Safety and effectiveness of Chloral Hydrate in Auditory Brainstem Response tests: a single-center and cross-sectional study

Xiangling Zhang[1], Haotian Liu[1], Xinyi Yao[1], Min Liu[1], Youyou Jin[1], Yun Zheng[1], Wei Zhang[1], Zhaoli Meng[1], and Yu Zhao[2]

[1]Sichuan University West China Hospital
[2]West China Hospital,Sichuan University

November 16, 2022

Abstract

Objective: Chloral Hydrate is the most commonly used sedative for Auditory Brainstem Response (ABR) test. The aim of this study was to retrospectively analyze the safety and effectiveness of Chloral Hydrate in patients undergoing ABR tests through a single-center and large sample size cross-sectional study. Methods: Data were collected from December 2015 to March 2022, which included 7,176 ABR tests (6,106 patients). Basic information was collected, then telephone follow-up was conducted for patients with two or more consecutive tests less than 60 days, and administration method, failure performance, and adverse events were collected. Total sedation failure rate, sedation failure rates in different age groups ([?]0.5 years, 0.5-3 years, 3-12 years, [?]12 years) and incidence of adverse events were calculated. Results: A total of 4,967(69.21%) ABR tests were younger than 3 years of age. The sedation failure rate was 3.11% with a Chloral Hydrate dose of 30 mg/kg of weight, which ranged from 1.44% to 4.31% in different age groups. In the sedation failure tests, insufficient sedation was found in 74.44% of the tests. The incidence of adverse events was 0.35%, with most commonly vomiting. Conclusion: The sedation failure rate and the incidence of adverse events in this study are relatively low compared with other previous studies, and Chloral Hydrate can be considered a safe and effective sedative with the permissible dose. However, there were still many patients who failed to complete the test due to insufficient sedation (mostly infants and children), which imply that alternative sedatives with easier preparation process are needed.

Safety and effectiveness of Chloral Hydrate in Auditory Brainstem Response tests: a single-center and cross-sectional study

Abstract

Objective: Chloral Hydrate is the most commonly used sedative for Auditory Brainstem Response (ABR) test. The aim of this study was to retrospectively analyze the safety and effectiveness of Chloral Hydrate in patients undergoing ABR tests through a single-center and large sample size cross-sectional study.

Methods: Data were collected from December 2015 to March 2022, which included 7,176 ABR tests (6,106 patients). Basic information was collected, then telephone follow-up was conducted for patients with two or more consecutive tests less than 60 days, and administration method, failure performance, and adverse events were collected. Total sedation failure rate, sedation failure rates in different age groups ([?]0.5 years, 0.5-3 years, 3-12 years, [?]12 years) and incidence of adverse events were calculated.

Results: A total of 4,967(69.21%) ABR tests were younger than 3 years of age. The sedation failure rate was 3.11% with a Chloral Hydrate dose of 30 mg/kg, which ranged from 1.44% to 4.31% in different age groups. In the sedation failure tests, insufficient sedation was found in 74.44% of the tests. The incidence of adverse events was 0.35%, with most commonly vomiting.

Conclusion: The sedation failure rate and the incidence of adverse events in this study are relatively low compared with other previous studies, and Chloral Hydrate can be considered a safe and effective sedative with the permissible dose. However, there were still many patients who failed to complete the test due to insufficient sedation (mostly infants and children), which imply that alternative sedatives with easier preparation process are needed.

Key words: Chloral Hydrate; Auditory brainstem response; Sedation; Failure rate

Key points

A single-center cross-sectional clinical study with large sample size.

The safety and effectiveness of ABR with chloral hydrate in 7176 patients were reported by telephone follow-up.

In this study, the sedation failure rate of Chloral Hydrate for ABR test was 3.11% and the incidence of adverse events was 0.35%.

Chloral Hydrate can be considered a safe and effective sedative with the permissible dose.

Many patients who failed to complete the ABR test due to insufficient sedation (mostly infants and children).

