Mid-latency auditory evoked potentials: monitoring the depth of hypnosis in children

MLAEP in children during anesthesia

Yuen Cheung

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Mid-latency auditory evoked potentials:
het meten van de diepte van narcose bij kinderen

MLAEP van kinderen tijdens anesthesie

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Chapter 1

General introduction

During anesthesia the depth of hypnosis is mostly evaluated by the skill and knowledge of the anesthesiologist. Clinical tools developed to assess the depth of hypnosis are generally cumbersome to use during a surgical procedure and are less reliable in patients receiving neuromuscular-blocking agents. Accidental awareness during general anesthesia in children has been reported to be 0.2% to 1.2% [1]. About 50% develops long-term psychological effects, while some develop PTSD further in their life with varying degree of disabilities [1].

There is also potential harm in giving too deep (i.e. too much) anesthesia, as it can result in hemodynamically instability or respiratory adverse effects (e.g. bronchospasm with desflurane). Concerns have been raised about possible neurotoxicity of anesthetics in the developing brain of children [2]. Animal model studies observed behavioral changes and increased neuro-apoptosis when administering anesthetics for a prolonged period [3]. These effects of anesthetics also seem to be more prominent with increasing doses [4].

It is unknown how to interpret and extrapolate these results in humans. A large international randomized controlled trial revealed that sevoflurane anesthesia for a short duration (less than 1 hour) did not impair the cognitive function of children at the age of 2 and 5 years old [5,6].

Whether these results can be generalized to longer durations of anesthesia or a mixture of anesthetics remain unknown. However, studies comparing hypnosis monitor guided anesthesia with conventional anesthesia demonstrate a reduction in cumulative anesthetic dose administered in adults and children [7-9]. Therefore, if the anesthetic depth can be reliably assessed and monitored, the exposure to potential harmful anesthetics can be reduced to a minimum level while maintaining an appropriate depth.

The discovery of the relationship between EEG patterns and the depth of hypnosis evolved the method used to monitor it. The B-Aware trial demonstrated a reduction of 82% in accidental awareness in the adult population [10], indicating that using a depth of hypnosis monitor might also improve the quality of anesthesia for children. Different commercially available devices exist to continuously monitor the depth of hypnosis. Most of these devices analyze the spontaneous EEG and calculate by algorithm an index value representing the depth of hypnosis. Along the EEG, mid-latency auditory evoked potentials (MLAEP) are also possible to be used to generate an index value. However, great heterogenicity exists in how to interpret and respond to these generated index values (EEG derived as well as MLAEP derived). There are also controversies about the reliability of such a monitor for different age groups and different anesthetics. What do anesthesiologists think about using depth of hypnosis monitoring in children? How

does this relate to the current literature? What do we currently know about the MLAEP in children during general anesthesia? How does a MLAEP based hypnosis monitor perform in children during anesthesia with commonly used anesthetics in our daily practice?

Commonly used EEG monitors analyze the whole EEG while filtering the noise. While these monitors are also widely used in the pediatric population, one cannot deny the differences between the EEG of an adult and one of a child as the EEG does not mature before adulthood [11]. The MLAEP on the other hand, which is a part of an EEG, mature earlier in life. Just like the EEG, an index value can be derived by analyzing the MLAEP waveform. It is induced by a sound stimulus and appears at about 40ms until 50ms after it. The waveform usually consists of two peaks (P) and three troughs (N) being named N0, P0, Na, Pa and Nb. Its relationship with the depth of hypnosis has been studied in children revealing a reasonable correlation [12-15]. These studies show that an increasing dose of anesthetics results in an increased time until specific waveforms appear, i.e. the latency, and a decreased amplitude of the waveforms [16-18]. In children however, few studies concerning the performance of such a monitor during anesthesia are available of which most of them are conducted with legacy devices or experimental setups not readily available to the anesthesiologist for daily practice.

Finally, we will assess the performance of the currently only commercially available MLAEP based monitor, the aepEX plus monitoring system, in children during propofol, sevoflurane and desflurane anesthesia. Studies concerning the aepEX monitor in the adult population demonstrated a reasonable detection of return of consciousness after anesthesia with propofol and sevoflurane [19-22], while the same studies in children were lacking. It is also unknown whether the results from the studies conducted in the adult population and previously conducted studies in children with other MLAEP monitors could be extrapolated to the aepEX monitor. This is especially true due to the fact that algorithms of these devices are undisclosed to the public.

AIMS OF THIS THESIS

- To assess the thoughts and opinions of (pediatric) anesthesiologists about the use of depth of hypnosis monitoring in children receiving anesthesia.
- To inventory the perceived need for a reliable depth of hypnosis monitor for children.
- To review the current literature concerning the use of MLAEP in children receiving anesthesia.
- To evaluate the performance of the aepEX monitor (since this is currently the only commercially available MLAEP based hypnosis monitor) in children receiving anesthesia with commonly available hypnotics.

OUTLINE OF THIS THESIS

Chapter 2 will set out the thoughts, practice, opinions and (mis)understandings towards depth of hypnosis monitoring during anesthesia in children. An attempt to answer research questions concerning the use of depth of hypnosis monitoring such as: "Why do they use it?", "Why don't they use it?", "When do they use it?", "Are there any particular paradigms obstructing an informed decision for its use?". We will also try to gauge the opinions about the shortcomings of the currently available depth of hypnosis monitors and what an ideal monitor should be capable of which might give direction for further development in this field.

MLAEP has a theoretically advantage over EEG based depth of hypnosis monitors. In **chapter 3** we will review the current literature concerning MLAEP in children during anesthesia, addressing the following research questions: "Does the MLAEP consistently change when different anesthetics are administered?", "How reliable can you assess the depth of hypnosis with an MLAEP based monitor?" and "Does MLAEP guided anesthesia make our anesthesia more efficient, i.e. do we need less anesthetics, can we reduce the recovery time?".

