

Clonidine Versus Chloral Hydrate for Recording Sleep EEG in Children

How to Cite This Article: Ashrafi MR¹, Mohebhi H, Mohamadi M, Azizi E, Zamani GR, Tavasoli A, Badv RS, Hosseini F². Clonidine Versus Chloral Hydrate for Recording Sleep EEG in Children. *Iran J Child Neurol*. Winter 2020;14(1): 85-92

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Received: 12-Apr-018

Last Revised: 11-Oct-2018

Accepted: 26-Nov-2018

Abstract

Objective

One of the difficulties to conduct electroencephalography (EEG) in pediatric patient population is that they are not always cooperative during the procedure. Different medications are used to induce sedation during EEG recording. In order to find a medication with the least adverse effects and high efficacy; the current study aimed at comparing clonidine and chloral hydrate as a premedication prior to EEG recording in pediatric population.

Materials & Methods

A prospective, randomized, single-blinded, controlled trial was conducted on 198 children (9 to 156 months old) to investigate the sedative and adverse effects of clonidine and chloral hydrate. Patients, partially sleep-deprived the night before, were randomly divided into two groups of clonidine (n=100) and chloral hydrate (n=98) on an alternative day basis.

Results

The average sleep onset latency was significantly longer in the clonidine group than chloral hydrate group (the Mann-Whitney test, $p < 0.0001$). Sleep duration ranged 15 to 150 minutes and it was not significantly different between the two groups (the Mann-Whitney test, $p = 0.2$). Drowsiness terminated faster with chloral hydrate than clonidine.

Drowsiness after arousal was observed in 58% and 26.1% of patients in the clonidine and chloral hydrate groups, respectively; the difference between the groups was significant (the Mann-Whitney test, $p = 0.058$). EEG results were reported normal in 77 subjects in the chloral hydrate group (77%) and 69 subjects (69%) in the clonidine group ($p = 0.161$). Generalized epileptiform discharges were significant in the clonidine group (the Mann-Whitney test, $p = 0.006$).

Conclusion

The results of the current study showed that both 5% chloral hydrate (1 mL/kg) and clonidine (4 µg/kg) could be administered as a premedication prior to EEG recording in children, although drowsiness after arousal was higher with clonidine than chloral hydrate. However, the yield of generalized epileptiform discharges in the clonidine group was greater than that of the chloral hydrate group.

Keywords: Premedication, Chloral Hydrate, Clonidine, Electroencephalography, Sedation, Sleep

Introduction

One of the difficulties to conduct electroencephalography (EEG) in pediatric population is that they are not always cooperative during the procedure. It is generally agreed that most children undergoing medical procedures get frightened and uncooperative, and should be managed with behavioral and non-pharmacologic techniques. Unfortunately, a small percentage of pediatric patients cannot be successfully managed solely with such techniques (1). Several sedative-hypnotic agents can be used in children for medical procedures including benzodiazepines, ketamine, hydroxyzine, melatonin, clonidine, chloral hydrate, sufentanil, dexmedetomidine, etc. Clonidine, an α -2 agonist, is suggested as an alternative agent for sleep induction in children. Mikawa et al. (1993), (2) concluded in a review study that clonidine, administered via oral, rectal, or caudal route is a promising adjunct to anesthetics and analgesics to enhance the quality of perioperative care in infants and children. Later publications also support the utilization of clonidine as premedication (3).

Chloral hydrate has some known adverse effects such as nausea, vomiting, agitation, ataxia, prolonged sedation, delayed apnea events,

gastric irritation, potential carcinogenicity, and genotoxicity even as a single low-dose (4–6).

A number of previous studies compared sedative and adverse effects of some premedication such as midazolam, melatonin and chloral hydrate, but there is still a lack of studies on comparing clonidine with chloral hydrate. The current prospective, randomized, single-blinded, controlled trial aimed at comparing the sedative and adverse effects of clonidine and chloral hydrate.

Materials & Methods

The protocol of the current prospective study was approved by the Ethics Committee of Tehran University of Medical Sciences. Written and oral informed consent was obtained from parents prior to inclusion in the study. The current study was conducted over one year at a major pediatric university hospital in Tehran, Iran. The enrolled subjects were children within the age range of 9 to 156 months scheduled for EEG recording in the center. The study had a randomized, single-blinded design; patients were randomly allocated to one of the two premedication options of oral clonidine or chloral hydrate.