Introduction

Hearing loss is common in society, which can have negative effects on speech, language development, and social communication.[1] For patients with suspected hearing loss, early diagnosis is significant for subsequent clinical intervention. The auditory brain stem response (ABR) is an objective, non-invasive method to estimate auditory threshold and neurological diagnosis in clinics, and commonly used in infants and children who cannot complete a subjective audiologic assessment. Guidelines for Early Hearing Detection and Intervention Programs (EHDI) emphasized ABR is the gold standard for hearing diagnosis in children younger than 6 months of age.[1,2] The successful completion of ABR is challenging for patients; as patients are required to sleep soundly during the procedure to minimize myoelectrical interference and get more accurate test results.[3] For some patients, especially in infants and children, it is not easy to get spontaneous sleep despite preferential intervention, , so using the appropriate sedative agent in patients plays a significant role in the successful completion of the procedure.[4]

Chloral Hydrate is a non-opiate and non-benzodiazepine sedative-hypnotic drug, which widely used in otolaryngology, imaging, and other clinical departments over the past decades in China. However, concerns have been expressed about safety and effectiveness, particularly with regard to potential advert effects, such as vomiting, restlessness, sedation-induced hypoxemia, bradycardia and so on.[3,5]Nevertheless, Chloral Hydrate is considered safe and effective for patients undergoing painless diagnostic procedures with appropriate doses and settings.[6]

In the Hearing Center of our hospital, as most other hospitals, Chloral Hydrate has been used for sedation of patients in ABR tests for nearly 30 years. Although Chloral Hydrate sedation has a low incidence of severe adverse events and is considered safe, it is still important to assess adverse events that may occur. Therefore, the aim of this study was to report the sedation failure rate as well as the incidence of adverse events and to analyze the safety and effectiveness of Chloral Hydrate for the ABR test. Furthermore, this study aimed to identify the potential risk through a large sample of data and was expected to provide a reference for future practice.

Materials and Methods

Clinical procedure

ABR was routinely conducted for patients to assess their auditory threshold and neurological diagnosis in our hospital. After a consultation with an otolaryngology department specialist, the Chloral Hydrate was

administered by a trained nurse or audiologist under the supervision of the Otolaryngologists, by the oral route without exceptional circumstances.

Chloral Hydrate was administered at a concentration of 10%, at a dose of 30 mg/kg. In consideration of safety, the drug was not further supplemented. Chloral Hydrate can be mixed with dairy products or other liquids to mask its bitter taste to help children complete ingestion. Furthermore, if not sedated after 45–60 minutes, the appointment would be rescheduled. Patients were required to perform sleep deprivation and fast for at least three hours before the ABR test, as these were believed to help them fall asleep.

Data Collection

The clinical study was approved by the Ethics Committee, and all clinical data use and telephone follow-ups were carried out after obtaining the consent of patients.

Medical records for patients who underwent sedated ABR tests between December 2015 and March 2022 were reviewed, and 7,176 ABR tests (6,106 patients) with sufficient data were included. The collected data were as follows: clinic registration number, gender, age, and telephone number. Telephone follow-up was conducted for patients with two or more consecutive tests within 60 days (according to hospital regulations and clinical experience, patients who failed sedation should complete the examination within 60 days), and 729 ABR tests were included (Figure 1). Telephone follow-up data were as follows: history of sedation failure, administration method (mixed or direct), sleep deprivation (yes or no), failure performance (failure to sleep, insufficient sedation, and superficial sleep), and adverse events (vomiting, agitation, etc.). The success of sedation was considered as patients who kept quiet and completed the test without incident. The failure to sleep was considered patients who were restless and unable to sleep. Insufficient sedation meant patients woke up in the middle of the tests and did not complete the tests on the same day. Superficial sleep meant patients did not reach the required sleep depth.

Data Analysis

Continuous variables are described as median and interquartile ranges (IQR). Categorical variables are presented as numbers with percentages. The chi-square test or Fisher's exact test was used to compare categorical variables among groups. Total sedation failure rate, sedation failure rates in different age groups ([?]0.5 years, 0.5-3 years, 3-12 years, [?]12 years) and incidence of adverse events were calculated. Grouped by administration method and failure performance in sedation failure patient, then calculated the proportion of patients in different age groups. All statistical analyses were performed using R (version 4.2.0. R Core Team,2022). All P values were 2-sided, and $P = 0.05$ was used to indicate statistical significance.