In the following chapters the aepEX plus monitoring system will be evaluated for its performance as a depth of hypnosis monitor in children. **Chapter 4** will describe its performance during propofol anesthesia, guided by the Paedfusor target controlled infusion model. In **chapter 5** the aepEX monitor will be assessed during sevoflurane anesthesia. The aepEX monitor is evaluated during desflurane anesthesia in **chapter 6**.

In **chapter 7** we will discuss the main findings and conclusions from this thesis.

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Chapter 2

Use, applicability and reliability of Depth of Hypnosis monitors in children: A survey among members of the European Society for Paediatric Anaesthesiology

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ABSTRACT

BACKGROUND: To assess the thoughts of practicing anaesthesiologists about the use of depth of hypnosis monitors in children.

METHODS: Members of the European Society for Paediatric Anaesthesiology were invited to participate in an online survey about their thoughts regarding the use, applicability and reliability of hypnosis monitoring in children.

RESULTS: The survey achieved a response rate of 30% (n=168). A total of 138 completed surveys were included for further analysis. Sixty-eight respondents used hypnosis monitoring in children (Users) and 70 did not (Non-users). Sixty-five percent of the Users reported prevention of intra-operative awareness as their main reason to apply hypnosis monitoring. Among the Non-users, the most frequently given reason (43%) not to use hypnosis monitoring in children was the perceived lack or reliability of the devices in children. Hypnosis monitoring is used with a higher frequency during propofol anaesthesia than during inhalation anaesthesia. Hypnosis monitoring is furthermore used more frequently in children >4 years than in younger children. An ideal hypnosis monitor should be reliable for all age groups and any (combination of) anaesthetic drug. We found no agreement in the interpretation of monitor index values and subsequent anaesthetic interventions following from it.

CONCLUSIONS: Prevention of intraoperative awareness appears to be the most important reason to use hypnosis monitoring in children. The perceived lack of reliability of hypnosis monitoring in children is the most important reasons not to use it. No consensus currently exists on how to adjust anaesthesia according to hypnosis monitor index values in children.

Keywords: Child; Consciousness Monitors; Infant; Surveys and Questionnaires.

BACKGROUND

With the introduction of processed electroencephalography, about 20 years ago, the electroencephalogram (EEG) became feasible to be used to easily monitor depth of hypnosis (DoH) in patients receiving general anaesthesia [1]. Whether or not DoH-monitors (DoH-M) have a beneficial impact on peri-operative outcomes, remains subject to discussion [2]. What all currently commercially available DoH-M have in common is that they have been developed for use in adult patients. Clear recommendations regarding the use of the currently available DoH-monitors in paediatric patients are still lacking [3].

The Paediatric Anaesthesia Research Group at Sophia Children's Hospital in Rotterdam designed and launched an online survey [4] to assess the thoughts of the members of the European Society for Paediatric Anaesthesiology (ESPA) regarding the use, applicability and reliability of DoH-monitoring in children. Besides general aspects regarding the use of DoH-M in children, we were also interested in the thoughts of ESPA members regarding the requirements of an ideal paediatric DoH-M and whether demographic characteristics of the anaesthesiologist (age, working experience, etc.) influenced their vision regarding DoH-monitoring in children.

METHODS

According to the Dutch regulations, questionnaire research does not fall under the scope of the Medical Research Involving Human Subjects Act (WMO), as declared by the Central Committee on Research Involving Human Subjects (http://www.ccmo.nl/en/questionnaire-research). Therefore, formal ethics approval was deemed unnecessary according to national regulations and was not obtained.

During the development of the survey, it was evaluated and tested by anaesthesiologists of our paediatric anaesthesia department. The survey consisted of two major parts, beginning with questions concerning the respondents' demographics, workplace, annual personal case-loads and availability of DoH-M at their institutions. The second part was related to the thoughts of the respondents regarding their personal practice of DoH-monitoring in children and their thoughts about paediatric DoH-monitoring in general. In order to minimize possible bias, the order of the answers to any of our multiple-choice questions were randomized for each respondent. The entire survey is available as supplementary content (see appendix).

On our request, ESPA invited their members (n=553) by email to participate in our survey. A single reminder was send by e-mail three weeks after the initial invitation. The survey was accessible online in the period from June 28, 2013 until August 18, 2013.

Statistical Analysis

Respondents were allocated to two groups; "Users" and "Non-users" of DoH-M in children. Non-users were excluded from further analysis when their only reason to not use DoH-M in children was due to the unavailability of a DoH-M in their institution since this was considered a circumstantial reason rather than a personal choice. For nominal data Pearson's Chi-Square or Fisher's test were used to analyse the differences between DoH-M Users and Non-users. When needed, data was recoded to maintain a minimum expected count of 5 to facilitate the Pearson's Chi-Square or, if applicable, the Fisher's Exact test. The Mantel-Haenszel test [5], labelled as a "Linear-by-Linear Association" in SPSS, was used for ordinal data (e.g. work experience, age or frequency of giving anaesthesia to certain age groups). P-values <0.05 were considered statistically significant.

The margin of error for our survey data, including a 95% confidence level was computed using an online-tool provided by SurveyMonkey [4]. The margin of error is an estimate of the appropriateness of the sample size to represent the whole population (ESPA members).

All analyses were performed using SPSS (IBM SPSS Statistics, version 21).

RESULTS

We received a total of 168 (30%) responses, of which 14 were incomplete and excluded from analysis. Sixteen respondents didn't use DoH-M in children due to the unavailability of any DoH-M in their institution and were excluded from further analyses. The margin of error of our sample size was 6%.

Our respondents came from 40 different countries. To present the data in a more comprehensible manner, we categorized them into continents. The majority (n=115; 83%) came from Europe. Baseline characteristics, i.e. professional title, age, type of institution they work in, years of experience in anaesthesiology, of the Users (n=68) and Non-users (n=70) are summarized in Table 1.

Table 1. Respondents' baseline characteristics.

