Original Article

Effect of Melatonin on the efficacy of Chloral hydrate in Sedating Children Undergoing Auditory Brainstem Response Test: A controlled randomized clinical trial

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ABSTRACT

Background: To obtain an accurate diagnosis, children with hearing impairment could be examined by auditory brainstem response test. Young children are usually uncooperative and could not be examined without sedation. The most commonly used sedative is chloral hydrate. Some investigators used melatonin as an alternative sedative. Our study aimed to evaluate the effect of melatonin as adjuvant when added to chloral hydrate.

Methods: The study was conducted at the Clinic for Hearing, Balance and Communication, Mosul, Iraq, from July to December 2018, and has been approved by the regional Research Ethics Committee with a design of the un-blinded randomized clinical trial. Parents provided a written informed consent. Two hundred and fifty-four children aged 8 months-7 years attending for auditory brainstem response test were allocated randomly to two groups. The group A children as controls (n=150), were receiving chloral hydrate oral dose 50mg/kg, while the group B cases (n=104), were receiving melatonin 0.1mg/kg plus chloral hydrate 50mg/kg. Both groups were compared in sleep latency, success rate of sedation within 30 minutes, as well as sleep duration. Relative risk (RR), t-test and chi-square were used.

Results: Within 30 minutes of the initial dose intake, the group of the combined melatonin and chloral hydrate achieved a higher success rate in the sleep induction than the group of the chloral hydrate, (n=98, 94.2% versus n=112, 74.6%), RR=1.262, *P<0. 001*.

Conclusion: Melatonin could enhance the efficacy of chloral hydrate when added to it, as an adjuvant agent.

Key Words: Adjuvant, chloralhydrate, Melatonin, sedation.

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INTRODUCTION

Loss of hearing of children remains a significant problem that demands prompt diagnosis and treatment. Accurate diagnosis could be obtained by auditory brainstem response test (ABR). Young children and those with neurodevelopmental abnormalities could not be examined without sedation. To get a valuable result, the child should be calm and sleeping throughout the auditory brainstem response test[1]. Numerous sedative agents are employed, such as intranasal dexmedetomidine, rectal pentobarbital, intravenous propofol, oral chloral hydrate and even the general anesthesia. Chloral hydrate is the most widely used sedative for brainstem response testing due to its reliable efficacy and safety, replacing the general anesthesia and those agents of potentially substantial adverse effects[2,3]. Although chloral hydrate is a safe sedative, few common side effects have been reported including nausea, vomiting, abdominal pain, agitation or hyperactivity, or in an over dose uncommon adverse effects; bradycardia, apnea, arrhythmia and convulsion[4]. As an alternative to chloral hydrate, melatonin is frequently used and recommended by many researchers due to its superior efficacy and safety for sedation in auditory brainstem response testing[5]. Naturally, melatonin is a hormone produced by the pineal body in the brain, secreted during the time of the sleep. It regulates the sleep-awake cycle[6] .As a medication, it is typically taken by mouth and available as dietary supplements in the form of tablets, lozenges, liquids or drops. It is a remarkably safe and effective agent when used for induction of sleep.

Symptoms of an overdose may include a headache, drowsiness, bed wetting and stomach upset[7,8]. In reviewing the previous studies, we could not find research works indicating the use of combination of melatonin with chloral hydrate in auditory brainstem response test.

Our study aimed to assess the effect of melatonin on the efficacy of sedation when added as an adjuvant to chloral hydrate for children undergoing auditory brainstem response test.

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SUBJECTS AND METHODOLOGY:

This research was conducted at the Clinic for Hearing, Balance and Communication, Mosul, Iraq, during the period from July to December 2018. This prospective study utilized a design of the un-blinded randomized controlled clinical trial. The local Medical Research Ethics Committee approved the study which was consistent with Ethical Principles of Helsinki Declaration.

The parents provided a written informed consent.