The following data were obtained: age, gender, weight, EEG indication, underlying medical

conditions, and medication history. Information concerning clonidine and chloral hydrate included the dose, sleep onset time, sleep duration, time to arousal, efficacy, side effects, and complications. A trained staff filled out a questionnaire for each patient to collect the following data: neurological diagnosis, sleep onset latency, sleep duration, drowsiness time, and adverse events that occurred within the first four hours after EEG recording.

The administered doses of clonidine and 5% chloral hydrate were 4 µg/kg and 1 mL/kg, respectively. Premedication was administered 30 minutes prior to EEG recording. An analog 21-channel Nihon Kohden EEG machine based on the standard international 10-20 system was used. Two trained and skilled pediatric neurologists interpreted recorded EEGs.

Patients who were thermodynamically unstable or had severe respiratory failure, patients with severe failure to thrive, infants younger than six months of age, the ones with a history of hypersensitivity to either clonidine or chloral hydrate, and those that their parents refused to provide consent were excluded.

Statistical Analysis

Based on the literature, the required study sample size was 100 in each group ($\alpha= 0.05$, $\beta= 0.2$). Data were analyzed for normal distribution using the Shapiro-Wilk test. Statistical analysis was performed using independent samples t-test and the Mann-Whitney-Wilcoxon test for continuous data. Categorical variables were analyzed using the Fisher exact and Chi-squared tests. A P-value of <0.05 was considered significant. A biostatistician blinded to the study groups performed the statistical analysis.

Results

Totally, 198 pediatric patients were enrolled in the study; 81 females (40.7%) and 117 males (58.8%). The patients' age ranged 9 to 156 months (mean \pm standard deviation (SD): 42.11 \pm 42.64 months). The two groups were matched for gender. The clonidine group consisted of 58 (49.6%) males and 42 (51.9%) females and the chloral hydrate group consisted of 59 (50.4%) males and 39 (48.1%) females ($p = 0.75$). The mean age of the subjects in the clonidine group was higher than that of the ones in the chloral hydrate group (57.4 \pm 30.5 vs. 27 \pm 21.8 months); the difference between the groups was significant ($p >0.0005$).

EEG indications

Top indication for referral for EEG in both groups was seizure disorders (84 (54.9%) subjects in the chloral hydrate and 76 (45.1%) patients in the clonidine groups); however, and the frequency of this etiology was not significantly different between the groups ($p=0.116$). Other indications were attention deficit hyperactivity disorder (ADHD) (2.5%), sleep disorders (0.5%), speech disorders (0.5%), and miscellaneous (11%). ADHD, as an indication for EEG, was observed only in the clonidine group (12 children vs. zero children) ($p <0.001$), but other etiologies were evenly distributed amongst subjects of both groups ($p=0.05$).

Efficacy of premedication

The time gap between premedication and the start of sleep (sleep onset latency) varied from 9 to 190 minutes in the studied subjects. The average sleep onset latency in the clonidine group was significantly longer than that of the chloral hydrate group (86 minutes and 17 seconds vs. 48 minutes and 48 seconds) ($p <0.0001$).

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Sleep duration in total subjects ranged 15 to 150 minutes and there was no significant difference between the two medications (74 minutes and 12 seconds for clonidine vs. 68 minutes and 8 seconds for chloral hydrate) ($p = 0.2$).

For patients medicated with clonidine, it took longer to be wide awake (drowsiness time: 26 minutes and 13 seconds for the chloral hydrate group vs. 32 minutes and 21 seconds for the clonidine group) ($p < 0.0001$). Sleep characteristics of the two groups are provided in Figure 1.

Premedication adverse effects

Unusual drowsiness occurred in 58 (58%) patients medicated with clonidine, while it was observed in 26 (26.1%) patients in the chloral hydrate group ($p = 0.058$). The only other adverse effect was vertigo, occurred in only 3% of patients medicated with clonidine. Other side effects such as nausea, vomiting, or agitation were not observed.

EEG interpretation

Recorded EEGs were twice interpreted by two trained and skilled pediatric neurologists. The EEG interpretations were similar in 70% of the cases. EEG results were reported normal in 77 subjects (77%) in the chloral hydrate group and 69 subjects (69%) in the clonidine group ($p = 0.161$). Focal epileptiform discharge and multifocal epileptiform discharge were not significantly different between the two groups ($p = 0.74$ and 0.2 , respectively). The reports on the focal background disturbance, diffuse background disturbance, and fast activity in the two groups were not significantly different ($p = 0.1, 0.15, \text{ and } 0.15$, respectively). Generalized epileptiform discharge was reported in 14 subjects in the clonidine group and three subjects in the chloral group ($p = 0.006$).

