*Original Article*

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# Efficacy of Chloral Hydrate and Promethazine for Sedation during Electroencephalography in Children; a Randomised Clinical Trial

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## Abstract

***Objective:*** The purpose of this study was to compare efficacy and safety of oral chloral hydrate (CH) and promethazine (PZ) for sedation during electroencephalography (EEG) in children.

***Methods:*** In a parallel single-blinded randomized clinical trial, sixty 1-10 year old children referred to EEG Unit of Shahid Sadoughi Hospital from January 2010 to February 2011 in Yazd, Iran, were evaluated. They were randomized to receive orally 70 mg/kg chloral hydrate or promethazine 1 mg/kg. The primary outcome was efficacy in adequate sedation and successful recording of EEG. Secondary outcome included clinical side effects, time from administration of the drug to adequate sedation, caregiver's satisfaction on a Likert scale, and total stay time in EEG Unit.

***Findings:*** Twenty four cases with mean age 2.9±1.9 years were evaluated. Adequate sedation (Ramsay sedation score of four) was obtained in 43.3% of PZ and 100% of CH group ($P$=0.00001). Also in 70% of PZ and 96.7% of CH group, EEG was successfully recorded ($P$=0.006). So, CH was a more effective drug. In CH group, EEG was performed in shorter time after taking the drug (32.82±9.6 vs 52.14±22.88 minutes, $P$<0.001) and the parents waited less in the EEG unit (1.29±0.54 vs 2.6±0.59 hours, $P$<0.001). They were also more satisfied (4.6±0.6 scores vs 3.1±1.4 scores, $P$=0.001). Mild side effects such as vomiting in 20% of CH (n=6) and agitation in 6.6% of PZ group (n=2) were seen. No significant difference was seen from viewpoint of side effects frequency between the two drugs.

***Conclusion:*** The results of the present study showed that chloral hydrate can be considered as a safe and more effective drug in sedation induction for sleep EEG in children.

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***Key Words:*** Chloral hydrate; Promethazine; EEG; Sedation

## Introduction

Seizure is one of the most common problems in pediatric neurology which occurs in 4-10 percent of children in the first 16 years of life. A detailed and reliable account of the event by an eyewitness is the most important part of the diagnostic evaluation, but it may not often be available. Electroencephalography (EEG) is recommended in evaluation of a child with first seizure presentation and it is a useful diagnostic tool in diagnosis of seizure and differentiating it from seizure-like attacks[1].

EEG needs cooperation and immobility of the patient and in all children, apart from the age, recording in natural sleep is preferred to drug-

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induced one. But, in children who do not naturally sleep, pharmacological agents and procedural sedation should be used to induce it[2].

Different sedation regimens may be used in children for sedation induction. Chloral hydrate is a non-opiate, non-benzodiazepines sedative-hypnotic drug which has been used for pediatric sedation induction in dosage of 40-100 mg/kg for years[3-6]. But, there are concerns about its long action duration, obstruction of airway and depression in respiration, desaturation of oxygen, sedative effects consistency and its potential for carcinogenicity[7]. Promethazine is a cheap and easily available antiemetic agent which can be used for sedation induction as an old sedative agent[8,90].

There has been no randomized trial to compare these two agents in drug-induced sleep EEG. So, the purpose of this study was to compare efficacy and safety of oral chloralhydrate (CH) and promethazine (PZ) in sedation induction for sleep EEG of children in Yazd, a central city in IR Iran.

## *Subjects and Methods*

We followed a randomized single-blind study on sixty referred children to EEG Unit of Shahid Sadoughi Hospital from January 2010 to February 2011.

Thirty children were required in clinical, open-label, parallel group study conducted on each group to detect a 20% difference in efficacy between the two drugs with type one error (alpha) of 0.05 and 80% power. Eligible participants included children aged 1-10 years, referred to EEG Unit by a pediatric neurologist based on standard indications after a clinical assessment which was indicative of seizure or unclear spells or seizure-like events, didn't sleep naturally, and were classified as American Society of Anesthesiology (ASA) class 1 (a normally healthy patient) or 2 (a patient with mild systemic disease: mild asthma, controlled diabetes mellitus)[10]. Exclusion criteria consisted of presence of gastritis or any other serious systemic diseases, severe systemic reaction and receiving a sedative or hypnotic agent within the past 48 hours.