Results

The study included 7,176 ABR tests (6,106 patients) between December 2015 and March 2022. A total of 3101(43.21%) ABR tests were females and 4075(56.79%) ABR tests were males. The median (interquartile range [IQR]) age was 1(8 – 0.42) year, with a range of 1 month to 84 years. There were 223(3.11%) ABR tests which were sedation failed. A total of 102(45.74%) ABR tests were females and 121(54.26%) ABR tests were males. The median (interquartile range [IQR]) age was 1(3 – 0.42) year, with a range of 1 month to 68 years. When we grouped patients by age ([?]0.5 years, 0.5-3 years, 3-12 years, [?]12 years), the failure rates ranged from 1.44% to 4.31%, with significant differences (P <0 .001) (Table 1)(Table 2).

Some infants and children need to mix the medicine with dairy products or other liquids, to facilitate better medication. There were 99(44.40%) ABR tests in the mixed group and 124(55.60%) ABR tests in the direct group. According to telephone follow-up results, the sedation performance was divided into three categories, of which 166(74.44%) ABR tests were insufficient sedation after taking Chloral Hydrate. Fifty (22.42%) ABR tests were unable to fall asleep and 7(3.14%) ABR tests were in superficial sleep. The vast majority of patients reported performing sleep deprivation, but the specific implementation has not been followed up. Most patients (43.05%) in the mixed group were younger than 3 years old, and patients over 3 years old were mainly taken Chloral Hydrate directly, there were significant differences between the administration method among different age groups (P< 0.001). Insufficient sedation was the main performance of sedation failure

in the [?]0.5 years group and the 0.5-3 years group. Failure to sleep was the main performance of sedation failure in the [?]12 years group. In addition, there were 6(2.69%) ABR tests in the[?]12 years group and only 1(0.45%) ABR tests in the group of [?]0.5 years who were in superficial sleep. There were significant differences in the failure performance among different age groups ($P < 0.001$) (Table 2).

No severe adverse event (apnea, bradycardia) was observed in our study. The adverse events included 25(0.35%) ABR tests that experienced minor adverse events such as vomiting, agitation, and tension. There were 18(0.25%) ABR tests experienced vomiting, and 5(0.07%) ABR tests experienced agitation, and 2(0.03%) ABR tests experienced tension throughout the test (Table 1).

Discussion

Chloral hydrate is a traditional sedative used for auditory and other clinical examinations for a long time, but there is lack of large sample reports to summarize its clinical application status. In addition, chloral hydrate has been listed as a class 2A carcinogen by the World Health Organization (WHO), and professional academic organizations suggested replacement or accelerated elimination, therefore, it is necessary to conduct a retrospective study on its safety and effectiveness.

Sedation failure is a great inconvenience to the patients and their families and requires rescheduling of another hospital admission to complete the procedure, and some patients even require general anesthesia (additional associated risks). The results of study showed that the total sedation failure rate was 3.11% at 30 mg/kg of Chloral Hydrate. The value obtained by us was approximate to that reported by Valenzuela et al.(2016), with 3.40% at 50 mg/kg.[3] At a single dose of 50mg/kg, the sedation failure rates reported by Guan(2020), Lai et al.(2019), Reynolds et al.(2016) and Dong&Qiu(2010) were all higher than that reported in this study, ranging from 6.80% to 21.50%.[7–10] However, at a single dose of 75mg/kg, the sedation failure rate reported by Many et al.(2022) and Hijazi O.M. et al.(2014), was 1.3% and 23.7%.[11,12] With the same dosage, the sedation failure rate was not same in different studies. Therefore, the sedative effect of Chloral Hydrate is not only affected by the total dose, but also by age, physical condition, and other factors.[5] More attention should be paid to the standardized use of Chloral Hydrate in clinical sedation and the study of sedative effect factors.

Sedation failure rates in different age groups were statistically different ($P < 0.001$), and the sedation failure rate was the highest in 0.5-3 years old group, with 4.31%. Previous studies showed that the coordination of infants' biological rhythms and their synchronization with the time of day developed rapidly in the first 6 months of life, and tended to be stable in the 6 months.[13] In addition, the sleep/wake architecture is regulated by neuronal networks among a number of nuclei located in the hypothalamus, midbrain, and pons, and the quantity, quality, and circadian patterns of infant sleep tend to stabilize as the brain develops. [14] [15] Brain function, sleep patterns, physical development, and compliance may be responsible for the different sedation failure rates at different ages.

