Comparison of Chloral Hydrate Nasal Spray With an Oral Solution for Sedation Before Electroencephalography in Children

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Research Article

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Abstract

Background The choice of route of drug administration is given depends not only on the compliance but also on the drug's pharmacokinetics pathway**.** In this study, the efficacy, and safety of nasal and oral administration of chloral hydrate in the pediatric ready for electroencephalography were evaluated.

Methods 143 infants who had to undergo EEG for the diagnosis of neurological disorders received chloral hydrate between January 2017 and December 2018. Chloral hydrate was administered nasally or orally to infants using doses of 50-100 mg/kg. Clinical parameters are being analyzed to measure the efficacy/safety of nasal spray Vs. oral administration was (a) Heart rate Pre-sedation, (b) Heart rate Post Sedation, (c) Hypoxemia, (d) Apnea), and (e) Oxygen Supplementation. Mean procedure time, mean recovery time, and total nursing times were calculated.

Results Oral chloral hydrate group showed a lower heart rate and also a significantly higher percentage of hypoxemia. Apnea was not statistically different between the groups. The mean procedure time for the nasal and oral solution was ranged from 10 to 15 and 15-25 min, respectively. The mean recovery time for the nasal and oral solution was 5-8 and 10-15 min, respectively.

Conclusion Chloral hydrate nasal spray is likely to be more safe and effective than oral in pediatric sedation.

What Is Known About This Subject?

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- Today, in some hospitals, oral chloral hydrate is used before diagnostic procedures to sedation.
- Oral chloral hydrate has a bitter taste and is unpleasant for children.
- The oral form of chloral hydrate often causes nausea and vomiting.

What this study adds

- The nasal spray of chloral hydrate showed a better dosage form for sedation in children than oral.
- Chloral hydrate nasal spray did not cause hypoxemia or apnea in children compared to oral.
- Recovery and procedure time in the chloral hydrate nasal spray were less than oral.

Introduction

Electroencephalography (EEG) is a useful method for evaluating the symptoms of seizures and pseudoseizures [1, 2], as well as helping to diagnose attention deficit hyperactivity disorders, developmental disorders, and autism spectrum disorders in children. Due to the poor cooperation of children to perform EEG, it is necessary to use sedatives before doing so [3, 4]. Motion and muscularity artifacts on EEG are

reduced by sedation, and also electrodes can be used without any anxiety and compulsion in children. Therefore, applying sedation before the EEG procedure is recommended [5, 6].

Chloral hydrate and midazolam have been found as good oral pre-medicants for anxiolysis in children undergoing surgery, however, chloral hydrate has an unpleasant taste [7]. Previously, to solve its taste problem, a stabilized form of chloral hydrate, called oral triclofos with better taste and fewer gastric irritants has been used [8, 9].

Despite the bitter taste of oral chloral hydrate, used during imaging studies of children, has marked side effects, such as unsteadiness, hyperactivity, poor appetite, and vomiting, drowsiness of more than four hours [10]. Also, The chloral hydrate before EEG recordings displayed a variety of pathology such as intermittent focal spike-wave activity [11]. Many randomized controlled trials have compared intranasal and oral drugs for procedural sedation [12].

Nasal spray advantages are absent drug effect on the gastrointestinal tract, hepatic first-pass metabolism, rapid drug absorption and quick onset of action, larger bioavailability [13]. Depending on the time and duration of the effect as well as the taste of the oral chloral hydrate, in this study, intranasal chloral hydrate and oral chloral hydrate have been compared in pediatric sedation before EEG recording.

Materials And Methods

Preparation of chloral hydrate oral solution and nasal spray

To prepare a 100 ml oral solution of chloral hydrate 5%, chloral hydrate (Merck, Germany) was dissolved in edetate disodium (Merck, Germany) (150 mg), sodium chloride (Merck, Germany) (556 mg), sodium metabisulfite (Merck, Germany) (100 mg), and distilled water (Merck, Germany) (100 mL). Every 10 ml of the solution contained 500 mg of chloral hydrate.