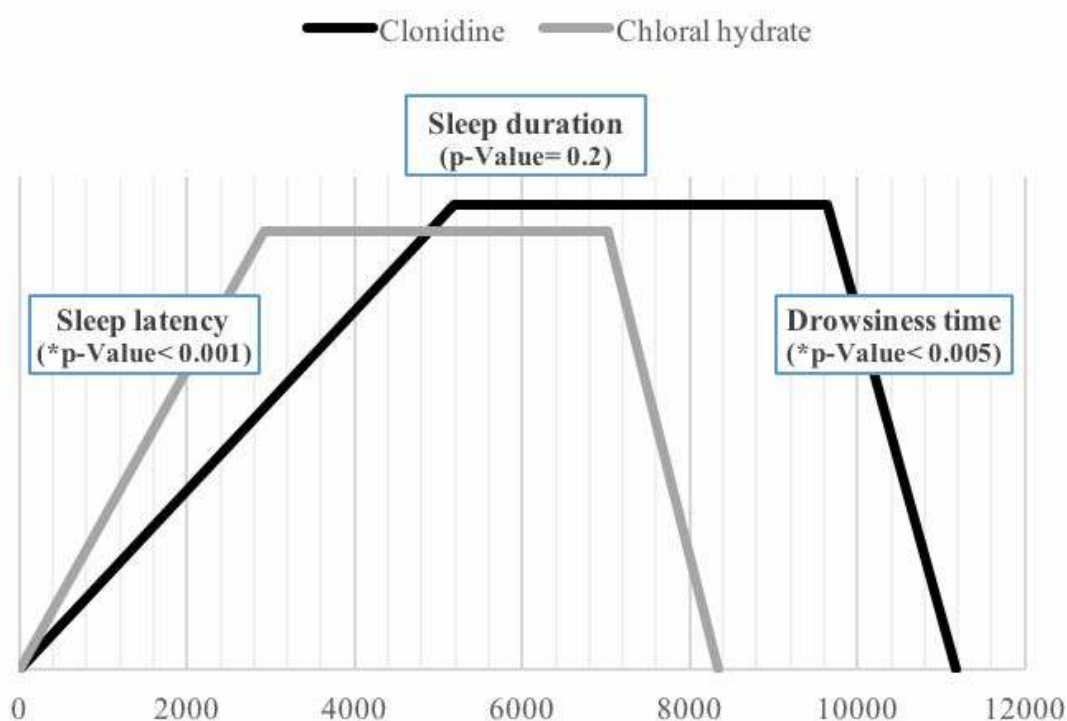


Figure 1: Sleep Characteristics in the Chloral Hydrate and Clonidine Groups

Discussion

Children undergoing EEG may experience significant anxiety and distress during the procedure, but the question whether routine premedication for children prior to EEG is necessary or not is currently under debate. Hatava and Olsson showed that pre-operative psychological preparation and the presence of parents were beneficial and could reduce the need for pharmacological premedication (7). However, sedative premedication with midazolam was more effective than either parental presence or no intervention at all to manage child/parent anxiety during the pre-operative period (8,9). According to these facts, researchers are looking for the best medication to induce sleep during EEG in children. An ideal medication for this goal should have rapid onset, long-acting sedative effect, low side effects, and the minimum impact on the EEG background (8). Benzodiazepines are drugs most widely used as premedication in pediatric anesthesia, and midazolam is at the top of the list of benzodiazepines used for induction of sedation in children (10). Midazolam, when used as the premedication in children, has a number of beneficial effects such as effective sedation, rapid onset, short acting, lower rate of vomiting, and less amnesia after sedation (11–13); although some paradoxical reactions such as agitation (14,15) and hypotonia (8) are observed following the utilization of midazolam in children. Some studies were also performed to compare chloral hydrate and midazolam, chloral hydrate, and melatonin as premedication in children. Recently, clonidine is suggested by anesthesiologists for the induction of sedation before anesthesia. A study investigated the application of clonidine as a pre-anesthetic agent in the children undergoing surgery and indicated that

oral clonidine was an effective premedication with few side effects (16). However, the current study suggests that further studies should be conducted to determine the optimal dosage and the safety of this drug in children. To the best of authors' knowledge, no studies compared clonidine and chloral hydrate for pediatric premedication, especially in children undergoing EEG.

This study designed for the clinical advantages and disadvantages of oral clonidine in comparison with chloral hydrate as premedication prior to EEG recording in children.