The trial used computer generated equal randomization and allocation ratio was 1:1 for the two groups. Randomisation was done by a computer generated random number list and blinding was done by employing an investigator with no clinical involvement in the trial. Data collectors, outcome assessors and data analysts were all kept blinded to the allocation but the interventionists (EEG staff). The trial adhered to established procedures to maintain separation between person who took outcome assessment and staff that delivered the intervention. The drug was delivered by EEG staff and primary and secondary outcomes were assessed by the resident of research who was not informed of the drug group assignment. Investigators, staff and participants were all kept masked to outcome measurements and trial results.

The children were randomized to receive either single dose of 70 mg/kg chloral hydrate which was diluted in water (Group I) or 1 mg/kg of promethazine dissolved in water (Group II). In both groups, the drugs were administered orally and before entering electroencephalography room. The sedation level was observed and recorded every 10 min. After the child was adequately sedated, EEG was recorded.

Ramsay sedation scale was used for assessment of sedation level[11]. If the child was not sedated after 30 minutes of drug ingestion, the second dose of the drug, in half of the first one, was administered. Heart rate, blood pressure and respiratory rate were measured before and every 15 minutes after two hours of drug taking. Pulse oximetry was also done before and within two hours after the drug was taken. A Ramsay score of four was considered as adequately sedated.

The primary outcome was efficacy in adequate sedation and successful recording of EEG. Secondary outcome included clinical side effects, serious adverse events (respiratory depression requiring assisted ventilation, cyanosis, hypoxia (oxygen saturation of less than 90%), hypotension or 25% or greater decrease in pre sedation mean arterial blood pressure, severe vomiting, intractable irritability and agitation, apnea, laryngospasm, bradycardia, time from administration of the drug to adequate sedation, caregiver's 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 EEG unit.

Any kind of clinical side effects were evaluated either by parents' report or by physical examination within two hours after taking the drugs. Failure to achieve adequate sedation (patient awakened or moved, interfered with completion of EEG, inadequate sedation and need to administration of other sedative drug) 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.

The data was analyzed using SPSS 15 statistical software. Chi-square test or Fisher exact test was used for data analysis of qualitative variables and mean values were compared using independent t-test. Differences were considered significant at *P* values of less than 0.05.

Informed consent was taken from the parents. The study has been approved by the ethic committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. The design and conduct of this trial was straightforward, and we did not have any exclusions or losses during follow-up.

## *Findings*

Twenty four girls (40%) and 36 boys (60%) with mean age of 2.9±1.9 years were evaluated. Comparison of demographic characteristics of the children is shown in Table 1 which indicates that no statistically significant differences were seen from view point of sex distribution, developmental status, mean age and mean weight of children in both groups.

With the first dose of the drugs, adequate sedation (Ramsay sedation score of four) was obtained in 13 (43.3 %) children in promethazine and in all of 30 (100%) children in CH group. Statistical analysis showed that chloral hydrate was a more effective drug in obtaining Ramsay sedation score of four (*P*<0.001). In promethazine group, second dose of drug was used in 17 children, in eight of whom a Ramsay sedation score of four was achieved.

EEG after adequate sedation was successfully recorded in 70% of PZ group (95% confidence interval of 0.53-0.86) and in 96.7% of CH group (95% confidence interval of 0.91-1.18) and statistical analysis showed that CH was a more effective drug in induction of sleep for recording of electroencephalography (*P*=0.006).

Table 2 shows comparison of mean values of some variables and indicates that in CH group higher Ramsay score was obtained following the first dose of the drug, the Ramsay sedation score four was obtained sooner, EEG was performed in shorter time after taking the drug and the parents waited less in the EEG unit and were more satisfied.

Mild side effects such as vomiting in 20% (n=6) of CH and agitation in 6.6% (n=2) of promethazine group were seen. No statistically significant differences were seen from viewpoint of safety between the two drugs (*P*=0.1). No serious adverse events (apnea and respiratory depression that needed ventilator support, hypotension, etc) were seen in these two groups.

## *Discussion*

Various drugs have been used for procedural sedation in children. In present study, efficacy and safety of oral chloral hydrate and promethazine in sedation induction for sleep EEG of children were compared.