In patients who have failed sedation, the failure performance of insufficient sedation (74.44%) accounted for the largest proportion, and it was mainly concentrated in children under 3 years old (67.72%). There are several reasons for this result. Firstly, the dose might be insufficient, because of potential safety issues, our hospital administered the minimum dose and there were no supplements. In the study of Keidan et al.(2004) and Reynolds et al.(2016), the Chloral Hydrate dosage was 50 mg/kg, the failure rate of sedation after initial administration was 15.5% and 21.5%, and the sedation failure rate decreased by 5.50% and 9.50% after tonic.[9,16] Secondly, there might be insufficient sleep preparation, because usually the parents did not wake the child as instructed by the doctor and did not keep the child awake on the way to the hospital. In addition, there is also a lack of generally accepted standards for sleep preparation before sedation for ABR tests. Sleep deprivation is usually carried out one night in advance, and the time of sleep as well as awake is suddenly changed, which results in the misalignment of circadian rhythm, complex adaptive responses in the brain, increased anxiety symptoms, and emotional impact.[17,18] In addition, sleep needs and the effects of sleep deprivation are different at different ages.[13,19] The ABR test is of profound significance for infants and children's auditory assessment, therefore, it is of great clinical significance to improve the examination

procedures, standardize sedative application, and seek better alternative sedative to reduce the sedation failure rate.

The most common adverse event in this study was vomiting (0.25%), but higher rates were reported by Avlonitou et al.(2011) at 11.4%.[6]The second followed was agitation (0.07%), which was lower than the 5% reported by Valenzuela et al.(2016) and the 8% reported by Avlonitou et al.(2011) .[3,6] Tension (0.03%) is more common in middle-aged and elderly people, which is an emotional reaction due to drug factors and uncertainties about test results. No severe adverse event was followed up in our study, however, Avlonitou et al.(2011) reported that in a group of 1,509 patients treated with Chloral Hydrate, the incidence of severe adverse events (Minor respiratory distress and apnea) was 0.7% at a single dose of 40 mg/kg.[6]The reasons for the different incidence of adverse events among previous studies may be as follows: firstly, the low dose of medication might lead to a low incidence of adverse events; secondly, some minor adverse events might occur after patients left the hospital and might not be observed; thirdly, the existing system of auditory sedation based on outpatient examination lacked electrocardiogram monitoring and mainly focuses on observation and reporting, resulting in some severe adverse events not found; fourthly, our data collection method was telephone follow-up with a long-time span which may lead to recall bias.

There was an overall significant and decreasing trend in the use of Chloral Hydrate, according to Kamat et al.(2020), early Chloral Hydrate utilization rates were 6.3% (decreased to <0.01%) in outpatient procedural sedation among people younger than 21 years from 2007 to 2018.[20] A serious concern with the use of Chloral Hydrate as a standard sedative in patients is its carcinogenic potential, which has been listed by the International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) as a probable human carcinogen (Group 2A),and it is banned in Italy and France,[21] However, there is currently no convincing evidence to support a causal relationship between human Chloral Hydrate exposure and cancer development, and the effects of Chloral Hydrate in humans remain uncertain.[22] In addition, numerous studies have demonstrated that there are many other effective sedatives with more predictable pharmacokinetic characteristics than Chloral Hydrate. As a result, the literature is full of recommendations for safer alternatives when sedating pediatric patients.[23,24]

This study reviewed the safety and effectiveness of Chloral Hydrate for the ABR test, which is a study with a long-time span and a large sample size. Therefore, this study may provide substantial evidence for the safety and effectiveness of Chloral Hydrate in ABR testing in clinical practice. In addition, this study highlighted some deficiencies in this field and put forward corresponding suggestions, such as standardized medication, scientific sleep preparation, etc.

The study had several limitations. Firstly, the inclusion criterion was that the interval between two or more examinations was less than 60 days, so there was selection bias. Some patients with a history of sedation failure and adverse events were not included in the follow-up cohort, which may be one of the reasons why the incidence of sedation failure and adverse events reported in this study was lower than that in other studies. Secondly, the long follow-up time and examination time interval led to recall bias, so the accuracy or completeness of the study might deviate from the real situation. Thirdly, the early data was not digitized and patients ABR test results were not available, so the effect of sedatives on patient test results was unclear, and we will continue to report this part of data in the future.