Several studies on premedication in the pediatric population showed that clonidine had slow onset of action (16,17,18). The current study finding on the clonidine onset of action was in agreement with those of the previous studies. Chloral hydrate induced sleep in the current study subjects faster than clonidine, although the sleep durations were similar in the two groups. The subjects medicated with clonidine had longer drowsiness period on average after the procedure compared to the ones medicated with chloral hydrate. The time of maintaining sedation with clonidine is long enough, which makes this drug a more suitable choice for premedication prior to EEG recording in pediatric patients. Other adverse effects such as nausea, vomiting, or seizure were not observed in any of the groups. In the current study, no agitation or hypotonia was reported, similar to what was observed with midazolam previously.

In the current study, there was no significant difference in gender distribution between the two groups, although the mean age of the subjects in the clonidine group was higher.

One important factor as premedication agent in EEG recording is its impact on EEG interpretation. According to EEG results, normal EEG was

observed in 77% of the subjects in the chloral hydrate group versus 69% in the clonidine group, which the difference between the groups was not significant ($p = 0.16$). Other EEG findings such as focal epileptiform discharge, multifocal epileptiform discharge, focal background disturbance, multifocal background disturbance, generalized background disturbance, and rapid activity were not significantly different between the two groups. The only exception was generalized epileptiform discharge, which was significantly higher among the clonidine-medicated subjects and this meant a higher diagnostic yield of clonidine group. Clonidine also had no impacts on the background of EEG, unlike midazolam with rapid EEG activity and melatonin with generalized rapid beta activity followed by slow delta activity in temporal regions.

There were no significant differences in the indications of EEG between the two groups except for patients with ADHD, which the EEG technicians tended to administer clonidine to such cases.

Chloral hydrate induced sleep faster than clonidine, but the sleep duration was similar for subjects in the two groups. The subjects medicated with clonidine had longer drowsiness time on average compared to the ones medicated with chloral hydrate.

Longer drowsiness time in clonidine group was the only difference between drug adverse effects in two groups. Other drug adverse effects such as nausea, vomiting, agitation, or seizure were not observed in both groups. Agitation and hypotonia that was reported in previous midazolam study was not seen in this study (16). Additionally, no respiratory failure or hypoxia was observed using these drugs, although infants younger than six months of age were excluded from the study.

In Conclusion, Results of the current study showed that both 5% chloral hydrate (1 mL/kg) and clonidine (4 μ g/kg) can be administered as a sedative agent prior to EEG recording in children. Clonidine with a high efficacy in inducing and maintaining sleep during EEG recording and minimal adverse effects can be one of the ideal choices for premedication prior to EEG recording in pediatric patients. The yield of generalized epileptiform discharges in the clonidine group was greater than that of the chloral hydrate group, with little confusing effects on EEG interpretation.

Acknowledgement

The authors are grateful to all parents and patients for their participation in this study. We also thank the staff of the Electrodiagnostic Department of Children's Medical Center, Parasto Saeedi and Mitra Zamani for their cooperation in the EEG recordings and data collection. The trial was funded by the Research Deputy of Tehran University of Medical Sciences (grant number: 89-04-80-1409), who had no role in study design, data collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

This study was approved by Ethical Code number: (IRCT201106286907N1) from Tehran University of Medical Sciences.

Author Contribution

Mahmoud Reza Ashrafi was responsible for the study design and interpretation of clinical data. Gholam Reza Zamani, Mahmoud Mohamadi, Firozeh Hosseini supervised the study, revised and edited the manuscript. Hossein Mohebbi, Alireza Tavasoli, Reza Shervin Badve,

collected the data and wrote the first draft of this manuscript. Elham Azizi was responsible for data analysis. After revision of final draft, all authors agreed to submit revision of final version of the article

