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Pre-treatment with Melamil Tripto® induces sleep in children undergoing Auditory Brain Response (ABR) testing

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ABSTRACT

Objectives: Previous studies have shown that tryptophan and vitamin B6 used in conjunction with melatonin induce sleep more effectively than melatonin alone. This study aims at evaluating the efficacy of different dosages and timings of administration of a solution containing melatonin, tryptophan, and vitamin B6 for inducing sleep in children undergoing ABR testing.

Methods: 294 children scheduled for Auditory Brain Response (ABR) evaluation were administered a solution containing melatonin, tryptophan, and vitamin B6 to induce sleep before the exam. Two different administration timings (pre-treatment and single shot treatment) and three dosages (0.5 ml in pre-treatment, 1.5 ml in pre-treatment, and 3 ml in single shot) were tested. The following parameters were evaluated: time needed for the subject to fall asleep before ABR testing, subject sl'eep features during ABR testing (quality, stability, duration), recorded ABR quality (including presence of abnormalities in amplitude and latency), subject waking up modality, and time needed for the subject to wake up at the end of the ABR exam.

Results: Quality of ABR signals was similar across treatments, and subjects responded in a similar manner in terms of time needed to wake-up and wake-up modality. However, pretreatment with the 1.5 ml dose induced sleep faster than the two other dosages, and the length of the induced sleep was longer than that induced by pre-treatment with 0.5 ml. In general, the pre-treatment with 1.5 ml led to a shorter ABR exam, because reduces the time for inducing sleep, allows a long sleeping phase with a good quality, without variation in the wakening up times.

Conclusions: Melamil Tripto® is an alternative to sedative drugs for inducing sleep in pediatric subjects undergoing ABR testing. A pre-medication with 1.5 ml of MT 1 week before ABR testing further improves the strength of the solution.

1. Introduction

Auditory brainstem response (ABR) testing is an elective investigation for assessing retrocochlear nerve damage and superior auditory pathways functions [1]. ABR testing entails recording of auditory evoked potentials. In order to minimize myogenic artifacts, the patient is asked to minimize body movement which requires his/her collaboration [2–4]. In children under 5 years old this is difficult to achieve, so sedation is needed [2,3].

In patients undergoing ABR testing, several drugs can be used for sedation. Unfortunately, they suffer from significant limitations. Chloral hydrate (CH) is commonly used, but its administration requires an anesthesiologist for monitoring patient's vital parameters during the ABR test [5,6] and its side effects include vomiting, lethargy, dizziness, and disorientation [7]. Major complications such as poisoning and cardiac arrest can also occur [8]. Similar to CH, Propofol requires medical monitoring during administration. Its side effects are more severe than those associated with CH, and include respiratory depression, dyspnea, cardiac arrest, hallucinations, and nausea [9]. Furthermore, Propofol needs to be administered intravenously, which is difficult in pediatric patients. Benzodiazepine can modify the shape of the ABR waves and thus reduce the accuracy of the ABR exam [10].

The sleep-inducing effects of melatonin in adults [12] and children [13] are known. Expanding on a study that proposed melatonin as an alternative sedative for ABR testing [11], in a 2017 case-control study, Della Volpe et al. [14] tested a solution containing melatonin,

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tryptophan, and vitamin B6 (all natural compounds with very low contraindications and risks) as an alternative method for inducing sleep in children undergoing ABR testing. Della Volpe et al. compared a control group that did not receive any solution with a group that was administered melatonin only (Melamil, Humana Italia S.p.A., Milano, Italia) and a group that received a solution containing melatonin, tryptophan, and vitamin B6 (Melamil Tripto, Humana Italia S.p.A, Milano, Italia). They concluded that the solution was able to induce sleep as well as reduce the number of signal acquisitions needed during ABR examination [14] thanks to the effect of tryptophan (a melatonin precursor) and vitamin B6 (an important cofactor of melatonin biosynthesis). In Della Volpe et al.' s study a 0.5 ml dose of solution was administered 1 week before the ABR exam, each evening 30 min before bedtime, and finally 30 min before ABR [14]. However, how different dosages and timings of administration affected ABR testing (e.g., overall signal shape, signal to noise ratio, etc) were not investigated.

This study aims at evaluating and comparing the effects of three different dosages and timings of administration of MELAMIL TRIPTO® (MT) (Humana Italia S.p.A., Milan, Italy), a solution that in 0.5 ml contains a 1 mg of melatonin, 20 mg of tryptophan, and 1.4 mg of vitamin B6, for inducing and maintaining sleep in children undergoing ABR testing.

