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Clinical Significant Effect of Chloral Hydrate: Diazepam Combination in the Induction of Sedation During Auditory Brainstem Response in Children with Hearing Loss

Hayder Mutter Al-Kuraishy[1], Maryam Mohammed Hammed[2], Haider W. Alsarhan[3]

[1]Department of clinical Pharmacology and Therapeutic, Medical Faculty, College of Medicine, Al-mustansiriya University, Baghdad, Iraq

[2]B. Sc. College of Pharmacy, Baghdad University, Baghdad, Iraq

[3]Department of Audiology College of Medicine, Al-mustansiriya, University, Baghdad, Iraq

Email address:

Hayderm36@Yahoo.com (H. M. Al-Kuraishy), Maryam33@yahoo.com (M. M. Hammed), hdrwork@yahoo.com (H. W. Alsarhan)

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Abstract: Hearing loss is the most common sensory disability in the world, hearing loss should be early diagnosed and treated since; it leads to speech and language disorders. Auditory brainstem response (ABR) or Auditory evoked potential (AEP) is a neurologic test done by an audiologist to measure auditory evoke potential. Different types of sedation levels are used during auditory brainstem response test. Therefore, the aim of present study was evaluation of the sedative effect of chloral hydrate during auditory brainstem response (ABR) on children with hearing problems. Randomized selection of 160 children with age ranged between 1-5 years with hearing disorders, they were divided into: Group A: Received 20 mg/Kg chloral hydrate orally. Group B: Received 20 mg/Kg chloral hydrate orally plus 0.5 mg/Kg diazepam rectally. Group C: Received 40 mg/Kg chloral hydrate orally. Group D: Received 40 mg/Kg chloral hydrate orally plus 0.5 mg/Kg diazepam rectally. Regarding ABR testing results, positive ABR test was superior in combined group compared to other groups p=0.005 whereas; negative ABR test was low in combined group compared to other groups p=0.006. At the end of ABR testing 118.52±9.88 of testing children in combined group completed the test compared to other groups p=0.0139 while; 98.21±7.22 of testing children in combined group not completed ABR test compared to other groups p=0.005.In conclusion, combined chloral hydrate plus diazepam give more significant sedative effect than chloral hydrate alone during ABR testing in children with hearing disorders.

Keywords: ABR, Chloral Hydrate, Diazepam, Hearing Loss

1. Introduction

Hearing loss is the most common sensory disability in the world, about 270 million people in the world are associated with hearing dysfunctions either conductive or sensori-neuroal hearing disorders [1]. Hearing loss should be early diagnosed and treated since; it lead to speech and language disorders that may cause communication and educational disorders which may lead to psychological impact, social stigmatization and social withdrawal [2]. Therefore, general screening test for hearing loss is recommended either by automated oto-acoustic or auditory brain stem evoked potential for assessment of auditory function [3, 4].

Auditory brainstem response (ABR) or Auditory evoked potential (AEP) is a neurologic test done by an audiologist or an electrophysiology technician to measure auditory evoke potential taking out from on-going brain electrical activity and documented by electrodes placed on scalp and done while the person is sleep or at a complete rest. This test is an exogenous response which depends on external factors. It's first described in 1971 by Jewett and Williston. The ABR test gives information about brain pathway for hearing and inner ear (cochlea) [5, 6].

Different types of sedation levels are used during auditory

brainstem response test these are, minimal sedation, in which the sedative drug relief anxiety only [7] moderate sedation, in which the sedative drug cause depression of consciousness but the patient can response to external stimuli [8] while; deep sedation: in which the sedative drug cause depression of consciousness, the patient cannot be awakened but can responds to repeated painful stimuli, the cardiovascular function is kept with assistant ventilation [9, 10]. Sedation scales like MSAT (Minnesota Sedation Assessment Tool), UMSS (University of Michigan Sedation Scale), Ramsay Scale, and the RASS (Richmond Agitation-Sedation Scale) are used to measure the level of sedation [11].