	Users (n=68)	Non-users (n=70)	P-value
Professional title			0.366*
Anaesthesiologist	67 (99%)	66 (94%)	
Anaesthesiologist in training (resident)	1 (1%)	4 (6%)	
Practicing in			n/a
Europe	57 (84%)	58 (83%)	
Middle East	6 (9%)	4 (6%)	
East Asia	1 (1%)	2 (3%)	
Australia	1 (1%)	3 (4%)	
South Americas	2 (3%)	1 (1%)	
North Americas	1 (1%)	2 (3%)	
Works in			0.064[a]
(university) children hospital	41 (60%)	31 (44%)	
non-children's hospital	27 (40%)	39 (56%)	
Years of practice			0.898[b]
<10 years	17 (25%)	20 (29%)	
11–20 years	27 (40%)	24 (34%)	
>20 years	24 (35%)	26 (37%)	
Age			0.908[b]
<40 years	20 (29%)	20 (29%)	
41–50 years	25 (37%)	28 (40%)	
>51 years	23 (34%)	22 (31%)	

Comparison of baseline characteristics of respondents either using (Users) or not using (Non-users) depth of hypnosis monitoring in children.
[a] Fisher's Exact test
[b] Mantel-Haenszel test

The workplace distribution was 60% children's hospital and 40% general hospital among DoH-M Users. For the Non-users the distribution was 44% children's hospital and 56% general hospital. Though not reaching statistical significance (Fisher's exact test, p= 0.064), these results indicate a weak evidence that anaesthesiologists working in children's hospitals are more likely to use DoH-M than those working in general hospitals.

Both Users (94%) and Non-users (86%) were "most" familiar with the Bispectral Index (BIS) monitor (p=0.09), followed by Entropy (Users 37%, Non-users 26%; p=0.11), the Narcotrend (Users 18%, Non-users 17%; p=0.56) and the AEP-monitor/2 (Users 13%, Non-

users 10%; p=0.37). The BIS monitor was used most frequently (77%), followed by Entropy (10%), Narcotrend (6%) and the Cerebral State Index, CSI (4%).

In order of descending frequency, DoH-M was used during major surgery (96%), neurosurgery (53%), minor surgery (32%), cardiac surgery (22%) and procedural sedation (19%).

A total of 70 respondents reported to never use DoH-M in children. The majority of them (49%) reported that they think DoH-M was unreliable and/or not validated for use in children. Other reasons were that using a DoH-M wouldn't affect their method of anaesthesia (30%) and the cost of using DoH-M (24%).

Prevention of intraoperative awareness was the most frequently reported primary reason to apply DoH-M, whereas preventing (possible) side effects of anaesthetic agents were most frequently reported as least relevant (for details see Figure 1).

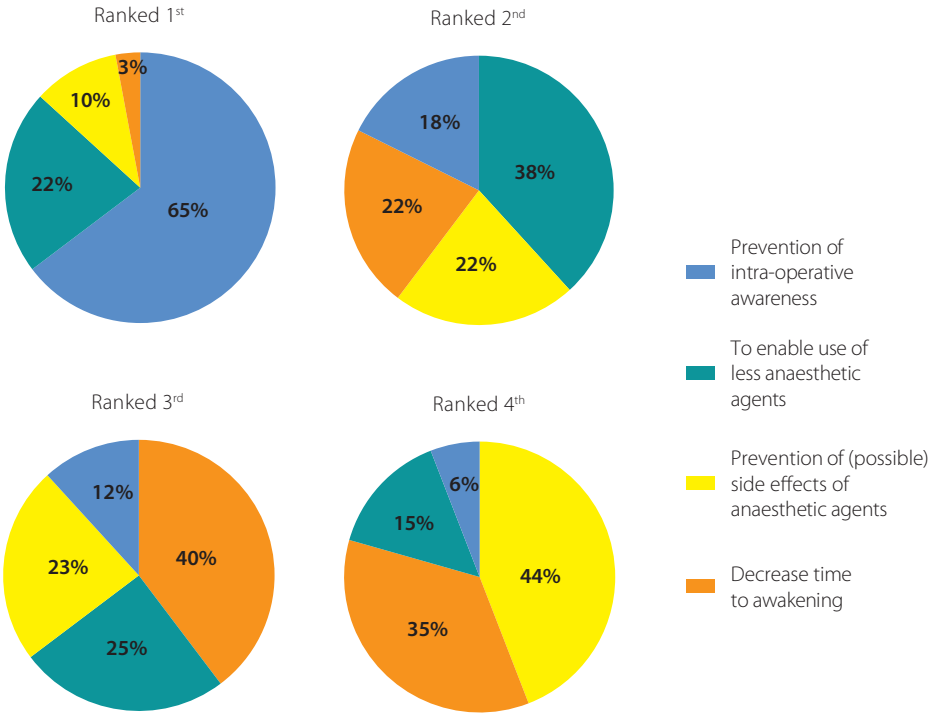

Figure 1. Reasons for hypnosis monitoring. Percentage Users reported their reasons to use depth of hypnosis monitoring in children ranked 1st, 2nd, 3rd and 4th.

The frequency of using DoH-M ranged from 25% in pre-term infants to 98% in teenagers. About 10% of the Users reported to apply DoH-M almost always in patients older than 4 years. Details are given in Figure 2.