2. Materials and methods

This study was conducted in the department of Otolaryngology of Santobono-Pausilipon, a tertiary pediatric referral center, from December 2017 to June 2018. All procedures were approved by the IRB committee of the hospital and were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

294 children were enrolled in the study. Subjects included 90 females and 204 males; the average subjects' age was 29,8 months (CI 95%: 11–72; SD: 11,5). Subjects were randomly assigned to one of three groups. Group A received 3 ml of MT (6 mg of melatonin, 120 mg of tryptophan, and 8,4 mg of vitamin B6) in a single shot 30 min before undergoing ABR testing. Group B and C started treatment with MT 1 week before ABR testing was scheduled. Group B received 1,5 ml/die of MT each evening (3 mg of melatonin, 60 mg of tryptophan, and 4,2 mg of vitamin B6) 1 week before ABR testing, 30 min before bedtime, and a second dose of 1,5 ml of MT 30 min before the ABR exam. Group C received 0,5 ml/die of MT each evening (1 mg of melatonin, 20 mg of tryptophan and 1,4 mg of vitamin B6) 1 week before ABR testing, 30 min before bedtime, and a second dose of 0,5 ml of MT 30 min before ABR testing.

The following data were collected for each subject: sex, age, time needed for the subject to fall asleep before ABR testing, subject sleep features during ABR testing (quality, stability, duration), recorded ABR quality (including presence of abnormalities in amplitude and latency), subject waking up modality (spontaneous or stimulated), and time needed for the subject to wake up at the end of the ABR testing.

Sleep quality and stability were evaluated by a physician observing subject movements during the ABR exam. Sleep quality was assessed with a score ranging from 0 to 2, where 0 corresponded to absence of sleep, 1 to superficial sleep, and 2 to profound sleep. Sleep stability during ABR testing was scored either 1 or 2, where 1 corresponded to discontinuous sleep and 2 corresponded to continuous sleep during the whole exam. Discontinuous sleep was defined as sleep characterized by occurrence of one or more intervals where the subject woke up, as visually assessed by the physician. Time for falling asleep, duration of sleep, and time needed to wake up were measured with a digital chronometer (Casio®). The time for falling asleep prior to ABR testing was calculated as the interval between the time the subject was administered the solution and the time she/he reached profound sleep (absence of spontaneous movements); the duration of sleep was defined as the interval between the time the subject reached profound sleep and the time the subject started to wake up (i.e., first exhibited response to stimulus); and the wake-up time was calculated as the interval between the time the subject initially responded to stimulus and the time she/he was fully awake.

ABR testing was performed using Eclipse (Interacustics (https://www.interacoustics.com)) in clinical, automatic modality. The operator sent a single click stimulus, starting at 100 dB and decreasing to 10 dB. ABR threshold was set to the average of the two ears' hearing level at 2/4 kHz: 440 dB Hearing Level (HL) used a click stimulus at 70 dB normal Hearing level (nHL), 40–60 dB HL used a click stimulus at 80 dB nHL, and 460 dB HL used click stimulus at 90 dB nHL Contralateral masking was applied if asymmetric responses were observed.

ABR quality during the exam was scored either 0 or 1, where 0 indicated that ABR signals were excessively affected by artifacts (e.g., caused by movements during sleep), and 1 indicated that ABR was performed without problem. After the exam, ABR waves were visually analyzed by an audiologist with over 10 years of experience and scored as follows: 0 = absence of waves, 1 = presence of waves with altered amplitudes and/or latencies, and 2 = normal ABR waves.

Statistical analysis was performed with STATA®. One-way ANOVA and Tukey ad-hoc tests were used for comparing groups A, B and C in terms of the following variables: time needed for subject to fall asleep/wake-up, sleep features during ABR testing, waking up modality, and ABR quality. For all tests the level of significance was set to $p < 0,05$.

3. Results

Group A included 108 children, 36 females and 72 males (mean age 27.8 months (CI 95%: 11–48; SD: 10.8)). Group B included 102 children (24 females and 78 males, mean age 31.8 months (CI 95%:18–72; SD: 13.9)). Group C included 84 children (30 females and 54 males, mean age 29.7 months (CI 95%: 24–48; SD 9.3)).

All subjects displayed normal ABR response and no statistically significant difference was found among group A, B and C. All recorded ABR waves were regular for the whole duration of the ABR exam, and no statistically significant difference was observed among the three groups.

MT induced sleep in 22.7 min in group A (CI 95%:10–30; SD: 5.9), in 14.7 min in group B (CI 95%: 5–30; SD:6,3), and in 22.7 min in group C (CI 95%: 16–30; SD: 5.2). One-way ANOVA showed statistically significant differences between the three groups ($p = 0.0002$); in particular, group B statistically differed from group A (Tukey: $p < 0.01$) and from C (Tukey: $p < 0.01$), while no statistically significant difference was found between group A and group C (Fig. 1).