Two hundred and fifty - four children suffering from hearing loss and attending the clinic for hearing assessment by Auditory Brain Stem Response test (ABR), were enrolled in the study. The test was carried out by the clinic audiologist using the instrument; "Otomertics ABR Chartr EP200" with software. Our role was limited to sedate and to observe the children throughout the procedure of the ABR test.

The clinic had the capacity to perform ABR test on 3-6 cases daily, from Saturday to Thursday. The clinic nurse was responsible for the allocation of the children to either group A (controls) or to group B (cases). The group A were receiving the standard sedative: chloral hydrate, while the group B (cases) were receiving the protocol under the investigation (melatonin and chloral hydrate), in a randomized way (according to CONSORT statement).

Allocation concealment to either group, was performed by using opaque sealed envelopes, which were sequentially numbered from 1 to 400.

All children involved in the study were assessed physically for the eligibility of the sedation by a pediatrician and checked for Spo2 to be > 93, and doing basic investigations including; urinalysis, complete blood count, liver function tests, chest X ray, ultrasound of the abdomen, as well as other more tests if indicated before doing the test. Children with acute respiratory illnesses, chronic severe respiratory problems, serious cardiac, renal or hepatic diseases, were excluded from the test. Each child's parent/guardian should sign the informed consent after receiving a brief explanation about the sedation procedures.

The group A with a total n=150 (<2years old n=26); received oral chloral hydrate as a flavored syrup of concentration 50mg/ml, in a dose 50mg/kg to induce sedation.

The chloral hydrate syrup was prepared by the pharmacist. Its taste was produced tolerable and palatable by adding some flavors such as vanilla and strawberry.

The group B with total n=104 (<2years old n= 22); received low dose of melatonin 0.1 mg/kg (1 drop/kg), in addition to the usual dose 50 mg/kg of chloral hydrate syrup[9]. Melatonin used in this study was of the brand named as "Benevolent Nourishment." It is in the form of liquid drops with a 3 mg per serving. One ml (3mg) is equivalent to 30 drops. Each drop contains 0.1mg melatonin.

Children in both groups were obviously looking normal without apparent significant diseases or any neurological impairment apart from suspected hearing problems except a few of them (total n=12), were suffering from Autism (Group A ; n =2 cases, group B; n=1 case), Cerebral palsy (Group A ; n= 2 cases, group B; n= 1 case), attention deficit hyperactive disorder ADHD (group A; n= 2 cases), and mental retardation (Group A; n;= 2 ,Group B; n=2).

Children receiving the sedative protocols were observed closely by the involved pediatrician, starting from the time of dose intake up to the end of the test; for the vital signs to ensure a good quality deep sleep with a normal breathing rhythm.

The clinic was equipped with the essential first-aid kits like amboo bag, Oxygen and endotracheal tubes.

Usually, ABR test takes 45 - 60 minutes.

After finishing the test, children ought to stay under observation further 2 hours before discharge. The time of the dose intake, the duration till the child fell asleep (sleep onset latency), the duration of the sleep, the assessment of the depth of sedation (sedation score level) every 10 minutes using the University Michigan Sedation Scale (UMSS) as shown in the (appendix), and any abnormal reaction or adverse effect, were recorded by the clinic nurse.

The target level of sedation required to achieve a deep sleep in children undergoing the test, was the UMSS sedation scor 3.

This score of sedation was the appropriate level required to perform the ABR test because the child will be in a deep sleep and could respond only to a significant physical stimulation. Cases in both groups who failed to get asleep in the 30th minute of the initial sedative dose, were considered unsuccessful. To complete their sedation, an additional half of the initial dose was given to each of these cases. To assess the role of melatonin upon the efficacy of sedation, both groups were compared. To measure the statistical significance for the difference in the success rates in sedation, Relative Risk (RR) estimate was calculated in a case-control analysis using four fold (2 x 2) tables. The test of significance of RR was provided by Chi-square test (pearson value) with one degree of freedom, with 95% Confidence interval CI. For the measurement of the statistical significance for the differences between the means from two independent groups, we used t-test, with 95% CI. P value was considered significant when it was

< 0.05. All the statistical analyses were performed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA)[10].