**Table 1:** Comparison of demographic characteristics of children in both groups

| Data | | Chloral hydrate | Promethazine | *P*-value |
|---|---|---|---|---|
| **Sex** | Female | 12 | 13 | 0. 9 |
| | Male | 18 | 17 | |
| **Developmental status** | Normal | 20 | 19 | 0. 8 |
| | Delay | 10 | 11 | |
| **Weight in kg [mean (SD)]** | | 12/6 (6/1) | 10/9 (3/21) | 0.2 |
| **Age in year [mean (SD)]** | | 2.8 (2.2) | 2.4 (1.6) | 0.4 |

**Table 2:** Comparison of mean of some variables in two groups

| Data | Chloral hydrate Mean (SD) | Promethazine Mean (SD) | *P*-value |
|---|---|---|---|
| **Acquired Ramsay scale with first dose of drug** | 4.4 (0.5) | 2.87 (1.4) | <0.001 |
| **Time from drug administration to adequately sedated (in minutes)** | 21.73 (7.24) | 33.84 (16.26) | 0.02 |
| **Time after taking the drug to record EEG (in minutes)** | 32.82 (9.6) | 52.14 (22.88) | 0.001 |
| **Caregiver's satisfaction scale** | 4.6 (0.6) | 3.1 (14) | 0.001 |
| **Stay time in EEG unit (in hours)** | 1.29 (0.54) | 2.6 (0.59) | <0.001 |

SD: Standard Deviation

Results of present study indicated that chloral hydrate was an effective drug for providing sedation in uncooperative children which is in agreement with other studies[4,12,13].

In this study, Ramsay score of four was achieved with 70 mg/kg chloral hydrate, in all of 30 children in 96.7% of whom electroencephalography recording was done successfully and success rate in doing the procedure was similar to other studies[4,14,15]. However, the lowest success rate of chloral hydrate in sedation induction was 56% in Fávero et al study[16] and in other studies this rate varied between 62.5% and 100%[3,15,17-19]. Possible explanation for these discrepancies is differences in dosage of the drug, race, sample size, type of procedure, medical condition of patients, etc.

In present study, no serious clinical adverse event was seen in the two groups. But, in Fávero et al study, respiratory complications occurred in two of 41 children who got 50 mg/kg of chloral hydrate[16] and in Heistein et al study in Texas, serious side effects occurred as apnea in 0.3%, airway obstruction in 1.4%, hypoxia in 5.9%, hypercarbia in 6.6% and hypotension in 0.4% of 1095 children who were sedated with chloral hydrate for echocardiography[20].

In this study, the only adverse effect of chloral hydrate was vomiting that occurred in 20% of children. In Ronchera-Oms et al study in Spain, 9.9% of 596 children who were sedated with chloral hydrate to undergo magnetic resonance imaging, faced side effects; the most common (1%) adverse effects were nausea, vomiting (6.9%), nervousness and unusual excitement[21].

In Heistein et al study, 10.8% showed adverse events most common of which were hypercarbia (6.6%) and hypoxia (5.9%)[20] and minor complications occurred in 7.4% of pre-school children in Roach et al study [4]. In the present study, vomiting occurred in 20% of children who were sedated by chloral hydrate, while 0.4 percent of children in Texas study[20] and 30% in Turkish study, had vomiting[16].

In our study, electroencephalography recording was done successfully in 43.3% of children who were sedated by 1 mg/kg oral promethazine. Padmanabhan et al in India, found that combination of promethazine plus tramadol was more effective than promethazine plus ketamine in sedation of uncooperative children for dental treatment (69% vs 42%, $P<0.001$)[22].

In present study, agitation as the only side effect of promethazine occurred in 6.6% of children. Adenipekun et al compared complications of parenteral and/or oral promethazine, diazepam, chlorpromazine and paraldehyde in children sedation induction during radiotherapy, and found that complications occurred in 48% of children and the most common side effect was injection cellulitis in 85.3%[23].

In a randomized double-blind crossover study in Michigan, children who received 0.2 mg/kg intranasal midazolam had less decrease in systolic and diastolic blood pressure and slept less and recovered faster as compared to those who got 62.5 mg/kg CH with 12.5 mg promethazine[24]. However, promethazine may be increased in EEG power spectra of the delta and theta bands at the frontal cortex in rats[25], but, EEG characteristic of children was not evaluated in present study.

The limitations of this study were its small sample size and short duration of follow up. Therefore, it is suggested that further studies be conducted with larger sample size, longer follow up periods and different dosages of chloral hydrate.

## Conclusion

The results of present study showed that chloral hydrate was more effective and less time consuming in EEG unit. Therefore, chloral hydrate can be considered as a safe, cheap and effective drug in sedation induction for electroencephalography and may be used in other procedures (echocardiography, CT scan, MRI, bone marrow aspiration, lumbar puncture) in children.

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***Conflict of Interest:*** There was conflict of interest or none of the drugs.

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