Chloral hydrate is an anxiolytic, sedative and hypnotic agent not related to opiate or benzodiazepine classes, chloral hydrate also called (chloral) is an organic compound with the chloride atoms that increasing the lipid solubility and CNS depressant effects, it is formulated as a hydrate to improve the stability, chloral hydrate has central nervous system (CNS) depressant effects by its active metabolite (trichloroethanol), that enhances the gamma amino butyric acid (GABA) receptor complex and activated chloride current thus; uses of flumazenil in a case of chloral hydrate intoxication, which is a GABA antagonist, pointed to the possible action of chloral hydrate at GABA level [12, 13]. On the other hand, diazepam is a long acting benzodiazepine with anticonvulsant, anxiolytic, sedative and muscle relaxant properties [14], it bind to benzodiazepine receptors which are coupled to Gamma-amino butyric acid-A (GABA-A) receptors (which are ligand-gated chloride-selective ion channels that are activated by GABA, this increase the affinity of GABA to the GABA receptor. Binding of diazepam to its receptor encourages the binding of GABA to GABA receptor that increase chloride ions conduction across neuronal cell membrane; led to hyperpolarization of neuronal membrane potential [15].

Therefore, the aim of present study was evaluation of the sedative effect of chloral hydrate during auditory brainstem response (ABR) on children with hearing problems.

2. Subjects and Methods

The study was conducted in Department of Clinical Pharmacology, College of Medicine, Al-Mustansiriya University in cooperation with ENT unite in Al-Yarmook teaching hospital. This study was approved by the specific Scientific Jury and Ethical Committee in the medical board college of medicine, Al-Mustansiriya, all of enrolled participants gave informed verbal consent from their parents for their participations in this study. Randomized selection of 160 children with age ranged between 1-5 years, the children have no history of any acute or chronic somatic or psychological diseases and not take any medication during this study.

An inclusion criterion includes physical state class 1 or 2 according to American society of anesthesiologists (ASA) [16], age between 1-5 years, have not been taken sedative or hypnotic agent within 48hrs and have not been diagnosed with gastritis, chest infection or any other serious systemic disease.

Participated children were divided equally and randomly into 4 groups, 40 children in each group and assigned as A, B, C, and D.

Group A: Received 20 mg/Kg chloral hydrate orally.

Group B: Received 20 mg/Kg chloral hydrate orally plus 0.5 mg/Kg diazepam rectally.

Group C: Received 40 mg/Kg chloral hydrate orally.

Group D: Received 40 mg/Kg chloral hydrate orally plus 0.5 mg/Kg diazepam rectally.

All children were prepared by give their parents specific instructions like weak up the child early and don't let him sleep until the time of test, simple breakfast should be taken, avoid drinking through the last 3 hour before the test.

Any child not reaches adequate sedation level within 30 minute after drug administrations; we give him additional dose of chloral hydrate as half of the initial dose.

After sedative agent have been given (chloral hydrate alone or in combination with diazepam), Ramsey sedation scale was used for assessment of the sedation levels within 10 minutes. Ramsey sedation scale (RSS) [17] is scale used to test the arousal and vigilance status; RSS have six different levels according to the patient arousal level these are:

- Level I: Patient is anxious and agitation or restlessness or both.
- Level II: Patient is cooperative, oriented and tranquilized.
- Level III: Patient responds to commands only.
- Level IV: Patient exhibits brisk response to loud auditory stimulus.
- Level V: Patient exhibits sluggish response to loud auditory stimulus.
- Level VI: Patient exhibits no response.

Statistical analysis

Analysis of data was carried out by using of SPSS-22 (Statistical Packages for Social Sciences- version 22). Data were presented as simple measures of frequency, percentage, mean and standard deviation. The significance of difference of different means was tested using ANOVA test for the difference among the independent means. Statistical significance was considered when the P value was < 0.05.