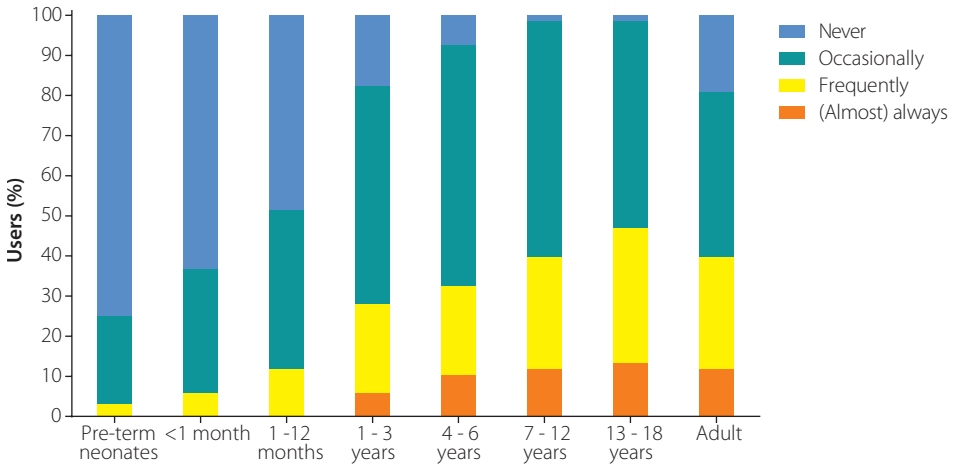

Figure 2. Hypnosis monitoring and age. Patient population in which depth of hypnosis monitoring is being used.

All Users reported to use DoH-M during propofol anaesthesia. DoH-M was less frequently used during inhalation anaesthesia (see Figure 3).

Being asked whether either the actual value of a DoH-Index or its trend over time best reflect the DoH, 62% of the Users preferred to rely on a combination of the actual index value and its trend. Such a combination would result in various drug interventions, such as increasing the hypnotic agent concentration (27%), analgesic agent application (3%), or both (60%), while 10% would not react without additional changes in physiological parameters, i.e. heart rate or blood pressure. Twenty-nine percent of the Users found the DoH best represented by the trend. In the case of an increasing trend they would increase the hypnotic drug concentration (35%), or give additional analgesic drugs (4%) or both (46%), while 13% would only react to the increasing trend when combined with changes in physiological parameters. Another 7% relied only on increases of the actual DoH-index value, resulting in increasing hypnotic drug concentration (24%), additional analgesic drug application (3%) or both (41%), with 31% of them also requiring physiological alterations for an intervention (1% answered "other").

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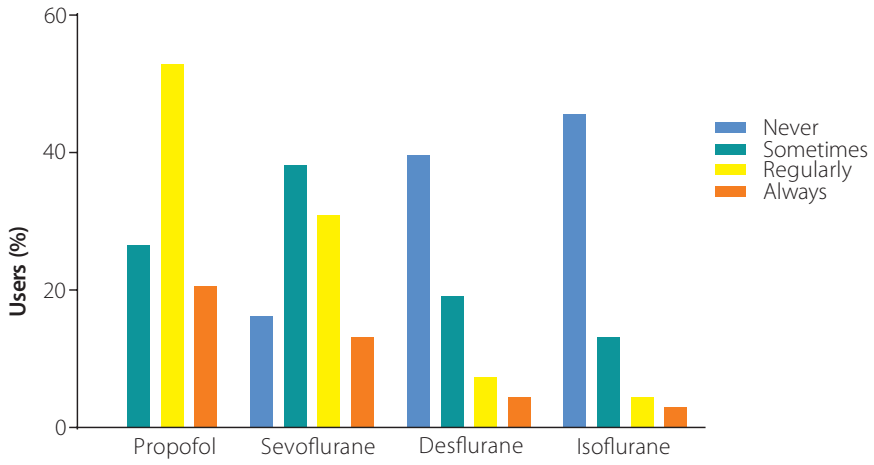

Figure 3. Hypnosis monitoring and anaesthetic. Percentage respondents who "never", "sometimes", "regularly" or "always" use depth of hypnosis monitoring with different anaesthetics.

According to all respondents, applicability in all patient age groups, reliability for any (combination of) anaesthetic drug, and low-cost disposables were the three most important requirements of a theoretical ideal DoH-M. For more details see Figure 4.

Eighty percent of the respondents (n=110) agreed that there is a need for a monitor which specifically measures analgesia. Fourteen of the respondents (10%) agreed to the need for a separate analgesia monitor, 43 (31%) preferred a combined analgesia/DoH-M monitor and 53 (38%) agreed to both options. Another fourteen (10%) respondents held a neutral position ("not knowing") and 14 (10%) disagreed with both types of analgesia monitors. With respect to their thoughts about the need for analgesia monitoring devices, a Mantel-Haenszel test revealed that Users are more optimistic towards it (p=0.04), while no evidence of a difference between DoH-M Users and Non-users regarding their thoughts about a stand-alone analgesia monitor (p=0.63) or a combined DoH/analgesia-monitor (p=0.12) was observed.

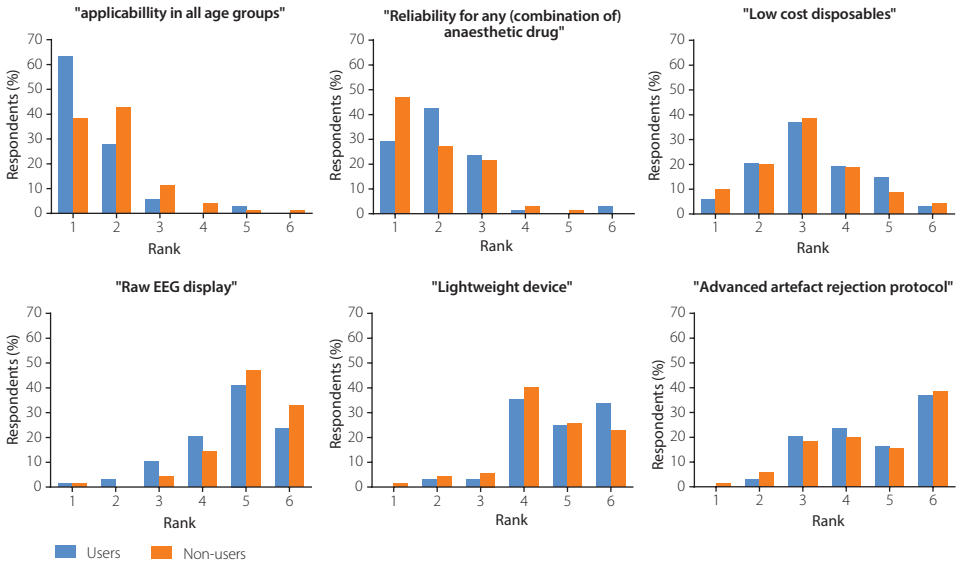

Figure 4. The ideal hypnosis monitor. Features of an ideal depth of hypnosis monitor ranked 1st, 2nd, 3rd, 4th, 5th and 6th by percentage Users and Non-users.