RESULTS:

As demonstrated in the figure 1 (flow chart), the total number of children was 254 (girls n = 110, 43.3%, boys n=144, 56.7%), and age range: 8 months-7 years, mean ±SD; (4.5±1.25). Many clinics un-sedate children with ages above 5 years, and they use other methods like music or video of cartons to keep them calm during the test. However, few children of these ages are still unable to cooperate with these measures and may require sedation.

These children were divided into two main groups: A and B, according to the type of sedative protocol. The group B (n=104, 40.9%) was with the new protocol under investigation (chloral hydrate and melatonin), while the group A (n=150, 59.1%) was with the standard sedative (chloral hydrate alone).

In each group, males were slightly more frequent than females (Group A 55%, Group B 58%), and those children under the age of 2 years constituted about one - fifth of the total (g A: 18.3%, g B: 21.2%). No obvious differences in the frequencies of children in both groups with the corresponding degrees of hearing thresholds, could be seen (Table 1).

Most of the sedated cases with the combined protocol, succeeded to achieve deep sleep within 30 minutes of the initial dose intake, opposed to about two-thirds of the chloral hydrate cases (n=98, 94.2% vs n=112, 74.6%) (Table 3).

An extra dose of the chloral hydrate (25 mg/kg) was required to complete the sedation of the remaining failed cases of chloral hydrate group A (38 cases, 25.3%). The majority of these cases (n= 30 out of n= 38) achieved the required sedation at the 60th minute of the initial dose. The remaining few cases (n=8) refused a further trial of the sedation.

All the failed cases (n=6, 5.7% of total n=104) of the combined group (B) achieved a good sedation with an extra dose of melatonin (0.05 mg /kg) plus chloral hydrate (25 mg /kg).

Almost all the children under the 2 years of age in both groups were nicely sedated without difficulty with the initial dose, while the challenge was noticed with the sedation of the older children.

Compared to the chloral hydrate group, the mean sleep latency in the combined protocol was significantly shorter; mean± SD min (20 ±5 vs 36±12). On the other hand, it shows a significant longer mean sleep time in hours, mean ±SD (4±0.30 vs 3±0.30) (Table 2).

In the Figure 2, the graph shows a wide area between the two curve lines corresponding to the significant differences in the mean sedation scores between both groups during the first 50 minutes of the whole sedation procedure. Moreover, table 4 clearly explains the details of the comparisons between the two sedative protocols. This table explores that combined sedative protocol was with significantly higher mean sedative scores than that of the chloral hydrate group, with first consecutive 10 minute intervals until the 50th minute of the initial dose intake.

After the 50th minute, the mean sedative scores of the both groups seem nearly equal with no significant differences until reaching the 100th minute, whence the sedative effect of the chloral hydrate protocol started to decline, while the that of the combined protocol continued for a longer time.

Following the ingestion of the sedatives, minor side effects were noted among few children from both groups. These include; nausea (gA 14% vs gB 8.1%), abdominal pain (gA 9.8% vs gB 7.1%) hyperactivity and irritability (gA 12.6% vs gB 6.1%). All these symptoms were mild and transient and appeared before the onset of the sleep induction. These side effects were noted to be slightly more frequent in the group A. However, statistically, they do not show any significant difference (Table 5).

Table 1. Demographic and clinical characteristics for the cases in groups A and B who underwent the ABR test .