3. Results

In the present study, 160 children out of 184 completed ABR tests since; 24 children were excluded, and they were randomly divided in to four groups regardless of age, gender, weight, family history and drug allergy, figure 1.

In the present study, the age of enrolled children was between 1-5 years, in group (A) age mean was (2.39±1.10), in group (B) (3.11±0.82), in group (C) (3.09±1.07) and in group (C) (2.99±1.02). Drugs allergy to the different type of drugs were (2) children in group (A), (2) children in group (B), (3) children in group (C) and (1) children in group (D). The family history for hearing loss was (2) children in group C and (1) child in group D, table (1).

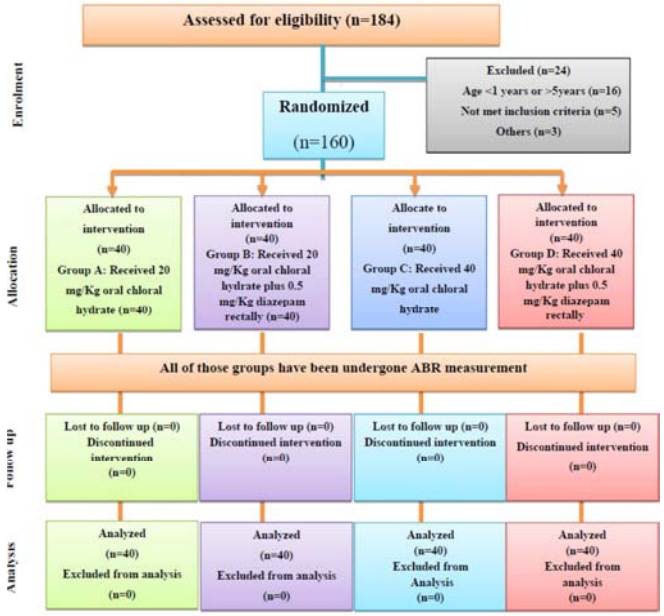


Figure 1. *Consort flow diagram of the present study*

Table 1. *Demographic data of participated children.*

Parameters		Group A n=40	Group B n=40	Group C n=40	Group D n=40
Age (years)		2.39±1.10	3.11±0.82	3.09±1.07	2.99±1.02
Gender	Male	28	25	17	18
	Female	12	15	23	22
Family history of hearing loss		-	-	2	1
Drug allergy		2	2	3	1
Body weight (kg)		16.05±3.83	17.97±4.67	19.48±4.59	18.25±3.91

Results are presented as mean ±standard deviation and number

3.1. Sedative Effect of Chloral Hydrate

In the present study, we gave chloral hydrate re-dose as half of the initial dose according to the body weight, once time only, and after 30 minutes of the initial dose if the child was not reach the adequate sedation during ABR testing according to the sedation score of RSS. When chloral hydrate used alone in group (A) and (C), higher numbers of the children were required chloral hydrate re-dose 40 children (100%) in group A and 35 children (87.5%) in group C compared with the uses of chloral hydrate in combination with diazepam in groups B and D, figure 2.