DISCUSSION

Practicing anaesthesiologists dedicated to paediatric anaesthesia perceive the avoidance of intraoperative awareness as the most important reason to use DoH-M in children. The most cited reasons of not using DoH-M in children were serious concerns regarding the reliability of the currently available devices in paediatric patients.

This survey gives an overview of the thoughts and attitudes of (European) anaesthesiologists affiliated with the ESPA concerning the use of DoH-M in children.

Not unexpectedly, the BIS monitor was the device most widely available, regardless of the personal preference to use it or not. Working experience (Table 1) and familiarity with DoH-M were not related to its use in children.

As expected, DoH-M was most often applied in older children, whereas its use in (preterm) neonates was infrequent (see Figure 2). This pattern is in accordance with a recommendation made by Davidson [3], who reported increasing evidence that DoH-M devices do not work in infants, while there is also increasing evidence they may work in older children.

Interestingly, despite the absence of scientific publications investigating the effect of DoH-M on the incidence of intraoperative awareness in children, this remains the most common indication reported by DoH-M Users to apply this technology. What we currently know, is that the incidence of awareness in children (approximately 1% [6]) is significantly higher than in adults (approximately 0.1–0.2 % [7]). In addition, the big trials performed in adult patients investigating the impact of BIS monitoring on the incidence of awareness showed conflicting results, reporting both a reduction of awareness cases [7] and no beneficial effect [8]. Use of less anaesthetics and decreased time to awakening, both reported in paediatric studies [9-12], were ranked 2nd and 3rd in the decision finding process to use DoH-M. At least 44% of the Users chose "prevention of (possible) side effect of anaesthetic agents" as the least important argument for using DoH-M. Bearing in mind the ongoing discussion about the safety and possible neurotoxicity of anaesthetic drugs in the developing brain [13-15], we regard this as an unexpected finding.

Not surprisingly, 39% of the Non-Users chose "Applicability in all age groups" as their most important feature of a hypothetical ideal DoH-M. Users on the other hand chose "prevention of intra-operative awareness" and "To enable use of less anaesthetic agents" as their main reason to use DoH-M in children. These opinions were also reflected by their preferences regarding the most important features of an ideal DoH-M, i.e. "Applicability in all age groups" and "Reliability for any (combination of) anaesthetic drug".

Index values are helpful and practical to make the EEG understandable during anaesthesia. However, subtle EEG-information will be lost. With no doubt, a raw EEG display on a DoH-M could contribute to assessing the DoH, under the prerequisite that the anaesthesiologist has at least some basic knowledge of clinical encephalography [16]. The latter applies only to a minority of clinical anaesthesiologists. Therefore, it is not at all surprising that this feature was ranked only 5th by most of the respondents.

All Users applied DoH-monitoring, with frequencies varying from "sometimes" to "always" during propofol anaesthesia. This is in accordance with recent UK guidelines published by the National Institute for Health and Care Excellence (NICE), recommending the use of DoH monitoring in all patients receiving total intravenous anaesthesia [17]. DoH-M was used much less frequently during inhalation anaesthesia. This could be due to the fact that it is nowadays well known that end-tidal concentrations of inhalation anaesthetics are closely linked to the likelihood of being awake. For paediatric patients the minimal alveolar concentration of sevoflurane associated with wakefulness (MACawake) has been found to be as low as 0.2–0.3% [18].

The survey also showed disparities in how to interpret the index values and how to intervene. While the device manufacturers typically advise to keep the values of their DoH-Index within a predefined range, the majority of our respondents (62%) believed that the combination of the actual index value and its trend best indicates DoH. In a recent study, performed in adult patients, Schneider et al. [19] demonstrated that combining the BIS with standard anaesthesia parameters (i.e. heart rate) resulted in a prediction probability [20] value of 1.0 to detect consciousness. This suggests that this combination is the perfect indicator of DoH; at least when assuming DoH equals losing and regaining consciousness. Being asked how to react on increasing DoH-index values, our respondents' answers showed a huge variability, ranging from increasing the hypnotic drug concentration, giving additional analgesic drugs, increasing both hypnotics and analgesics or even deciding not (yet) to intervene at all. An analgesia monitor could assist in deciding which intervention is probably needed and most respondents agreed with the need for an analgesia monitor.

Since the majority of the ESPA members did not voice their opinions (30% response rate), we have to bear in mind that the results of this survey could be biased. On the other hand, the relatively low margin of error indicates that our sample size represents 95% of the all ESPA members with a ±6% margin. The low response rate can be regarded as a result in its own right. This could be interpreted as if the majority of paediatric anaesthesiologists have either significant reservations regarding the reliability and/or applicability of DoH-M in children or, more generally a low level of interest in this subject. We cannot claim to present data which is representative for the European paediatric anaesthesiology community. Nonetheless, we still consider our results relevant, because they very well reflect the tenor of the usual informal inter-collegial conversation regarding paediatric DoH-M during conferences or daily practice.

There is at least a theoretical possibility that respondents who did not have DoH-M available at their institutions would have favoured use of these devices, if given the choice. The design of our survey did not take into account this possibility, which could be regarded as a shortcoming. On the other hand, it would not be correct to assign these respondents to the Non-user group, which consisted by default of respondents who had DoH-M available but decided not to use them in children.