Conflict of Interest

The authors declare that there is no conflict of interest

References

1. Lansky LL. An Unusual Case of Childhood Chloral Hydrate Poisoning. *Arch Pediatr Adolesc Med* [Internet]. 1974 Feb 1 [cited 2017 Apr 17]; 127(2):275. archpedi.1974.02110210125019
2. Mikawa K, Maekawa N, Nishina K, Takao Y, Yaku H, Obara H. Efficacy of oral clonidine premedication in children. *Anesthesiology* [Internet]. 1993 Nov [cited 2017 Apr 17];79(5):926–31. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8239010>
3. Almenrader N, Passariello M, Coccettib, Haiberger R, Pietropaoli P. Premedication in children: a comparison of oral midazolam and oral clonidine. *Pediatr Anesth* [Internet]. 2007 Dec [cited 2017 Apr 17];17(12):1143–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/17986032>
4. Pershad J, Palmisano P, Nichols M. Chloral hydrate: the good and the bad. *Pediatr Emerg Care* [Internet]. 1999 Dec [cited 2017 Feb 15];15(6):432–5. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10608336>
5. D'Agostino J, Terndrup TE. Chloral hydrate versus midazolam for sedation of children for neuroimaging: a randomized clinical trial. *Pediatr Emerg Care* [Internet]. 2000 Feb [cited 2017 Feb 15];16(1):1–4. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/10698133>
6. Sezer T, Alehan F. Chloral hydrate versus hydroxyzine HCL for sedation prior to pediatric sleep EEG recording. *Int J Neurosci* [Internet]. 2013 Oct 7 [cited 2017 Feb 15];123(10):719–23. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/23594140>
7. Hatava P, Olsson GL, Lagerkranser M. Preoperative psychological preparation for children undergoing ENT operations: a comparison of two methods. *Paediatr Anaesth* [Internet]. 2000 [cited 2017 Jun 13];10(5):477–86.
8. Hijazi OM, Ahmed AE, Anazi JA, Al-Hashemi HE, Al-Jeraisy MI. Chloral hydrate versus midazolam as sedative agents for diagnostic procedures in children. *Saudi Med J* [Internet]. 2014 Feb [cited 2017 Jun 13];35(2):123–31. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24562510>
9. Layangool T, Sangtawesin C, Kirawittaya T, Prompan W, Attachoo A, Pechdamrongsakul A, et al. A comparison of oral chloral hydrate and sublingual midazolam sedation for echocardiogram in children. *J Med Assoc Thai* [Internet]. 2008 Oct [cited 2017 Jun 13];91 Suppl 3:S45-52. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/19255992>
10. Kain ZN, Caldwell-Andrews AA, Krivutza DM, Weinberg ME, Wang S-M, Gaal D. Trends in the Practice of Parental Presence During Induction of Anesthesia and the Use of Preoperative Sedative Premedication in the United States, 1995-2002: Results of a Follow-Up National Survey. *Anesth Analg* [Internet]. 2004 May [cited 2017 Apr 17];1252–9.
11. Kogan A, Katz J, Efrat R, Eidelman LA. Premedication with midazolam in young

- children: a comparison of four routes of administration. *Paediatr Anaesth* [Internet]. 2002 Oct [cited 2017 Apr 17];12(8):685–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12472704>
12. Splinter WM, MacNeill HB, Menard EA, Rhine EJ, Roberts DJ, Gould MH. Midazolam reduces vomiting after tonsillectomy in children. *Can J Anaesth* [Internet]. 1995 Mar [cited 2017 Apr 17];42(3):201–3. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7743569>
 13. Buffett-Jerrott SE, Stewart SH, Finley GA, Loughlan HL. Effects of benzodiazepines on explicit memory in a paediatric surgery setting. *Psychopharmacology (Berl)* [Internet]. 2003 Aug 1 [cited 2017 Apr 17];168(4):377–86. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/12845417>
 14. McGraw T, Kendrick A. Oral midazolam premedication and postoperative behaviour in children. *Paediatr Anaesth* [Internet]. 1998 [cited 2017 Apr 17];8(2):117–21. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/9549736>
 15. Golparvar M, Saghaei M, Sajedi P, Razavi SS. Paradoxical reaction following intravenous midazolam premedication in pediatric patients - a randomized placebo controlled trial of ketamine for rapid tranquilization. *Pediatr Anesth* [Internet]. 2004 Nov [cited 2017 Apr 17];14(11):924–30. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15500492>
 16. Mikawa K, Maekawa N, Nishina K, Takao Y, Yaku H, Obara H. Efficacy of oral clonidine premedication in children. *Anesthesiology* [Internet]. 1993 Nov [cited 2017 Apr 17];79(5):926–31. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/8239010>
 17. Fazi L, Jantzen EC, Rose JB, Kurth CD, Watcha MF. A comparison of oral clonidine and oral midazolam as preanesthetic medications in the pediatric tonsillectomy patient. *Anesth Analg* [Internet]. 2001 Jan [cited 2017 Jun 12];92(1):56–61. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11133600>
 18. McCann ME, Kain ZN. The management of preoperative anxiety in children: an update. *Anesth Analg* [Internet]. 2001 Jul [cited 2017 Jun 12];93(1):98–105. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11429348>