To prepare the nasal spray, five grams of chloral hydrate was dissolved in fifty ml of distilled water. In another beaker, disodium edetate (150 mg) in 30 ml of warm water dissolved. The solution was then allowed to cool and sodium metabisulfite (100 mg) and sodium chloride (556 mg) were added. Next, the two solutions were combined and brought to a volume of 100 ml with distilled water. There was 75 mg of chloral hydrate in each nasal spray (each puff). The color, weight, volume, pH, and specific gravity were examined for quality-control assessment. At the time of the project, the prepared drugs were stored at 2-8°C [14]. Excipients to be used in formulations for the oral and nasal selected with special care and GMP guidelines.

Patients and design

All patients were selected for the EEG preparation procedure at the pediatric neurology department of the Ilam University of medical sciences. The study was simple random sampling. A simple random sample is a randomly selected subset of a population. In this sampling method, each member of the population has

an exactly equal chance of being selected. Simple random sampling is used when the total population is accessible and the examiners have a list of all subjects in this target population [15]. Four children in the oral route and three children in the intranasal route were removed due to poor medical conditions and a change of location. Therefore, 65 patients were randomly selected for intranasal use and 78 for oral administration. This study was performed as double-blinded and prospective. Blinded participants underwent double-blinded testing using a method described previously [16]. Blinded oral and nasal chloral hydrate was prepared by a pharmacist and pediatric neurologist (professional 1&2) in random order. Testing was performed by a pediatric nurse (professional 3) who was blinded to reagent order. The children were continuously monitored by an allergist supervising the drug provocation (professional 4).

Parents of children were given full explanations before the study and they signed the informed consent. The ethical approval for this study was obtained from the Ilam University of medical science (IR.MEDILAM.REC.1397.54). In all pediatric patients from 6 months to 6 years old, sedative medication was used to perform EEG. During the study period, the technicians' team members remained the same. The study was performed according to the American Academy of Pediatrics (AAP) guidelines for sedation [17]. Chloral hydrate groups (oral and nasal) sedation were provided by the expert team including a pediatric nurse. Pediatric procedural sedation using chloral hydrate can be provided sedation method guidelines based on the previous study [18]. Physiologic parameters such as heart rate, respiratory rate, and oxygen saturation were continuously monitored. Noninvasive blood pressure was measured every 5 min throughout the procedure and every 15 min after its completion until the patient was fully awake. For the nasal (20 ml Nasal Spray Bottle) and oral chloral hydrate groups (10 mL syringes without needle), a dose of 50-100 mg/kg was used. Sedation started with 50 mg/kg of chloral hydrates (10 mL syringes without needle) and was followed by small subsequent doses (25 mg/kg) within 15 min intervals to a maximum dose of 100 mg if needed to achieve a moderate sedation level. Pediatric patients who were not sedated by chloral hydrate were treated with another drug but excluded in this study.

Procedure time (PT) was defined as the time between the first doses of sedation until the EEG was completed. Recovery time (RT) was defined as the interval between the completions of the procedure until the patient's level of consciousness returned to baseline. Nurse time (NT) was defined as the total time spent by the sedation nurse during the whole process starting from patient arrival to the sedation suite till discharge home [19].

Statistical analysis

Comparisons between the nasal and oral chloral hydrate groups were performed using Chi-square tests. The differences between treatments or groups were determined using t-tests. A p-value of < 0.05 was defined as statistically significant.

