The use of melatonin for auditory brainstem response audiometry in children with comorbidities

THE USE OF MELATONIN FOR AUDITORY BRAINSTEM RESPONSE AUDIOMETRY IN CHILDREN WITH COMORBIDITIES

Declarations

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Abstract

Purpose: In this study, the efficacy and feasibility of melatonin in young children with and without comorbidities, undergoing auditory brainstem response audiometry (ABR) was evaluated. The aim of this study was primarily to evaluate the use of melatonin for ABR investigations in children with comorbidities. Secondly, the efficacy of melatonin was evaluated based on several factors like sleep-onset latency, sleep duration, frequency of awakenings as well as adverse events.
Methods: Click-induced ABR tests were performed at the outpatient clinic between January, 2018 and August, 2020. Investigations were considered successful when binaural testing was completed. A dose of melatonin depending on age, 5 milligrams for children younger than 6 years and 10 milligrams if older than 6 years, was administered after placement of electrodes.
Results: 131 children were included in this study. 87 percent of all ABR investigations were performed successfully. Comorbidities such as neurodevelopmental disorders or developmental delays were present in 70% of all children. There was no significant difference in age (p=0.36) or gender (p=0.97) between the success and failed group. Additionally, comorbidities were equally distributed between both groups. Mean sleep duration was 38 (SD 21) minutes and sleep-onset latency was 28 (SD 20) minutes. No adverse events were documented.
Conclusion: Melatonin is effective for ABR examinations in infants and children with and without comorbidities. Furthermore, it allows for sequential testing in those at risk for progressive hearing loss. Clear instructions to caregivers and expertise of audiologists are a prerequisite for optimal outcomes.

Key words: melatonin, hearing test, brainstem evoked response audiometry, children, infants

1. Introduction

Auditory brainstem response audiometry (ABR) is the golden standard for the evaluation of hearing status in children if behavioral audiometry is not feasible [1]. ABR is a non-invasive procedure that requires sleep or profound relaxation of the child throughout the investigation for optimal testing conditions. Newborns can be tested during their natural sleep which becomes more challenging in children older than 6 months as their sleeping pattern becomes more fragmented. In these cases sedation or general anesthesia is often necessary in order to obtain accurate hearing thresholds.

Several sedation methods are described in literature such as the use of chloralhydrate, pentobarbital with alimemazine or ketamine [2-4]. Chloral hydrate is the most widely accepted sedative for young children undergoing investigations such as magnetic resonance imaging (MRI) and ABR testing, however Avlonitou et al. observed complications in 20% of children such as hyperactivity, vomiting and rash as well as respiratory distress (0,5%) or apnea (0,2%)[2]. Pentobarbital is another popular sedative used in this setting but it can cause paradoxical hyperexcitability, disorders of balance and prolonged sleep [3]. Ketamine induces deep sedation. This drug on the other hand can induce disorders of consciousness, breathing disorders and memory disorders [4].

Since most of these sedation protocols can have serious complications, monitoring is required. Therefore, different studies evaluated the efficacy of melatonin to induce natural sleep for children undergoing brainstem audiometry [5-9].

Melatonin, primarily released by the pineal gland, is a hormone that regulates several biological functions including the circadian rhythm and sleep by its effect on the suprachiasmatic nucleus [10]. Sanchez-Barcelo et al. described the clinical use of exogenous melatonin in children including the treatment of insomnia as well as sedative properties in a diagnostic context such as EEG and MRI [11, 12]. No adverse events for melatonin have been reported in literature, neither for chronic use nor for use in neurologically impaired children [13]. Additionally, melatonin used as a natural sleep inducer, doesn't influence morphology and latencies of the ABR physiology [14].

The clinical feasibility of the use of Melatonin for ABR has already been demonstrated by other authors[5-9]. The aim of this study was primarily to evaluate the use of melatonin for ABR investigations in children with associated disorders. The efficacy of melatonin was evaluated in children with and without comorbidities based on several factors like sleep-onset latency, sleep duration, frequency of awakenings as well as adverse events. In addition, the use of melatonin was evaluated for repeated testing in the context of long-term follow-up, for example in children with Down Syndrome and congenital CMV infection.

2. Materials and methods

2.1 Inclusion criteria

All children who underwent an ABR investigation with melatonin-induced sleep at the Department of pediatric otolaryngology of the Antwerp University Hospital, Belgium, throughout the period January 1st, 2018 and August 31st, 2020 were included, regardless of the presence of comorbidities.

As in our routine clinical practice, ABR testing was performed when no reliable hearing thresholds could be obtained with behavioral audiometry or when objective audiometry was preferred, for example after failed neonatal hearing screening. Also, ABR testing for patients younger than 6 months was performed during natural

sleep. For patients older than 6 months, ABR testing was performed using melatonin induced sleep when no signs of middle ear problems are seen upon clinical examination or tympanometry. When associated middle ear effusion was present, ABR testing was conducted under general anaesthesia after placement of a ventilation tubes.