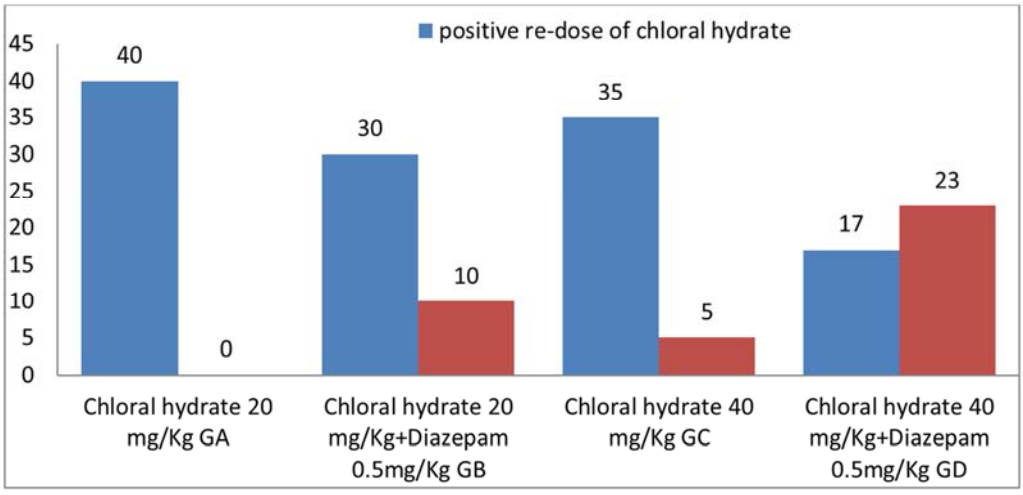


Figure 2. *Frequency of children that required chloral hydrate re-dosing.*

Regarding the total times (in minutes) spent at ABR centre for each child [from reach the centre till discharge it was significant; in group A (100.58±7.42 min) and in group C (96.66±5.16 min) completed ABR test significantly figure 3.]

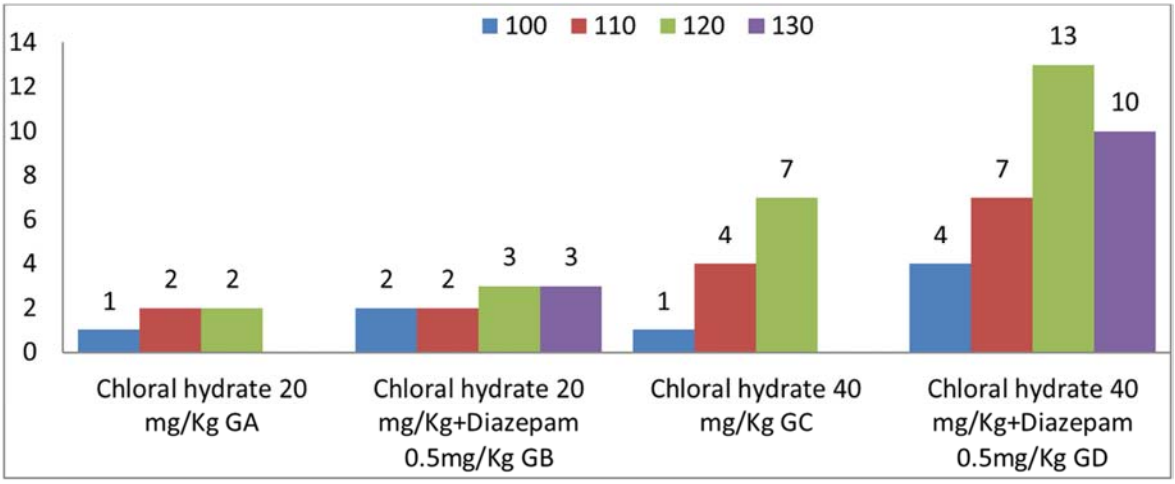
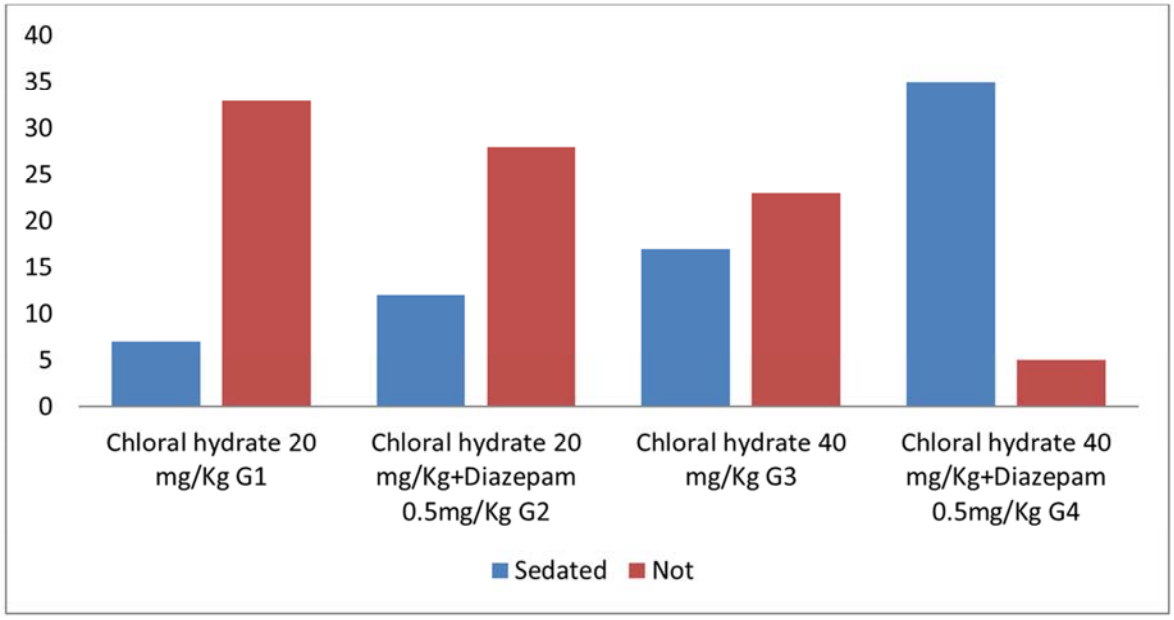