Results

There were no detectable changes between nasal and oral chloral hydrate in color (colorless), odor (slightly bitter), specific gravity (≥ 1.30 g/mL), and pH (5.9 ±0.8). The bioavailability of chloral hydrate (trichloro acetaldehyde hydrate) given amounted to 94.8–101.6% of that given as a solution. The 143 children patients that had to be electroencephalogram procedures were sedated by nasal and oral chloral hydrate during the years 2017 and 2018 and demographics are summarized in Table 1. The nasal chloral hydrate group's patients were older and weightier than the oral. Patients in the oral chloral hydrate group had a lower heart rate at procedure completion and also had a significantly higher percentage of transient hypoxemia and patients receiving supplemental oxygen. However, apnea was not statistically different between the groups (Table 2). Hypoxemia, Oxygen supplementation 12% (10 patients), and apnea 1.3% (1 patient) were seen in the oral chloral hydrate group and not observed in the chloral hydrate nasal spray group. No serious adverse effects occurred in either group. Patients in the nasal chloral hydrate group had shorter procedure time, recovery time, and total nurse time (Table 3). Adjusting for age and weight did not affect the group comparisons ($p < 0.05$ for the heart rate at procedure completion, procedure time, recovery time, and total nurse time; $p = 0.27$ for apnea).

Table 1

Demographics of the nasal and oral Chloral hydrate sedative regimen [a]

	Chloral hydrate(*n* = 65) nasal spray	**Chloral hydrate(*n* = 78) oral solution**	**P value**
Age (years)	2.5 ±1.2	2.1 ±1.6	<0.05
Weight (kg)	12.2 ± 3.8	9.5 ±1.8	<0.05
Male	47%	53%	0.811

[a] Data presented as Mean (SD) or *n* (%).

Table 2

Comparison between the nasal and oral Chloral hydrate sedative regimen dosing and adverse effects.[a]

	Chloral hydrate(*n* = 65) Nasal spray	**Chloral hydrate(*n* = 78) oral solution**	**P-value**
Heat rate pre-sedation (beats/min)	125±15	121±13	0.15
Heart rate after sedation (beats/min)	115±12	112±11	0.12
Hypoxemia	0	10(12%)	<0.05
Apnea	0	1(1.3%)	0.2
Oxygen supplementation	0	10(12%)	<0.05

[a]Data presented as Mean (SD) or *n* (%).

Table 3

Comparison between the nasal and oral Chloral hydrate sedatives'times.[a]

	Chloral hydrate (*n* = 65) Nasal spray (min)	Chloral hydrate(*n* = 78) oral solution (min)	P value
procedure time	13±2	20±5	<0.05
recovery time	6±1.2	12±3	<0.05
Total nurse time	55±5	70±10	<0.05

[a]Data presented as Mean (SD).

Discussion

Sedating for the diagnosis of various diseases in children and therapeutic procedures has always been challenging [20]. It seems to increase efficiency, and the method of relaxation should be associated with the reduction of anxiety and side effects in patients [21]. Midazolam, diazepam, triazolam (benzodiazepines), chloral hydrate (aldehydes), thiopental (barbiturates), zolpidem (imidazoles pyridine derivatives z types), and ketamine (glutamate antagonists) are prescribed in the current clinical diagnostic and therapeutic procedures. Moreover, within these categories of sedatives, chloral hydrate, midazolam, dexmedetomidine are prescribed for sedation in children in the guideline [22]. Chloral hydrate is recommended by the NICE 2010 guideline for children under 15 kg who are unable to tolerate a painless procedure had a wide margin of safety [23].

It has been reported that chloral hydrate adverse effects included respiratory depression, cardiac arrhythmias, motor imbalance, agitation, and local skin and mucosal lesions [24–27]. But in our study, these adverse events occurred rarely. Our results indicated a high success rate for sedation and few complications and a low rate of adverse reactions for chloral hydrate sedation in infants that makes chloral hydrate a safe drug for sedation of children undergoing EEG.

In the present study, 94% of children in the nasal and 92% in the oral chloral hydrate group achieved a moderate level of sedation using an average dose of 55 mg/kg, successfully. These results were similar to what was reported where the majority of pediatric patients were successfully sedated using oral chloral hydrate [28].

Our results showed that pre and post-sedation heart rate was higher in the nasal spray than in the oral solution of chloral hydrate, however, hypoxemia, apnea, and oxygen supplementation were higher in the oral chloral hydrate group before the EEG procedure. Although hypoxia and apnea of intranasal chloral hydrate have not been reported so far, it has been shown that, similar to our results, the rates of hypoxia and apnea in the sedation of children with oral chloral hydrate were 5.9% and 0.3%, respectively [27]. It has

also been shown that during sedation with oral chloral hydrate, oxygen saturation decreased by 6% of children and required oxygen supplementation [29].