Patient characteristics such as age, gender, comorbidities and indication for ABR testing were registered. Comorbidities were categorized in 7 subgroups to analyze the obtained data (figure 1 and table 1). The group neurodevelopmental disorders covers patients with (amongst others) perinatal asphyxia and syndromic neurodevelopmental disorders. Patients with Down Syndrome were categorized separately. The subgroup developmental disorders covers neurologic disorders such as cerebral palsy and microcephalia.

2.2 *Setting*

ABR testing was performed at the outpatient clinic by certified pediatric audiologists. Prior to the ABR test, the parents received an information brochure explaining the procedure in more detail. This brochure contains information on the properties of Melatonin and the procedure of the ABR study, and emphasizes the need for sleep deprivation. Parents were requested to put their child to bed an hour later, and wake up 2 hours earlier than usual. Furthermore, it was emphasized that the child should not take a nap before the time of the appointment.

2.3 Test procedure - protocol

Upon arrival at the outpatient clinic, children were installed in a comfortable sound proof booth where testing took place. Oral melatonin in syrup suspension (3mg/ml) was ordered and prepared in the hospital pharmacy. The dosage depended on age: 5 mg melatonin for children below 6 years and 10mg in children older than 6 years. A second dose of 5mg melatonin was administered for all ages if still awake after 30 minutes, in accordance with the timing and dosage used by Guerlin et al.[6] Four electrodes were placed on the scalp of the child (one on the vertex, one 2cm below and two on the mastoid process bilaterally), after which the first dose of melatonin was administered in a quiet setting. Afterwards, insert phones were placed using 'foam tips' and ABR testing was initiated using click stimuli at an intensity of 80dBnHL. This intensity allowed easy detection of reliable peaks as well as changes in latency times when decreasing the intensity from this volume with gradual steps of 20dBnHL.

If no response occurred at 80dBnHL, stimulation intensity was increased up until 95dBnHL. The hearing status was evaluated bilaterally for all patients based on air conduction. Hearing thresholds were determined for each ear separately with contralateral masking. The intensity of the contralateral masking was 40dB under stimulation level of the tested ear. This protocol was adjustable according to patient characteristics or circumstances, since the measurement was performed manually (Bio-Logic Navigator Pro, Cordial Medical).

2.4 Outcome measures

Investigations were considered successful when binaural testing was completed with reliable results regardless of the frequency of awakenings during the measurement. Additionally, factors such as sleep onset latencies, duration of sleep, awakenings and adverse events were reported.

2.5 Data analysis

The following statistical tests were used: Chi-Square for sex, the Fisher exact's test for comorbidities and non-parametric Mann-Whitney U Test for age among success and failure group. All analyses were carried

out using IBM SPSS® Statistics version 23.0.0.3. P-values < .05 were considered significant. Data are presented as mean with standard deviation or median with 25-75% percentile.

2.6 ethical approval

All patients were managed in accordance with the routine clinical practice and ethical standards of the Antwerp University Hospital Antwerp. This paper describes the results of a retrospective chart review and informed consent of the parents or legal caregivers was not required.

3. Results

3.1 participants

During the study period, 155 children were tested at the pediatric ENT Department of the Antwerp University Hospital, Belgium. One hundred thirty-one unique binaural ABR investigations could be included for analyses, of which 70 boys and 61 girls. Children's age ranged between 6 months and 9,2 years (median 1.9). Different indications for ABR testing were noted such as unreliable audiometry (59%, n=77), delayed speech and/or language development (13%, n=17), suspected unilateral hearing loss (10%, n=13) and failed neonatal hearing screening (18%, n=24) (Table 1). Mean sleep duration was 38 (SD 21) minutes and sleep-onset latency was 28 (SD 20) minutes.

3.2 Successful ABR testing

Eighty-seven percent of all ABR investigations were performed successfully.

Sub-analysis of the success group (n=114) shows a median age of 2.32 years, a sex ratio (males to females) of 1,1 and 71% (n=81) of the children had comorbidities. Unreliable audiometry was the main indication for ABR testing in this subgroup (60%, n=68), followed by failed neonatal screening (18%, n=20). All children fell asleep after melatonin was administered; 1 dose was sufficient for 70% while 2 doses were required for 30%. Sixty-five children (57%) remained asleep during testing, 33 children (29%) showed some awakenings but remained asleep and 16 children (14%) woke up and remained calm upon completion of the test. Mean sleep-onset latency was 27 minutes (SD 18) and mean sleep duration was 41 minutes (SD 19) (Table 2). ABR results of the success group (n=114) showed that 47% of children (n=54) had bilateral normal hearing, 15% (n=17) mild, 14% (n=16) moderate and 6% (n=7) have profound hearing loss. Unilateral severe/profound hearing loss was found in 15% (n=17).