Figure 3. *Total staying time during ABR testing.*

3.2. Sedative Effect of Chloral Hydrate Alone or in Combination with Diazepam

The number of sedated children was increased as chloral hydrate dose was increased, compared with the uses of chloral hydrate alone or in combination with diazepam in groups B, and D the number of children that required chloral hydrate re-dose to reach optimal sedation level were decreased (30 children 75% in group B, and 17 children 42.5% children in group D) and better sedative results were seen in group D that take a high dose of chloral hydrate (40 mg/Kg) in combination with diazepam (0.5 mg/Kg) significantly=*0.0048* figure 4.



p=0.0048

Figure 4. *Numbers of children sedated in each group.*

Therefore, there is insignificant difference in the onset of sedation time among different doses of chloral hydrate alone or in combination with diazepam, it was 37.14±3.93, 36.66±6.15, 37.05±6.13 and 38.68±5.56 for groups A,B,D and C respectively p=0.1961. The sedated numbers were higher in combined group (chloral hydrate plus diazepam) compared to other groups p=0.0062. Regarding ABR testing results, positive ABR test was superior in combined group compared to other groups p=0.005 whereas; negative ABR test was low in combined group compared to other groups p=0.006. At the end of ABR testing 118.52±9.88 of testing children in combined group completed the test compared to other groups p=0.0139 while; 98.21±7.22 of testing children in combined group not completed ABR test compared to other groups p=0.005, table 2.

Table 2. *Variations in ABR test variables among the treated groups.*

Variables	Group 1 (n=40)	Group 2 (n=40)	Group 3 (n=40)	Group 4 (n=40)	F statistic	P value
Sedation time	37.14±3.93	36.66±6.15	37.05±6.13	38.68±5.56	1.5812	0.1961
Sedated (n)	7(17.5%)	12(30%)	17(42.5%)	35(87.5%)	416.75	0.0062**
Not sedated(n)	33(82.5%)	28(70%)	23(57.5%)	5(12.5%)	352.47	0.0048**
Positive ABR test	5(12.5%)	10(25%)	12(30%)	34(85%)	383.33	0.005**
Negative ABR test	35(87.5%)	30(75%)	28(70%)	6(15%)	407.11	0.006**
ABR testing (min)						
Completed	112±8.36	117±11.59	115±6.74	118.52±9.88	3.6557	0.0139*
Not completed	100.58±7.42	101.33±5.71	96.66±5.16	98.21±7.22	4.446	0.005**