Characteristics	Group A (n,%) chloralhydrate(n=142)	Group B(n,%) combined chlor+melatonin (n=104)
Age group<2 year(n)	26/142(18.3%)	22(21.2%)
>2 years(n)	116 (81.7%)	82 (78.8)
Gender: males (n)	78 (55%)	61 (58.7%)
females (n)	64 (45%)	43 (41.3%)
Neurodevelopmental problems	8/142 (5.6%)	4/104(3.8%)
* Hearing threshold: dB		
(1) 0-25	12/142(8.5%)	9/104(8.7%)
(2) 26-40	17 (12%)	10 (9.6%)
(3) 41-55	39 (27.5%)	20 (19.2%)
(4) 56-70	27 (19%)	26 (25%)
(5) 71-90	25 (17.6%)	21 (20.2%)
(6) 91+	22 (15.5%)	18 (17.3%)

(*) Device used for hearing test “Otometrics ABR ICS Chartr EP200”. (1) normal, (2) mild hearing loss, (3) moderate hearing loss, (4) moderate severe hearing loss, (5) severe, (6) profound; n=number, ABR = auditory brainstem response.

Table 2. Group A vs Group B in the sleep onset and sleep duration.

Sleep onset and duration	Chloralhydrate group A	Chloralhydrate+Melatonin group B	*P value**	95%CI
Sleep onset: minutes mean (SD).	36(±12)	20(±5)	<0.0001	-18.454-13.5460
Sleep duration: hrs mean(SD)	3(±0.30)	4(±0.30)	<0.0001	0.9246-1.0754

* t- test was used to estimate the significance of differences between the means of the groups.

Table 3. Group B vs Group A in the success rate in sleep induction within 30 minutes of the dose intake.

success of sedation within 30 minutes of intake	Combined chloral hydrate and melatonin (group B). (n= 104)	Chloral hydrate (group A) (n=150)
Successful cases	98/104 (94.2%)*	112/150 (74.6%)
<2year	22/22(100%)	26/26 (100%)
>2year	76 /82(92.7%)	86/124(69.4%)
Unsuccessful cases	6/104((5.8%)	38/150 (25.3%)

*Relative Risk RR = 1.2620, 95% CI (1.1366 to1.4012), *p<0.0001*

Table 4. Group B vs Group A in the mean sedation scores over time.

Time in minutes	Melatonin+chloral hydrate (B) sedation score : mean ±SD n=104	Chloral hydrate (A) score: means ±SD n=150	*P value*	95%CI: Confidence interval
0	0	0	0.00	0
10	1.8 ±0.45	0.8 ±0.2	<0.0001	-1.0920-0.9180
20	2.6±0.35	1.3±0.32	<0.0001	-1.3836 to-1.2164
30	2.8±0.25	2.3±0.33	<0.0001	-0.5754 to 0.4246
40	2.8±0.25	2.5±0.33	<0.0001	-0.3754 to -0.2246
50	2.8±0.15	2.7±0.2	<0.0001	-0.1455 to 0.0545
60	2.7±0.26	2.7±0.3	=1.000	
70	2.5±0.16	2.5±0.2	=1.000	
80	2.5±0.4	2.4(±0.45)	=1.000	
90	2.4±0.55	2.4±0.3	=1.000	
100	2.3±0.6	2.1±0.25	<0.001	-0.3078 to – 0.0922

SD: standard deviation. *P<0.00*, *p<0.0001*:significant. (t-test used)

Table 5. Group B vs Group A in the frequencies of the side effects.

Side effect of the sedative	Melatonin+chlor (total n=98) group B	Chloral hydrate (total n=142) group A	*P value*
Nausea	n=8/98 (8.1%)	n= 20/142 (14%)	*p=0.169*
Abdominal pain	n=7/98 (7.1%)	n=14/142 (9.8%)	*p=0.467*
Hyperactivity or irritability	n=6/98 (6.1%)	n= 18/142 (12.6%)	*p=0.1080*

n : number of cases. Chi-Square analysis used for estimation of *P value*.

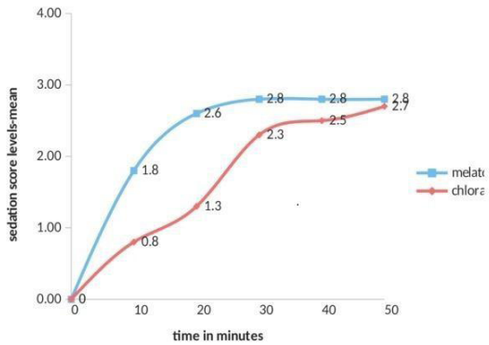

Figure 2. Shows the comparison between the chloralhydrate and the combined protocol in the sedation score level means over time.The combined protocol shows a rapid induction of sleep within first 30 minutes of initial dose intake.