3.3 Failures

The group of children who failed testing (n=17) shows a median age of 1.7 years, a sex ratio (males to females) of 1,1 and 71% (n=12) had comorbidities. The two main indications for ABR testing were unreliable audiometry (53%, n=9), failed neonatal hearing screening (24%, n=4) and delayed speech and/or language development (24%, n=4). All these children received 2 doses of melatonin after which 65% (n=11) did not fall asleep and 35% (n=6) children fell asleep but woke up before completion of testing of both ears. Mean sleep-onset latency was 55 minutes (SD 43) and mean sleep duration was 8 minutes (SD 6) (Table 2).

Prior to the test, 29% of the children had already taken a nap. There were no significant differences in age (p=0.36), sex (p=0.97) and the presence of comorbidities (p= 1.00) among the success and failure group.

3.4 Comorbidities

Seventy percent of patients have comorbidities among which developmental disorders (n=25, 19%) and Down Syndrome (n=20, 15%) were the most prevalent (figure 1 and table 1). Seventy-one percent (n= 12) of patients with CMV infection were asymptomatic.

3.5 Repeated testing

Of all children, only the first testing was included for analysis. However, 14 children were tested multiple times, ranging from two to eight times per child (table 3). The most common indication for repeat testing was follow-up in the context of congenital CMV infection. Two of the children had a failed test the first time and had successful testing with melatonin induced sleep upon follow-up.

3.6 adverse events

No adverse events were observed or registered even though one patient vomited after the first dose of melatonin. This patient received melatonin through a nasogastric tube because of feeding difficulties.

4 Discussion

4.1 Efficacy of Melatonin

This study shows an eighty-seven percent success rate of auditory brainstem response audiometry performed with melatonin induced sleep in infants and children with and without comorbidities. This outcome corresponds with literature about the use of melatonin sedation in ABR testing. A recent systematic review showed a success rate ranging from 65 to 86.7% in the existing publications concerning this subject, with a number of subjects ranging from 29 and 249 in the individual studies [15]. Furthermore, no adverse events were reported for the use of melatonin. After publication of this review, another series has been published by Hajjij et al. which describes a similar success rate of 83% in 247 tested children, and no adverse events were reported [8].

4.2 predictive factors

Factors that may influence the chance of a successful test that have been described are age, depth of sleep, dosage of melatonin and comorbidities such as psychomotor retardation. In our study, no statistically significant difference could be found with regard to age or comorbidities [15].

Even though 14% of the children woke up in the success-group, they remained calm and a reliable ABR testing could be completed. In the group with failed tests, only 5 children fell asleep but were not calm enough to take a reliable test of both ears. Remarkably, 29% of the children in this group had already taken a nap, despite the instructions given to the parents beforehand. This finding emphazies the need for detailed instructions of the parents to increase the chance of success.

4.3 clinical applicability

Containing reliable audiometry is often not possible in children with comorbidities, such as Down Syndrome or developmental disorders. In addition, some children with comorbidities have an increased risk of hearing loss. Therefore, investigating whether melatonin can be used to perform a reliable ABR measurement in this subgroup is clinically relevant. However, most of the studies published to date did not investigate the role of comorbidities as determinant for success. In our data we did not see a difference in the distribution of children with or without comorbidities in the groups with passed or failed ABR examinations.

Another interesting feature is that melatonin could be used in the children who had to be tested repeatedly, with the majority being successfully tested. This is relevant in a large group of patients, including

monitoring of hearing loss in children with congenital CMV infection, ototoxic medication, meningitis, and so on.

By using melatonin, ABR under general anesthesia with all the associated disadvantages (risks of general anesthesia, longer admission duration, higher costs) can be avoided in a large group of children. In the small proportion of patients in whom it is not possible to perform reliable measurements under melatonin, a subsequent ABR test under general anesthesia could be performed.

4.4 *Limitations*

A limitation of this study might be the classification of comorbidities, which was necessary to be able to analyze the data. Some of the comorbidity categories might represent a heterogenous group of patients despite our best effort to classify each subject accordingly. For example, congenital CMV infection contains symptomatic as well as asymptomatic patients. Also, patients with Down Syndrome or other disorders show a heterogenous clinical image regarding their neurodevelopmental status, while categorizing these subjects in one group. Nevertheless, we do not think that this limits our study results because our data shows that melatonin can be used for a wide range of children with comorbidities despite its degree of developmental delay or comorbidities.