The average sleep duration was 29 min in group A (CI 95%:25–40;

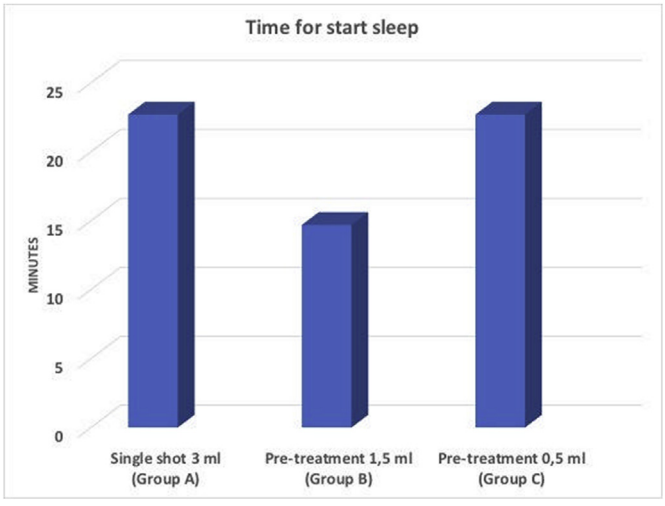

Fig. 1. The graphic illustrates the different times for starting to sleep in the three groups expressed in minutes.

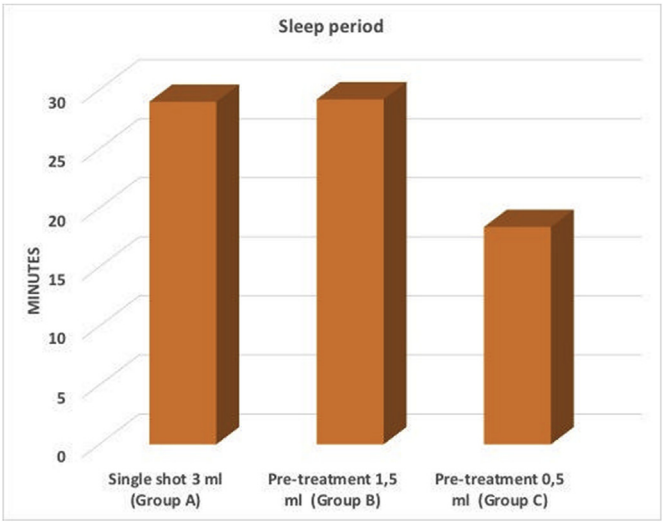

Fig. 2. The image shows the different length of sleep period in the three groups (A, B and C).

SD: 7.3), 29.2 min in group B (CI 95%: 15–60; SD: 11.4), and 18.4 min in group C (CI 95%: 15–30; SD: 5.7). A statistically significant difference was observed among the three groups (ANOVA: $p = 0.0013$). Tukey test showed a statistically significant difference between group C and group A ($p < 0.01$) and between group C and group B ($p < 0.01$), while no statistically significant difference was observed between group A and group B in terms of sleep duration (Fig. 2).

Sleep was continuous during the whole duration of the ABR registration in 98% of children without statistically significant differences in the three groups; 6 children (2%), all belonging to group A, presented discontinuous sleep during the ABR exam.

All subjects (100%) spontaneously woke up. The mean wake-up time was 16.5 min (CI 95%: 7–20; SD:4.9), 12.4 min (CI 95%: 7–30; SD: 6.9), and 14.4 min (CI 95%:9–30; SD: 5.9) in group A, group B, and group C, respectively. No statistically significant difference was found among the three groups (ANOVA: $p = 0.14$) (Fig. 3).

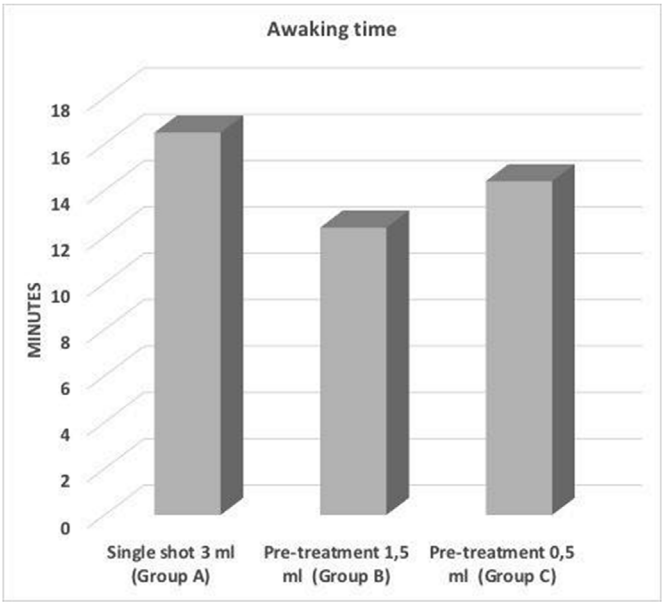

Fig. 3. The graphic illustrates the time for complete wake-up in the three groups.