As long time users of various DoH-monitoring devices in children we would like to share our vision on this controversial topic with our readers and provide the following recommendations: In accordance with the current UK NICE guidelines [17] we highly recommend the use of DoH-monitoring during propofol anaesthesia in all paediatric

patients beyond infant age [3]. In children receiving inhalational anaesthesia we recommend the use of DoH-monitoring devices which provide the anaesthesiologist with additional information regarding the raw-EEG. This information is vital to prevent the child, in particular of the youngest age group, from EEG burst suppression patterns, indicating anaesthetic drug overdose.

Future research in this field should focus on the youngest patient age group. A very promising recent approach is the interpretation of the EEG power spectrum, displayed as Density Spectral Array (DSA). The major advantage of DSA is that it uses raw-EEG information in real time and that drug specific EEG-signatures have been identified [21], even for paediatric patients [16,22]. This new technology is already implemented in several commercially available DoH-monitors.

CONCLUSIONS

In conclusion, for ESPA affiliated anaesthesiologists who filled in our survey, prevention of intraoperative awareness was the most important reason to use DoH-M in children. The perceived lack of reliability of the currently available devices, when used in children, was the most important reason for not using DoH-M. No consensus currently exists on how to adjust anaesthesia according to DoH-M indices in children. According to the respondents to this survey an ideal DoH-M should be reliable for all age groups and any (combination of) anaesthetic agent.

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APPENDIX

The survey as presented to our respondents.

Dear colleague,

Thank you very much for agreeing to complete our survey on depth of anaesthesia monitoring in children. Your input is highly appreciated.
We estimate that it will take you approximately 7 minutes to complete the survey.

Sincerely,

Yuen M. Cheung
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1. What is your professional title

- ❍ Anaesthesiologist
- ❍ Anaesthesiologist in training (resident)
- ❍ Nurse Anaesthetist
- ❍ Physician Assistant
- ❍ Other (please specify)

2. What is your age?

- ❍ <30 years
- ❍ 30–40 years
- ❍ 41–50 years
- ❍ 51–60 years
- ❍ >60 years

3. In which country are you presently working?

4. In which hospital do you give your most anaesthetics?

5. How many years have you been practicing anaesthesiology?

	<5	5–10	11–20	>20
Years of pracatice	❍	❍	❍	❍

6. How often do you give anaesthesia for the following different patient age groups?

	Never	Occasionally	Frequently
Pre-term neonates	❍	❍	❍
Full-term neonates to 1 month	❍	❍	❍
Infants 1 month to 1 year	❍	❍	❍
1–3 years	❍	❍	❍
4–6 years	❍	❍	❍
7–12 years	❍	❍	❍
13–18 years	❍	❍	❍
Adult patients (>18 years)	❍	❍	❍

7. How often do you give anaesthesia for the following types of surgery in paediatric patients

	Never	Occasionally	Frequently	(Almost) always
Minor surgery	❍	❍	❍	❍
Major surgery	❍	❍	❍	❍
Neurosurgery	❍	❍	❍	❍
Cardiac surgery	❍	❍	❍	❍

8. Which of the following depth of anaesthesia monitors are you familiar with?
(you can choose multiple answers)

- ❍ Bispectral Index
- ❍ Entropy (Datex Ohmeda/ GE)
- ❍ aepEX
- ❍ cAAI
- ❍ AEP-monitor/ 2
- ❍ Cerebral State Index
- ❍ Narcotrend
- ❍ I don't know any depth of anaesthesia monitor
- ❍ Other (please specify)

9. Which of the following depth of anaesthesia monitors are available at your institution? ***(you can choose multiple answers)***

- ❍ Bispectral Index
- ❍ Entropy (Datex Ohmeda/ GE)
- ❍ aepEX
- ❍ cAAI
- ❍ AEP-monitor/ 2
- ❍ Cerebral State Index
- ❍ Narcotrend
- ❍ I don't know any depth of anaesthesia monitor
- ❍ Other (please specify)

10. Do you use depth of anaesthesia monitoring in pediatric patients? *(respondents were redirected to question 12 when answered "yes")*

- ❍ Yes
- ❍ No

11. What is/are your reason(s) for not using depth of anaesthesia monitoring in paediatric patients? ***(you can choose multiple answers)*** *(respondents were redirected to question 23 after completing this question*

- ❍ It's too expensive
- ❍ It's unreliable
- ❍ It doesn't effect my method of anaesthesia
- ❍ No particular reason
- ❍ Other (please specify)

12. How often do you use depth of anaesthesia monitoring in the following age groups?

	Never	Occasionally	Frequently	(Almost) always
Pre-term neonates	❍	❍	❍	❍
Full-term neonates to 1 month	❍	❍	❍	❍
Infants >1 month <1 year	❍	❍	❍	❍
1–3 years	❍	❍	❍	❍
4–6 years	❍	❍	❍	❍
7–12 years	❍	❍	❍	❍
13–18 years	❍	❍	❍	❍
Adult patients (>18 years)	❍	❍	❍	❍

13. For which of the following procedures do you use depth of anaesthesia monitoring? ***(you can choose multiple answers)***

- ❍ Minor surgery
- ❍ Procedural sedation
- ❍ Major surgery
- ❍ Cardiac surgery
- ❍ Neurosurgery
- ❍ Other (please specify)

14. Please rank the following monitors in order from those most to least frequently used in your personal practice *(you can drag and drop the options)*

▼	Bispectral Index	❑ Not available
▼	Entropy (Datex Ohmeda/GE)	❑ Not available
▼	aepEX	❑ Not available
▼	CAAI	❑ Not available
▼	AEP-monitor/2	❑ Not available
▼	Cerebral State Index	❑ Not available
▼	Narcotrend	❑ Not available

15. Please rank the following reasons for using depth of anaesthesia monitoring in order from the most to least important for you *(you can drag and drop the options)*

▼	To enable use of less anaesthetich agents
▼	Preventrion of intra-operative awareness
▼	Decrease time to awakening
▼	Preventrion of (possible) side effects of anaesthetic agents

16. Do you have any other reasons for using depth of anaesthesia monitoring?

- ❍ Yes
- ❍ No

17. What is/are your additional reason(s), in order of decreasing importance, for using depth of anaesthesia monitoring in paediatric patients?