5.**Conclusion**

In conclusion, melatonin can be helpful for ABR examinations in infants and children with and without comorbidities. Furthermore, it allows for sequential testing in those at risk for progressive hearing loss, for example in context of congenital CMV infection or exposure to ototoxic chemotherapy. Clear instructions to caregivers and expertise of audiologists are a prerequisite for optimal outcomes.

Disclosure statement

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Table 1. Patient characteristics

	Total (n=131)	**Success (n=114)**	**Failure (n=17)**
Age			
Median age	1,9 years	2,3 years	1,7 years
range	0,5 – 9,9	0,6 – 7,2	0,5 – 9,9
Gender			
Male	53% (n=70)	53% (n=61)	53% (n=9)
Female	47% (n=61)	47% (n=53)	47% (n=8)
Comorbidities			
None	30% (n=39)	31% (n=35)	24% (n=4)
Congenital CMV Infection	13% (n=17)	11% (n=13)	24% (n=4)
Down Syndrome	15% (n=20)	15% (n=17)	18% (n=3)
Neurodevelopmental disorders	19% (n=25)	18% (n=20)	29% (n=5)
Screening for ototoxicity during chemotherapy	2% (n=3)	3% (n=3)	0%(n=0)
Autism spectrum disorder	3% (n=4)	4% (n=4)	0%(n=0)
Meningitis	6% (n=8)	6% (n=7)	5,9% (n=1)
Other (e.g. cleft palate, prematurity)	12% (n=15)	13% (n=15)	0%(n=0)

Table 2 Melatonin induced sleep-characteristics in both success and failed group.

	Success (n=114)	Failed (n=17)
Sleep quality		
Quiet sleep	57% (n=65)	0% (n=0)
Few awakenings but remained asleep	29% (n=33)	0% (n=0)
Woke up and stayed calm	14% (n=16)	0% (n=0)
Sleep absent and/or not calm	0% (n=0)	100% (n=17)
Sleep-onset latency	Mean: 27 minutes (SD 18)	Mean: 55 minutes (SD 43) (n=6)*
Sleep duration	Mean: 41 minutes (SD 19)	Mean: 8 minutes (SD 6) (n=6)*
Dosage		
1 dose	70% (n=80)	0% (n=0)
2 doses	30% (n=34)	100% (n=17)

* Only 6 out of 17 children fell asleep

Table 3 Cases with repeated ABR examinations

Case	Number of ABR examinations	Fails	Passes	Comorbidity
1	2	1	1	None
2	2		2	Congenital CMV-infection
3	2		2	Congenital CMV-infection
4	3	1	2	Congenital CMV-infection
5	3		3	Congenital CMV-infection
6	3		3	Congenital CMV-infection
7	2		2	Down Syndrome
8	2		2	Developmental disorder
9	2		2	Developmental disorder
10	2		2	Chemotherapy ototoxicity screening
11	8	1	7	Chemotherapy ototoxicity screening
12	2		2	Meningitis
13	2		2	Meningitis
14	3	1	2	Other

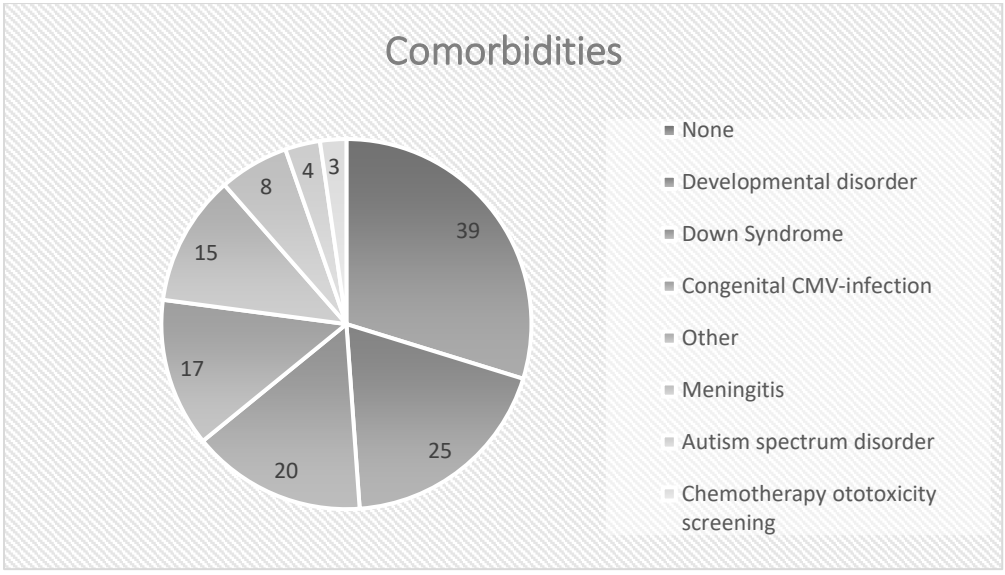

Figure 1. Patient comorbidities

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