Results are expressed as mean± SD, n (%),*p<0.01; ABR: auditory brainstem response

4. Discussion

The present study showed significant sedative effect of chloral hydrate during auditory brainstem evoke potential at a low dose 20 mg/kg and high dose 40 mg/kg, low dose of chloral hydrate required re-dosing 100% whereas high dose of chloral hydrate required re-dosing 87.5% for reaching a full sedation as revealed by Koo *et al*, study that demonstrated an initial dose of choral hydrate (48±2) mg/kg was not harmfully affect the sedation level or the requirement for extra-dose during ABR testing [18]. Also, 80.8% of sedated children completed ABR testing without any complications therefore; chloral hydrate is regarded as reliable sedative agent [19]. Furthermore, re-dosing of chloral hydrate was more required in children receiving 20 mg/kg than children that received 40 mg/kg for reaching the adequate sedation during ABR testing; the cause of choral hydrate re-dosing was the low dose of choral hydrate in order to reduce of adverse effects since; choral hydrate is linked with significant serious side effects [20]. Also, the difference was significant in the numbers of non-sedated children that received a low dose of chloral hydrate; this fail in reaching the sedation level for ABR test was due to the low doses of chloral hydrate that was used or due to other factors that reported by Keidan *et al,* study that demonstrated children anxiety, fasting and rapid sedation procedure may affects the initial sedation [21]. The mechanism of sedative effect of chloral hydrate may be due to its active metabolite that augments GABA-receptor complex which activates chloride current, augment acetylcholine effect at neuromuscular junction, potentiating 5-HT3 at ganglion neurons and intensification of GABA effect on the duration and amplitude of GABA-A receptors at hippocampal neurons [22-24]. Additionally, chloral hydrate and its active metabolites enhanced GABA currents at hippocampal neurons only when GABA activity and concentration is low thus; a chloral hydrate effect on GABA activity wasconcentration dependent [25]. Indeed, the precise effect of trichloroethanol is mainly on chloride channel since bicuculine (chloride-channel antagonist) block trichloroethanol effects regardless of GABA concentration [26]. On the other hand, trichloroethanol inhibits NMDA receptors in different manner [27].

The results of present study also showed the beneficial effects of combination of chloral hydrate plus diazepam as a sedative agent during ABR testing compared with the uses of chloral hydrate alone, this combination led to increased in numbers of sedated children, increased in number of children that completed ABR, decreased in numbers of children that required chloral hydrate re-dose but this beneficial effect was associated with longer staying time at ABR center. Diazepam not affects automated behavior recognition in animal model study as documented by Van *et al*, study [28] so; diazepam was selected in the present study during auditory brainstem evoked response.

Interestingly, no reported recent studies documented the uses of diazepam as sedative agent during auditory brainstem evoked response in newborns and children, but other benzodiazepine types were used like, intranasal midazolam compared with chloral hydrate, where 0.5 mg/kg of midazolam lead to significant sedation but; chloral hydrate was more potent than intranasal midazolam regarding successful sedation, rapid recovery and onset of sedation [29]. Previously, diazepam administration was used as sedative agent during auditory brainstem evoked response since; it not affects ABR amplitudes [30]. Moreover, Schweder *et al*, study revealed that diazepam, midazolam and flunitrazepam were not affecting the mid-latency auditory evoked potential (MLAEP) that reflect the brain cortical processing of auditory stimuli during ABR testing [31], thus benzodiazepine is more preferred than general anesthetic agents during ABR recording since; general anesthetic agent affects ABR wave and temporal precision response at brainstem neurons causing a significant delayed in transitory of sensory information from brainstem toward cortical and sub-cortical brain neurons [32], thus; benzodiazepine effect on ABR recording is a drug selective since; GABA receptors at auditory pathway showed extra-ordinary response due to differences in GABA-A subunits when alpha and gamma subunits are expressed differentially so; the pharmacological effect of benzodiazepines at GABA receptors are different [33] recently, modulation of GABA activity may affecting the glutamatergic neurotransmission seeing as GABA counterbalance the glutamate at NMDA receptors [34].