Conclusion

As a traditional sedative with long-term use, the sedation failure rate and the incidence of adverse events of Chloral Hydrate in this study were relatively low compared with other previous studies, and Chloral Hydrate can be considered a safe and effective product within the permissible dose. However, there were still many people who failed to complete the test due to insufficient sedation (mostly infants and children), which suggests alternative sedatives with easier preparation process are needed.

References

1. The Joint Committee on Infant Hearing. Year 2019 Position Statement: Principles and Guidelines

for Early Hearing Detection and Intervention Programs. The Journal of Early Hearing Detection and Intervention. 2019;4(2):1–44.

2. Eggermont JJ. Auditory brainstem response. Handb Clin Neurol. 2019;160:451–64.

3. Valenzuela DG, Kumar DS, Atkins CL, Beers A, Kozak FK, Chadha NK. Chloral hydrate sedation for auditory brainstem response (ABR) testing in children: Safety and effectiveness. Int J Pediatr Otorhinolaryngol. 2016 Apr;83:175–8.

4. Fong CY, Lim WK, Li L, Lai NM. Chloral hydrate as a sedating agent for neurodiagnostic procedures in children. Cochrane Database Syst Rev. 2021 Aug 16;8(8):CD011786.

5. Mace SE, Brown LA, Francis L, Godwin SA, Hahn SA, Howard PK, et al. Clinical policy: Critical issues in the sedation of pediatric patients in the emergency department. Ann Emerg Med. 2008 Apr;51(4):378–99, 399.e1-57.

6. Avlonitou E, Balatsouras DG, Margaritis E, Giannakopoulos P, Douniadakis D, Tsakanikos M. Use of chloral hydrate as a sedative for auditory brainstem response testing in a pediatric population. Int J Pediatr Otorhinolaryngol. 2011 Jun;75(6):760–3.

7. Guan C. Comparison of Sedative Effects of Chloral Hydrate in Different Ways on Infants of Different Ages. China Health Standard Management. 2020;11(15):98–100.

8. Lai D, Huang Y, Pu J, Liu L, Xiao Y. Effect of Short-term sleep deprivation on auditory brainstem response test in children. China Journal of Modern Medicine. 2019;29(9):85–9.

9. Reynolds J, Rogers A, Capehart S, Manyang P, Watcha MF. Retrospective Comparison of Intranasal Dexmedetomidine and Oral Chloral Hydrate for Sedated Auditory Brainstem Response Exams. Hosp Pediatr. 2016 Mar;6(3):166–71.

10. Dong W, Qiu J. Nursing Research on Chloral Hydrate Sedation before Child Brain Stem Auditory Evoked Potential Examination. Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease. 2010;10(18):1427–8.

11. Many YA, Berkenstadt H, Henkin Y. The safety and efficacy of a nurse-led sedation service using Chloral Hydrate for auditory brainstem response testing. J Pediatr Nurs. 2022 Apr;63:e143–8.

12. Hijazi O.M., Ahmed A.E., Anazi J.A., Al-Hashemi H.E., Al-Jeraisy M.I. Chloral hydrate versus midazolam as sedative agents for diagnostic procedures in children. Saudi Med J. 2014;35(2):123–31.

13. Bathory E, Tomopoulos S. Sleep Regulation, Physiology and Development, Sleep Duration and Patterns, and Sleep Hygiene in Infants, Toddlers, and Preschool-Age Children. Curr Probl Pediatr Adolesc Health Care. 2017 Feb;47(2):29–42.

14. Saper CB, Fuller PM, Pedersen NP, Lu J, Scammell TE. Sleep state switching. Neuron. 2010 Dec 22;68(6):1023–42.

15. Peirano P, Algarín C, Uauy R. Sleep-wake states and their regulatory mechanisms throughout early human development. J Pediatr. 2003 Oct;143(4 Suppl):S70-79.