The mean procedure time, recovery time, and total nurse time were significantly lower in the nasal group compared to the oral chloral hydrate group. The average time for the nasal and oral chloral hydrate procedures was about 55 and 70 min, respectively. Our findings demonstrated that time efficacy was explained by the extremely rapid onset and short duration of action of the nasal spray. It has been shown that midazolam (0.5 mg/kg) compared to oral chloral hydrate (75 mg/kg) had a lower sedation success rate, a longer time to achieve sedation, a longer length of stay in the hospital, and a shorter sedation duration [30]. Also, it has been reported that the averages time from oral administration of chloral hydrate to the onset of sedation was 15 to 60 min [31, 32].

Conclusion

Our experience suggested that nasally administered chloral hydrate was a safe and efficacious agent in the conscious sedation of infants before the EEG procedure because of its ease of administration, high success rate, and low adverse reactions.

Declarations

Conflict of interest

The authors declare no conflicts of interest.

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Ethics approval and consent to participate

The study was approved by the Ilam University of Medical Sciences, Ilam, Iran (IR.MEDILAM.REC.1397.54).

Consent for publication

Written consent to test and publish the results was received from the parents of the child and is kept in the hospital archives and the University Medical Ethics Committee.

Availability of data and materials

Not applicable

Author contributions

All the authors have contributed equally.

References

1. J. A. Chevallier, G. K. Von Allmen, M. K. Koenig, *Epilepsia* **2014**, *55*, 707-12 10.1111/epi.12570.
2. D. A. Hsu, K. Rayer, D. C. Jackson, C. E. Stafstrom, M. Hsu, P. A. Ferrazzano, K. Dabbs, G. A. Worrell, J. E. Jones, B. P. Hermann, *Clin Neurophysiol* **2016**, *127*, 1196-1205 10.1016/j.clinph.2015.07.027.
3. K. J. Slifer, K. T. Avis, R. A. Frutchey, *Epilepsy Behav* **2008**, *13*, 189-95 10.1016/j.yebeh.2008.01.013.
4. A. Mahyar, A. Varasteh-Nejad, *Acta Medica Iranica* **2008**, *46*.
5. J. Loewy, C. Hallan, E. Friedman, C. Martinez, *J Perianesth Nurs* **2005**, *20*, 323-32 10.1016/j.jopan.2005.08.001.
6. K. P. Mason, E. O'Mahony, D. Zurakowski, M. H. Libenson, *Paediatr Anaesth* **2009**, *19*, 1175-83 10.1111/j.1460-9592.2009.03160.x.
7. L. Saarnivaara, L. Lindgren, U. M. Klemola, *Br J Anaesth* **1988**, *61*, 390-6 10.1093/bja/61.4.390.
8. J. G. Millichap, *Am J Dis Child* **1972**, *124*, 526-7.
9. S. Chaudhary, R. Jindal, G. Girotra, R. Salhotra, R. Rautela, A. Sethi, **2014**, *30*, 53-58 10.4103/0970-9185.125704.
10. S. C. Kao, S. D. Adamson, L. H. Tatman, K. S. Berbaum, *Pediatr Radiol* **1999**, *29*, 287-90 10.1007/s002470050590.
11. M. Thoresen, O. Henriksen, E. Wannag, L. Laegreid, *Electroencephalogr Clin Neurophysiol* **1997**, *102*, 152-7 10.1016/s0921-884x(96)96509-1.
12. L. Lourenco-Matharu, P. F. Ashley, S. Furness, *Cochrane Database Syst Rev* **2012**, Cd003877 10.1002/14651858.CD003877.pub4.
13. S. Chhajed, S. Sangale, S. Barhate, in *Book ADVANTAGEOUS NASAL DRUG DELIVERY SYSTEM: A REVIEW*, ed., ed. by Editor, City, **2011**, Chap. Chapter.
14. V. A. Loyd , Jr., *US Pharm* **2018**, *43*, 43-44.
15. M. Elfil, A. Negida, *Emergency (Tehran, Iran)* **2017**, *5*, e52.
16. P. Bégin, F. Graham, K. Killer, J. Paradis, L. Paradis, A. Des Roches, *Allergy* **2016**, *71*, 1762-1771 10.1111/all.12956.
17. C. J. Cote, S. Wilson, *Pediatrics* **2016**, *138*, 10.1542/peds.2016-1212.
18. P. P. Kamat, C. E. McCracken, S. E. Gillespie, J. D. Fortenberry, J. A. Stockwell, J. P. Cravero, K. B. Hebbar, *Pediatr Crit Care Med* **2015**, *16*, 11-20 10.1097/pcc.0000000000000273.
19. K. Abulebda, V. J. Patel, S. S. Ahmed, A. J. Tori, R. Lutfi, S. Abu-Sultaneh, *Braz J Otorhinolaryngol* **2019**, *85*, 32-36 10.1016/j.bjorl.2017.10.003.