Moreover, Nobre *et al*, study revealed that GABA receptors play a vital role in the auditory evoked potential since; anxiety and fear during ABR testing is represented by wave V that generated by inferior coliculus of auditory pathway that contains a high density of GABA receptors so;

diazepam was effective in reduction of anxiety and induction of sedation during ABR testing without effect on the sensory information processing [35]. Diazepam bind to benzodiazepine receptors that increase chloride ions conduction across the neuronal cell membrane; led to hyper polarization of neuronal membrane potential, reduced excitatory postsynaptic potential through inhibition of glutamate release at hippocampal area [36]. As well, acute dose of diazepam leads to significant reduction in brain derived neurotophic factor which play a role in activation of NMDA receptors since; enhancement of glutamatergic neurotransmission causing anxiety and induction of fear [37]. Therefore, all of these studies may explain the sedative effect of diazepam during ABR testing.

Furthermore, combination of chloral hydrate with diazepam decreased the need for chloral hydrate re-dosing this was may be due to the additional sedative effect of diazepam. Also, high dose of chloral hydrate (40 mg/Kg) in combination with diazepam (0.5 mg/Kg) produced more significant sedative effect these findings are supported by different studies that showed the additive effect of diazepam on choral hydrate sedative effect [38-40]. The preferential sedative effect of diazepam or choral hydrate is related to their effect on orexine cells in the perifornical area of the hypothalamus via activation of GABA receptors and inhibition of histaminergic receptors [41], as well; Norman and Anderson 2016 study revealed that orexin antagonist suvorexant (block orexin A and orexin B receptors) leads to induction of sleep, reduced time for sleep onset, increasing sleeping time and induction of sedation [42], these findings are in agreement with our results since both diazepam and chloral hydrate causing GABA activation and orexin antagonist activity that participated in the additive sedative effect of diazepam and chloral hydrate combination. Furthermore, Ghazal *et al*, study showed that diazepam produced sedative effect in mice through modulation of neuropeptide S that play a role in anxiolytic effect, arousal and wakefulness [43] this may explain the augmented sedative effect of chloral hydrate plus diazepam that led to improvement in the sedation time during ABR test.

In addition, GABA-Ais consist of three main subunits called alpha, beta and gamma which regarded as binding site for different CNS depressant drugs, diazepam binds to alpha subunit of GABA-A receptor that triggering the opening of inhibitory chloride channel so; diazepam is unable for opening of inhibitory chloride channel directly whereas; other sedative agent like propofol, choral hydrate and barbiturate are capable for opening of inhibitory chloride channel directly independent on GABA action causing severe sedation and coma so; they classified as drug with low therapeutic index thus; combination of diazepam with choral hydrate lead to more sedative effect with less choral hydrate induced complications [44, 45].

Moreover, chloral hydrate combination with other CNS depressant agent have been trailed, Maheras and Gow study, revealed that administration of chloral hydrate 200 mg/kg plus 375 mg/kg of tribromoethanol provides optimal anaesthesia for sixty minutes with minor effects on ABR wave's thresholds and latencies [46]. Recently, Reynolds *et al*, studies illustrated that single intranasal dexmedetomodine is superior to oral chloral hydrate regimen or combination of chloral hydrate plus dexmedetomodine for induction of sedation during ABR recording [47, 48]. On the other hand, not all combination is of value during ABR testing regardless of sedation effect, since many anaesthetic and sedative agents may affect ABR wave amplitudes since, ketamine-xylazine combination lead to significant prolongation in wave latencies and wave amplitude [49], thus; chloral hydrate in spite of suboptimal anaesthetic effects it preserve waveforms of ABR so; it recommended alone or in combination with other agents during ABR recording.

5. Conclusion

Combined chloral hydrate plus diazepam give more significant sedative effect during ABR testing in children with hearing disorders.

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