4. Discussion

Overall our results show that MT is able to induce a continuous sleep that allows to properly conduct an ABR testing thanks to the combination of melatonin (a hormone (N-acetyl-5 methoxytryptamine) normally synthesized by the pineal gland and secreted during the early morning hours) [15] with tryptophan (which increases the bioavailability of melatonin and its concentration in blood [16,17]) and vitamin B6 (which further improves melatonin's effect by increasing the level of tryptophan synthetized by the serotonin present in the blood [18]).

Our results confirm the results of Della Volpe et al.'s study [14], which previously showed that MT is a valid alternative to common sedative drugs [14]. Additionally, they show that pre-medication with 1.5 ml of MT one week before the ABR exam allows a reduction of the dose to be taken immediately before the exam from 3 ml (single shot dose) to 1,5 ml, while inducing sleep of duration comparable to that induced by the single shot (sleep duration was 29 and 29.2 in group A and group B, respectively, with no statistically significant difference between groups). We speculate that these effects are due to the fact that premedication with 1.5 ml of MT followed by a second dose of 1.5 ml of MT allows a progressive increase of the MT molecules in blood, which has a stronger effect of the single 3.0 ml dose administered 30 min prior the ABR testing. Furthermore, our results show that compared to the 0.5 ml pre-medication dose, the 1.5 ml pre-medication dose induced sleep more quickly (14.7 vs 22.7 min) and allowed a longer sleep duration (29.2 vs 18.4 min). The rationale of pre-medicating with MT is supported by past studies, which have shown the effects of melatonin [19] on sleep regulation [21] and of tryptophan [20] on mood disorders stabilization [22].

All the dosages and timings of administration of MT we tested in this study allowed subjects to sleep continuously and profoundly in a similar manner, which confirms that MT is a valid alternative to pharmacological, hypnotic drugs commonly used for inducing sleep in children that have to undergo ABR testing. Also, the time necessary for the subject to wake-up was similar across groups, and all subjects woke-up spontaneously.

Fig. 4 shows that for subjects in group B the time necessary to complete ABR testing was about 15 min less than for subjects of group A and C; this reduction in exam length was associated to a shorter time for inducing sleep.

Future studies should focus on comparing the effects of MT with those induced by hypnotic drugs and on using quantitative metrics derived from EEG and ABR signals to objectively measure the effects of MT on sleep and ABR execution.

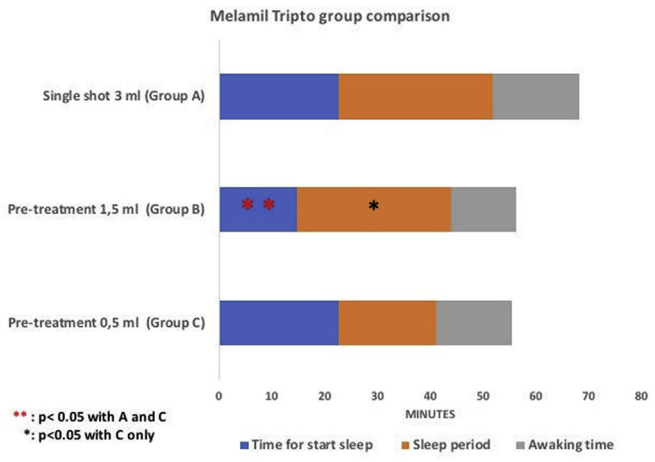

Fig. 4. The general graphic summarizes the overall time starting from the administration of MT. Groups B and C present reduced times when compared with A, but in group B the sleep period is longer than in C and the inducing sleep time is reduced, so by looking at the general aspect group B is the best.

5. Conclusions

Melamil Tripto® is an alternative to sedative drugs for inducing sleep in pediatric subjects undergoing ABR testing. A pre-medication with 1.5 ml of MT 1 week before ABR testing further improves the strength of the solution; in fact, administration of MT with such dosage/timing induces sleep more quickly than a single shot with 3 ml and, than pre-medication with 0,5 ml, while it ensures a sleep quality suitable for ABR recording. Furthermore, this dosage with 1,5 ml of MT allows a reduction of the time necessary for inducing the subject to sleep, which in turns reduces the overall ABR exam time. In conclusion, we recommend MT in place of common sedatives in pediatric patients undergoing ABR testing, and in particular we recommend using a pre-treatment with 1.5 ml solution (3 mg of melatonin, 60 mg of tryptophan and 4,2 mg of vitamin B6) 1 week before the ABR exam, each evening 30 min before bedtime, and 30 min before ABR testing.

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Conflict of interest

None of the authors have conflict of interests.

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