05±13.84	32.93±8.91	27.76±7. 77	CH, CH + P	0.04
				CH, CH + H	0.001
				CH + P, CH + H	0.06
Caregiver's satisfaction scale	3.27±1.38	3.91±1.06	4.11±1.23	CH, CH + P	0.02
				CH, CH + H	0.01
				CH + P, CH + H	0.41
Total stay time in EEG unit (in min)	58.93±16.45	49.91±11.53	45.17±13.45	CH, CH + P	0.01
				CH, CH + H	0.001
				CH + P, CH + H	0.19

CH Chloral hydrate; *CH + P* Chloral hydrate and promethazine; *CH + H* Chloral hydrate and hydroxyzine

The statistical test used: ANOVA for comparing on mean values and Tukey test was applied for post hoc pair wise comparisons

Table 3 Comparison of success in EEG recording in both groups based on developmental status

Success in EEG recording			Yes	No	*P* value
Data					
Developmental status	Normal	Chloral hydrate (CH)	11	4	0.07
		CH and promethazine	15	1	
		CH and hydroxyzine	10	1	
	Delay	Chloral hydrate	10	5	0.23
		CH and promethazine	14	0	
		CH and hydroxyzine	15	4	

The statistical test used: Chi-square test

in patients receiving or not receiving chloral hydrate during routine EEG [17].

In an another study in from authors' department, successful completion of EEG was done in 96.7 % of children who received 70 mg/kg chloral hydrate [4].

In Ashrafi et al. study in Tehran, Iran, chloral hydrate in dosage of 50 mg/kg was effective in recording sleep EEG of 96.6 % children who aged 1 mo to 6 y. But, yield of epileptiform discharges in melatonin group was higher than in chloral hydrate group (53 % *vs.* 46 % and $P=0.005$) [3]. In another Ashrafi et al. study, yield of epileptic discharge detection in children who received 50 mg/kg chloral hydrate was higher than in oral midazolam group (87 % *vs.* 45 %, $P<0.001$) [18].

In Loewy et al. study, music therapy and chloral hydrate were equally effective for sleep inducing for EEG recording in children [19].

In Aksu et al. study, efficacy and safety of dexmedetomidine and midazolam for sedation in EEG recording of children with febrile seizure were evaluated. Dexmedetomidine group showed less change in EEG peak frequency and amplitude. But, hypoxia was more frequent in midazolam group [20].

In Mehta et al. study, adequate sedation and completion of EEG was achieved in 93 % (25 of 27) of children with autistic disorders who received clonidine which included five patients who had previously failed to be sedated with chloral hydrate [21].

In other studies, efficacy of drugs in sedation induction for dental procedures was evaluated. Torres-Pérez et al. study showed that 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 sole 2 mg/kg hydroxyzine in sedation induction for dental procedures [22] and in da Costa et al. study, 75 mg/kg of chloral hydrate alone and a combination of 50 mg/kg chloral hydrate and 2 mg/kg plus hydroxyzine were effective in pediatric dental sedation in 62.5 % and 61.5 %, respectively [12] and Wilson et al. study showed that, combination of chloral hydrate, meperidine, and hydroxyzine caused more remarkable quiet and sleeping behaviors than chloral hydrate- hydroxyzine or oral midazolam. Also, CH + H combination produced lower mean arterial pressure [23] and in a study in Mexico City, combination of 70 mg/kg chloral hydrate and 2 mg/kg hydroxyzine in comparison to sole 70 mg/kg chloral hydrate significantly caused decrease in crying and movement in 45–60 min after a rubber dam insertion [24].

In Roach et al. study, efficacy of chloral hydrate, combination of chloral hydrate and diphenhydramine, chloral hydrate - hydroxyzine hydrochloride combination and sole midazolam was compared in sedation induction for echocardiography. In chloral hydrate group, children fell asleep most quickly and chloral hydrate and diphenhydramine group experienced the most prolonged sedations [25].

Possible discrepancies justification are differences in age, dose of drug, race, sample size, procedure type, time of administration of the drug, usage as a premedication before anesthesia or sleep deprivation before drug use in some of the researches.

In the present study, the three sedation regimens were safe and not life-threatening and severe side effects were witnessed in the three groups. But, in Fávero et al. study, two of 41 children who received chloral hydrate in dosage of 50 mg/kg had respiratory depression [26] and in Heistein et al. study, severe adverse events such as apnea happened in 0.3 %, airway obstruction in 1.4 %, hypoxia in 5.9 %, hypercarbia in 6.6 % and hypotension in 0.4 % of kids who received chloral hydrate for echocardiography sedation [27].

In the present research, 16.7 % of kids had vomiting. However, vomiting occurred in 0.4 % of kids in a research in Texas [27], 10 % in a study in Yazd, Iran [28], 11.4 % in Greek research [29] and 30 % in a research in Turkey [30].

In the present study, obtaining sleep in majority of children who were adequately sedated with the three sedation regimens appeared up to 30 min after the administration of the drugs. Therefore, administration of these sedative drugs 30 min before the procedure, may be more effective.

The limitations of the present study are its small sample size and short duration of follow up. So, it is recommended that other studies be done with larger sample sizes, longer follow up duration and the lowest effective dosages of antihistamines.

In conclusion, based on findings of the present research, a combination of chloral hydrate in the lowest dose and

antihistamines is safer and more effective in children EEG sedation. But, the drugs should be administered 30 min before the procedure.

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Contributions RF: Writing the manuscript; AA and AS: Gathering the data; SAK: Editing the manuscript. RF will act as guarantor for this paper.

Conflict of Interest None.

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