Reason 1

Reason 2

Reason 3

Reason 4

18. Which aspect of the index value do you think best indicates to the depth of anaesthesia?

- ❍ The trend (i.e. decreasing trend or increasing trend)
- ❍ The exact values
- ❍ The trend and exact values (depends on the monitor)
- ❍ Other (please specify)

19. How would you intervene if ONLY the trend of the index values is increasing?

- ❍ Increase the hypnotics
- ❍ Increase analgesics
- ❍ Combination of hypnosis and analgesics
- ❍ Do nothing; I only intervene when also other variables change (e.g. resp rate, pulse, bp etc)
- ❍ Other (please specify)

20. How would you intervene if ONLY the exact value of the index values is too high?

- ❍ Increase the hypnotics
- ❍ Increase analgesics
- ❍ Combination of hypnosis and analgesics
- ❍ Do nothing; I only intervene when also other variables change (e.g. resp rate, pulse, bp etc)
- ❍ Other (please specify)

21. How would you intervene if the index value is increasing and too high?

- ❍ Increase the hypnotics
- ❍ Increase analgesics
- ❍ Combination of hypnosis and analgesics
- ❍ Do nothing; I only intervene when also other variables change (e.g. resp rate, pulse, bp etc)
- ❍ Other (please specify)

22. With which of the following anaesthetic drugs do you use depth of anaesthesia monitoring in paediatric patients?

	Never	Sometimes	Regularly	Always	Not applicalbe
propofol	❍	❍	❍	❍	❍
sevoflurane	❍	❍	❍	❍	❍
desflurane	❍	❍	❍	❍	❍
isoflurane	❍	❍	❍	❍	❍
halothane	❍	❍	❍	❍	❍

23. Do we need the following devices in paediatric anaesthesia?

	Completely disagree	Disagree	I don't know	Agree	Completely agree
Separate analgesia monitor	❍	❍	❍	❍	❍ ❍
Combined analgesia & depth of hypnosis monitor	❍	❍	❍	❍	

24. Please rank the following requirements for your ideal depth of anaesthesia monitor in the order from those most (1) to least (6) important. ***(you can drag and drop the options)***

- ▼ Applicability in all age groups
- ▼ Low costs disposables
- ▼ Reliability for any (combination of) anesthetic drug
- ▼ Lightweight device
- ▼ Raw EEG display
- ▼ Advanced artefact rejection protocol

This was our last question. We thank you for taking the time to fill in our survey.

Chapter 3

Mid-latency auditory evoked potentials during anesthesia in children: a systematic review

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ABSTRACT

The brain is considered as the major target organ of anesthetic agents. Despite that, a reliable means to monitor its function during anesthesia is lacking. Several depth of hypnosis monitoring devices are available and most of them are electroencephalography (EEG) derived. In children the EEG develops until adulthood, while mid latency auditory evoked potentials (MLAEP), which are known to be sensitive to anesthetic agents, mature during the first decade of life. MLAEP might therefore be a more reliable parameter to measure the state of the brain in pediatric patients. This review investigates the available literature describing various aspects of MLAEP monitoring in pediatric anesthesia.

Keywords: Adolescent; Anesthesia, general; Child; Consciousness monitors; Evoked potentials, auditory; Infant; Systematic review.

BACKGROUND

The relationship between anesthesia and the electrical activity of the brain has been described as early as in the 1940's [1]. Development in this field has been extended to the investigation of the relationship between the brain activity and depth of anesthesia [2]. Research of the brain activity as a surrogate to monitor the depth of hypnosis during anesthesia has mostly focused on the spontaneous electroencephalogram (EEG). However, the spontaneous EEG does not mature before adult age, which could influence its reliability in children [3]. Mid-Latency auditory evoked potentials (MLAEP) are, though electrical brain activity as well, fundamentally different from the spontaneous EEG. These potentials are electric responses of the brain to an auditive stimulus. They occur at about 8 to 50 ms after the stimulus, which is after the auditory brainstem response (0 to 8 ms) and before the late cortical response (>50 ms). A typical MLAEP waveform consists of 3 troughs and 2 peaks of a few microvolt. These are commonly labeled as N0, P0, Na, Pa and Nb and occur, in the awake adult, at respectively about 9 ms, 12 ms, 16 ms, 25 ms and 36 ms after the application of an auditive stimulus [4]. In anesthetized adult patients, the peaks and troughs decrease in amplitude and the interval when they occur, i.e. latencies, increases [5-9]. MLAEP mature after the first decade of life, around 10 to 12 years, which is earlier compared to the EEG [10]. It is therefore likely that MLAEP could be more reliable than the spontaneous EEG, as a parameter to measure the depth of hypnosis in anesthetized children.

This systematic review describes the current literature concerning the use of MLAEP and its implications in anesthetized children.

METHODS

This study adheres to the Preferred Reporting Items for Systematic Reviews and MetaAnalysis (PRISMA) guidelines. A systematic literature search was performed with the assistance of an experienced librarian of the medical library (W.B.) at Erasmus University Medical Center in Rotterdam. The databases of Embase, Medline, Web-of-science, CINAHL, Cochrane, PubMed publisher and Google Scholar were consulted on March 18th 2019. The query consisted, but not solely, of the following search terms: "evoked potential", "anesthesia" and "children". A detailed description of the search query per database can be found in supplement 1.

Manuscript titles were screened for relevance by two authors (Y.C. and I.H.). Any type of clinical study investigating MLAEP during general anesthesia in children with any type of outcome measurements was considered relevant. Manuscripts published in languages other than English or Dutch, case reports and review manuscripts were excluded from analysis. When no consensus could be reached between the two authors about the relevance of a study, the abstract and/or full text was reviewed. When needed a third author (F.W.) was consulted to resolve the matter.