20. O. Hijazi, A. Ahmed, J. Anazi, H. Al-Hashemi, M. Al-Jeraisy, *Saudi medical journal* **2014**, *35*, 123-31.
21. S. Z. Wang, Y. Yao, X. J. Zhang, X. Duan, L. R. Guo, Y. Jia, D. Wang, Y. S. Tian, *Int J Clin Pharmacol Ther* **2020**, *58*, 195-197 10.5414/cp203562.
22. S. E. Mace, L. A. Brown, L. Francis, S. A. Godwin, S. A. Hahn, P. K. Howard, R. M. Kennedy, D. P. Mooney, A. D. Sacchetti, R. L. Wears, R. M. Clark, *Ann Emerg Med* **2008**, *51*, 378-99, 399.e1-57 10.1016/j.annemergmed.2007.11.001.
23. P. Coulthard, D. Craig, C. Holden, N. D. Robb, M. Sury, S. Chopra, I. Holroyd, *British Dental Journal* **2015**, *218*, E14-E14 10.1038/sj.bdj.2015.338.
24. K. L. Sandberg, S. D. Poole, H. W. Sundell, *Acta Paediatr* **2013**, *102*, 391-6 10.1111/apa.12151.
25. S. Ozsoylu, *Turk J Pediatr* **2010**, *52*, 560; author reply 560-1.
26. P. Han, H. Song, P. Yang, H. Xie, Y. J. Kang, *Cardiovasc Toxicol* **2011**, *11*, 128-33 10.1007/s12012-011-9106-2.
27. L. C. Heistein, C. Ramaciotti, W. A. Scott, M. Coursey, P. W. Sheeran, M. S. Lemler, *Pediatrics* **2006**, *117*, e434-41 10.1542/peds.2005-1445.
28. M. R. Ashrafi, H. Mohebbi, M. Mohamadi, E. Azizi, G. R. Zamani, A. Tavasoli, R. Shervin Badv, F. Hosseini, *2019* **2019**, *14*, 8 %J Iranian Journal of Child Neurology 10.22037/ijcn.v14i1.21008.
29. K. L. Napoli, C. G. Ingall, G. R. Martin, *J Pediatr* **1996**, *129*, 287-91 10.1016/s0022-3476(96)70256-1.
30. O. M. Hijazi, A. E. Ahmed, J. A. Anazi, H. E. Al-Hashemi, M. I. Al-Jeraisy, *Saudi Med J* **2014**, *35*, 123-31.
31. J. Pershad, P. Palmisano, M. Nichols, *Pediatr Emerg Care* **1999**, *15*, 432-5.
32. J. K. Martinbiancho, P. R. Carvalho, A. Trotta Ede, A. P. Schweiger, R. Rau, L. B. Moreira, *Eur J Clin Pharmacol* **2009**, *65*, 1253-8 10.1007/s00228-009-0694-8.