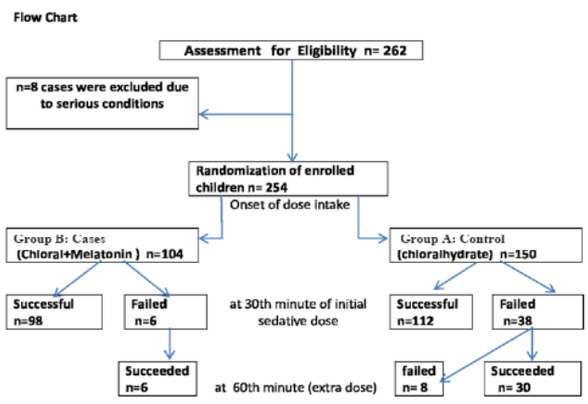

Figure 1. ***Flow Chart showing the eligibility, randomized allocation, follows up for outcome of*** sedative protocols.

DISCUSSION

Sedation is an essential aspect of auditory brainstem response test for young children[1]. Safe and reliable sedative agents are preferred to be utilized in an outpatient setting. This study suggested a new protocol of the sedation other than the conventional one (chloral hydrate) which includes these criteria. The use of low dosage of chloralhydrate alone as 40-50mg/kg, was found to be associated with a high failure rate in sedating children, but with fewer side effects, while higher doses 70-100/kg produce higher success rates approaching 95% or more in sedation, with a possible increase in the incidence of critical adverse effects like apnea, bradycardia or respiratory obstruction[11,12]. We tried to add melatonin to chloralhydrate, to achieve a high successful sedation rate with a relatively low dosage of chloralhydrate, and to reduce the possible undesirable side effects as well. Melatonin is generally safe in children and no studied have revealed any serious effects to date[13]. It could be effective as a sedative alone or if combined with other sedative like chloralhydrate, the onset of sedation could be quicker and the required dose of chloralhydrate will be reduced, without harmful drug interaction[14].

Melatonin is a dietary supplement and its dose ranges widely from a very minimal dose to higher doses depending on the child's sensitivity of response. Overdoses might be associated with a few irritating unpleasant side effects like dizziness, nausea, a headache, but without reported severe events. Due to this point, it is a preferable to begin with a minimal dose and to adjust the dose as necessary[14]. In this study, we found a higher success rate of sleep induction among the group B (combined melatonin and chloral hydrate) within 30 minutes of the dose intake, when compared with the group A (chloral hydrate alone). Many previous studies utilized melatonin as an alternative to chloral hydrate for sedation. Schmidt M., *et al*. Studied the use of melatonin alone for sedation in auditory brainstem response test and found that melatonin – induced sedation is a good alternative to sedation due to the higher success rate of sedation compared to chloral hydrate with no significant side effects, like our study outcome[15]. Similarly, another research work conducted by Castell L., *et al*., about the efficacy of Melatonin for Auditory Brainstem response testing in children. The author demonstrated that melatonin allowed partial or complete successful rate in sedating children for ABR testing in 90% of children[16]. On the contrary of our finding, one research work has relatively same methods, conducted by the anaesthetist: Sury MR. *et al*., tested the role of Melatonin when added to chloral hydrate upon sedation of children undergoing MRI, and concluded that melatonin did not contribute to sedation and did not add any more sedation than that yielded by choral hydrate alone[14]. We found a higher failure rate among the group sedated with the choral hydrate compared with that of the group of combined melatonin and chloral hydrate. These cases got drowsy and sleepy, but not achieving the required deep sleep level (UMSS score 3). They needed an extra dose of chloral hydrate 25m/kg to complete their sedation. This result resembles that seen with the study done by Fong CY. *et al*., (chloral hydrate as sedating agent for neurodiagnostic procedures in children). They found a higher failure rate with one dose 50mg/kg in comparison with two doses[17], whereas a study done by C. L.Yuen *et al*; (Melatonin versus chloral hydrate as a sedating agent in performing EEG in pediatric patients) found that melatonin has a similar success and failure rates in sedation[18]. In our study, all the failed cases, whether sedated with the tested protocol, or the chloral hydrate (controls), were recorded among the groups of children older than 2 years. This note is consistent with that reported by the study of Schmidt CM *et al*. They recognized the failure rate for melatonin in sedation was with age dependent starting from the age of 3 years and above[19]. We explored that melatonin contributes to a faster sleep onset latency in the group sedated with the combined protocol than that in chloral hydrate group. However, the sleep duration of combined protocol was longer. Abdelgadir IS. *et al*, showed similar findings in his systemic review and meta-analysis about the use melatonin in the management of sleep problems in children with neurodevelopmental disorders[20]. He reported that melatonin reduced the sleep onset latency and prolongs the sleep duration. Ashrafi M., *et al*. in his study: Melatonin versus chloral hydrate for recording sleep EEG; found that the sleep onset latency in chloral hydrate group was similar to that of melatonin group. He also reported that the sleep duration of the group sedated with melatonin was shorter than that of the group sedated with chloral hydrate[21].