16. Keidan llan, Gozal D, Minuskin T, Weinberg M, Barkaly H, Augarten A. The effect of fasting practice on sedation with chloral hydrate. Pediatr Emerg Care. 2004;20(12):805–7.

17. Cox RC, Upender RP, Olatunji BO. Linking inhibition and anxiety symptoms following sleep restriction: The moderating role of prior sleep efficiency. Behav Res Ther. 2020 Apr;127:103575.

18. Depner CM, Stothard ER, Wright KPJ. Metabolic consequences of sleep and circadian disorders. Curr Diab Rep. 2014 Jul;14(7):507.

19. Ong HT, Lim KJL, Low PC, Low PS. Simple instructions for partial sleep deprivation prior to pediatric EEG reduces the need for sedation. Clin Neurophysiol. 2004 Apr;115(4):951–5.

20. Kamat PP, McCracken CE, Simon HK, Stormorken A, Mallory M, Chumpitazi CE, et al. Trends in Outpatient Procedural Sedation: 2007-2018. Pediatrics. 2020 May;145(5):e20193559.

21. Cozzi G, Norbedo S, Barbi E. Intranasal Dexmedetomidine for Procedural Sedation in Children, a Suitable Alternative to Chloral Hydrate. Paediatr Drugs. 2017 Apr;19(2):107–11.

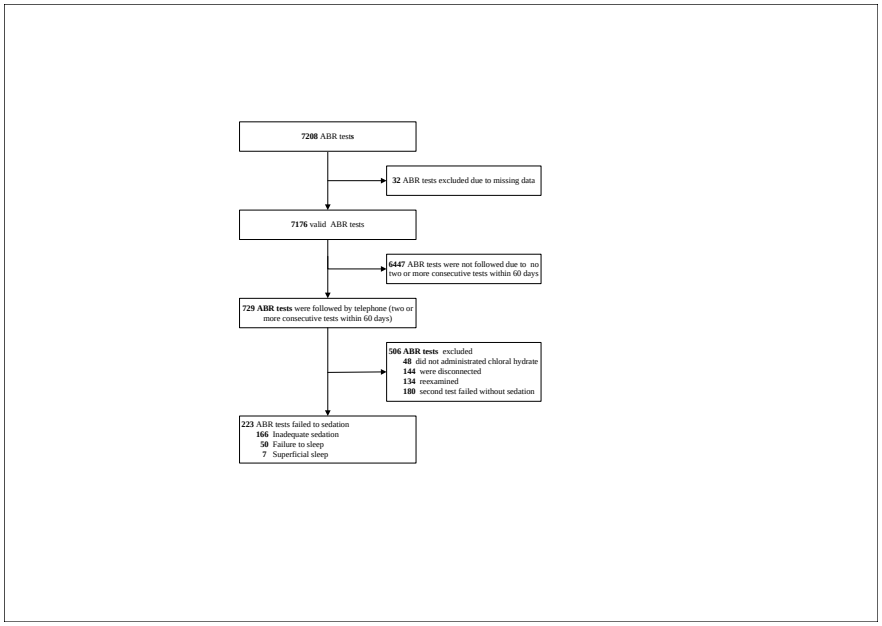
22. Haselkorn T, Whittemore AS, Udaltsova N, Friedman GD. Short-term chloral hydrate administration and cancer in humans. Drug Saf. 2006;29(1):67–77.

23. Abulebda K, Patel VJ, Ahmed SS, Tori AJ, Lutfi R, Abu-Sultaneh S. Comparison between chloral hydrate and propofol-ketamine as sedation regimens for pediatric auditory brainstem response testing. Braz J Otorhinolaryngol. 2019 Feb;85(1):32–6.

24. Coté CJ, Wilson S. Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures. Pediatrics. 2019 Jun;143(6):e20191000.

Figure Legends

Figure 1. Flow diagram of study participants



Hosted file

Table 1.docx available at https://authorea.com/users/525233/articles/595699-safety-and-effectiveness-of-chloral-hydrate-in-auditory-brainstem-response-tests-a-single-center-and-cross-sectional-study

Hosted file

Table 2.docx available at https://authorea.com/users/525233/articles/595699-safety-and-effectiveness-of-chloral-hydrate-in-auditory-brainstem-response-tests-a-single-center-and-cross-sectional-study