Our study described the sedation scores over time for both groups, during the 100 minutes of the dose intake.It showed significant differences in the mean sedation scores between the two protocols. At the 60th minute, the mean sedation scores for both protocols became nearly equal till the 100th minute whence the sedative effect of the choral hydrate started to decrease, while that of the combined protocol continued for a while. This result concludes that the combined protocol has a higher efficacy than that of the chloral hydrate alone. We believe that the longer sleep duration noted in the group of combined sedatives, might be due to the effect of melatonin as well as that of chloral hydrate. In this research, few minor side effects were detected among children during the sleep latency. These were mild and rapidly disappeared. They

include nausea and vomiting, abdominal discomfort and hyperactivity or agitation. Although the frequency of each of these side effects appeared slight more in children of the chloralhydrate group, but it does not show a statistical significance. As a result of these findings, we suggest that the addition of melatonin to chloral hydrate might be a safe sedative procedure and having few side effects. This result is supported by the work of the studies of Buscemi N., Schmidt CM *et al*, and Abdelgadir IS. *et al*. They noted few side effects with sedation by melatonin like a headache, dizziness, nausea, and drowsiness[8,15,20].

Limitations of our study include: First: some parents refused the test. Second; a few children were resisting the oral intake of the sedative doses and were not fully sedated and were considered as failed cases. Third; the number of cases were more in group B than group A, because the study allocated patients to each of the two groups by a simple random way according to the number stored inside the opaque envelopes Fourth; there were difficulties to follow-up some the slept children at home after discharge from the clinic and unclear feedback recall of data about their exact sleep duration.

CONCLUSION

Our study concludes that melatonin might be a safe and effective sedative and could enhance the efficacy of sedation when added to chloral hydrate in auditory brainstem response testing.

To be effective in sedating children, frequently, high doses of chloral hydrate might be required and harmful side effects could not be avoided.

The add-on melatonin to chloral hydrate in low doses can contribute to a rapid and a peaceful sedation as well as a reduction in the incidence of major side effects due to the high doses of chloral hydrate.

Finally, we suggest that a new protocol of combined melatonin and chloral hydrate might be tried in sedation of children undergoing auditory brainstem response test in an outpatient setting.

To support our study, we recommend a further study to evaluate the effect of melatonin upon the efficacy of chloral hydrate in the sedation of children.

CONFLICT OF INTEREST

There are no conflicts of interest.

5. Appendix: University of Michigan Sedation Scale (UMSS).

score	characteristics
0	Awake and alert
1	Minimally sedated :tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleepy, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated/deep sleep, arousable only with a significant physical stimulation
4	unarousable

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