The quality of the studies was assessed with the "Quality Assessment of Diagnostic Accuracy Studies v 2" (QUADAS-2) tool [11]. This tool systematically screens the risks of bias and applicability of the studies included in a systematic review in four key domains: patient selection, index test, reference standard, and flow and timing of the study. As recommended in the background document, the tool was tailored to suit our review question [12]. The assessment for the "reference standard" was omitted, since all types of outcome measurements were marked as relevant (e.g. MLAEP compared to clinical hypnotic depths, anesthetic use, hypnosis index of other types of monitors).

RESULTS

The search resulted in 1471 manuscripts of which 868 remained after removal of duplicates (Figure 1). Manual screening of titles, keywords and abstracts resulted in 45 manuscripts. A careful review of the remaining studies revealed that 15 included only adult patients, 6 were written in a language other than Dutch or English, four concerned patients from the pediatric intensive care unit, one was a case report, one investigated children without pharmacological sedation and in three cases the full-text was unavailable. This resulted in the inclusion of 15 studies which were considered relevant for analysis in this review (Supplement 2).

Table 1 summarizes the quality of the studies according to the QUADAS-2 tool. Since none of the manuscripts described a randomized or blinded patient selection method, the risk for bias due to patient selection was rated "unclear" for all studies. The study by Alvarez et al. was only published as an abstract and was therefore missing details concerning "patient selection" and "flow and timing" [13]. Accordingly, these domains were rated unclear for risk as well as for applicability concerns. Depth of hypnosis was assessed by three studies with clinical parameters, e.g. movement and/or vocalization, without the use of validated tools [14-16]. In one study the same researcher recorded the index values and assessed the depth of hypnosis [17]. For these four studies the risk of bias in the

reference standard were rated as unclear. Two studies were rated unclear for their risk of bias in the domain of "Flow and Timing", because one study was terminated prematurely due to change in the anesthesia practice [15] and the other failed to generate data from 4 of the 14 patients [18]. Seven studies allowed premedication for their patients and were therefore rated as "unclear" for applicability concerns of patient selection [14,15,17-21]. Studies were conducted with 3 different commercially available MLAEP hypnosis monitors or unprocessed MLAEP for analysis. Because each MLAEP derived hypnosis monitor has its own unpublished algorithm, it is unclear how different devices relate to each other. Therefore, the applicability concerns of the index test (MLAEP monitor) was rated "unclear" for all manuscripts.

Table 1. Quality evaluation of studies according to Quality Assessment of Diagnostic Accuracy Studies v 2 (QUADAS-2) tool.

Study	RISK OF BIAS				APPLICABILITY CONCERNS	
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test
Liao et al. 2001	😐	☺	😐	☺	☺	😐
Weber et al. 2004	😐	☺	☺	☺	😐	😐
Alvarez et al. 2004	😐	☺	😐	😐	😐	😐
Weber et al. 2005	😐	☺	☺	☺	😐	😐
Ironfield et al. 2007	😐	☺	😐	😐	😐	😐
Disma et al. 2007	😐	☺	😐	☺	😐	😐
Daunderer et al. 2007	😐	☺	😐	☺	😐	😐
Blussé van Oud-Alblas et al. 2008	😐	☺	☺	☺	☺	😐
Blussé van Oud-Alblas et al. 2008	😐	☺	☺	☺	☺	😐
Feuerecker et al. 2011	😐	☺	☺	☺	😐	😐
Kuhnle et al. 2013	😐	☺	☺	😐	😐	😐
Cheung et al. 2013	😐	☺	☺	☺	☺	😐
Cheung et al. 2014	😐	☺	☺	☺	☺	😐
Cheung et al. 2018	😐	☺	☺	☺	☺	😐
Blussé van Oud-Alblas et al. 2019	😐	☺	☺	☺	☺	😐

Legend: ☺Low Risk 😐Unclear Risk ☹High Risk

Unprocessed MLAEP (measurement of the actual latencies), were used as the index test by three studies [14,18,19]. The remaining 12 studies used commercially available depth of hypnosis monitors. Three of them used the A-line monitor (Danmeter A/S, Odense, Denmark) [16,17,20]. To extract a reliable MLAEP from the EEG and its background activity, measurements have to be repeated several times (usually 250 to 1000 times). The A-line monitor applies an autoregressive model to compute the MLAEP waveform faster (after 15 repetitions), which results in the A-line Autoregressive Index (AAI) as a measurement for the depth of hypnosis [22].

The AEP monitor/2 (Danmeter A/S, Odense, Denmark) is the successor of the A-line monitor and was used by 6 studies [13,15,21,23-25]. It addressed the occasional difficult to measure MLAEP, due to interference or (too) deep anesthesia, by analyzing the spontaneous EEG when a measurable MLAEP was absent. The computed index value was called the composite A-line Autoregressive Index (cAAI) [24].

The studies by Cheung et al. were conducted with the aepEX PLUS monitor (Medical Device Management Ltd., Braintree, Essex, UK) [26-28]. Instead of an autoregressive model, it applied the more conventional "moving time averaging" technique to extract the MLAEP and to compute the aepEX index. This technique requires 256 repeated measurement to extract an entirely new MLAEP waveform, which takes about 37 seconds. Due to that the average "moves", the MLAEP and aepEX index is updated every 0.3 seconds [26]. Seven studies using a commercially available MLAEP monitor reported the average index values observed during different depths of hypnosis [17,20,23,24,26-28]. These values are illustrated in figure 2. The primary objective of these seven studies was to evaluate the performance of a MLAEP monitor to detect different levels of depth of hypnosis in children (Table 2) [17,20,23,24,26-28].

Six studies investigated the relationship between anesthetics and MLAEP monitoring [14-16,18,19,21,25] and 3 studies investigated the effect of MLAEP monitoring on efficiency of the anesthetic regime (Table 3).

Of the included studies two investigated the effect of age on the MLAEP as the primary objective [14,15] and four manuscripts investigated it as their secondary objective [19,26-28]. A brief summary of these studies can be found in Table 4.

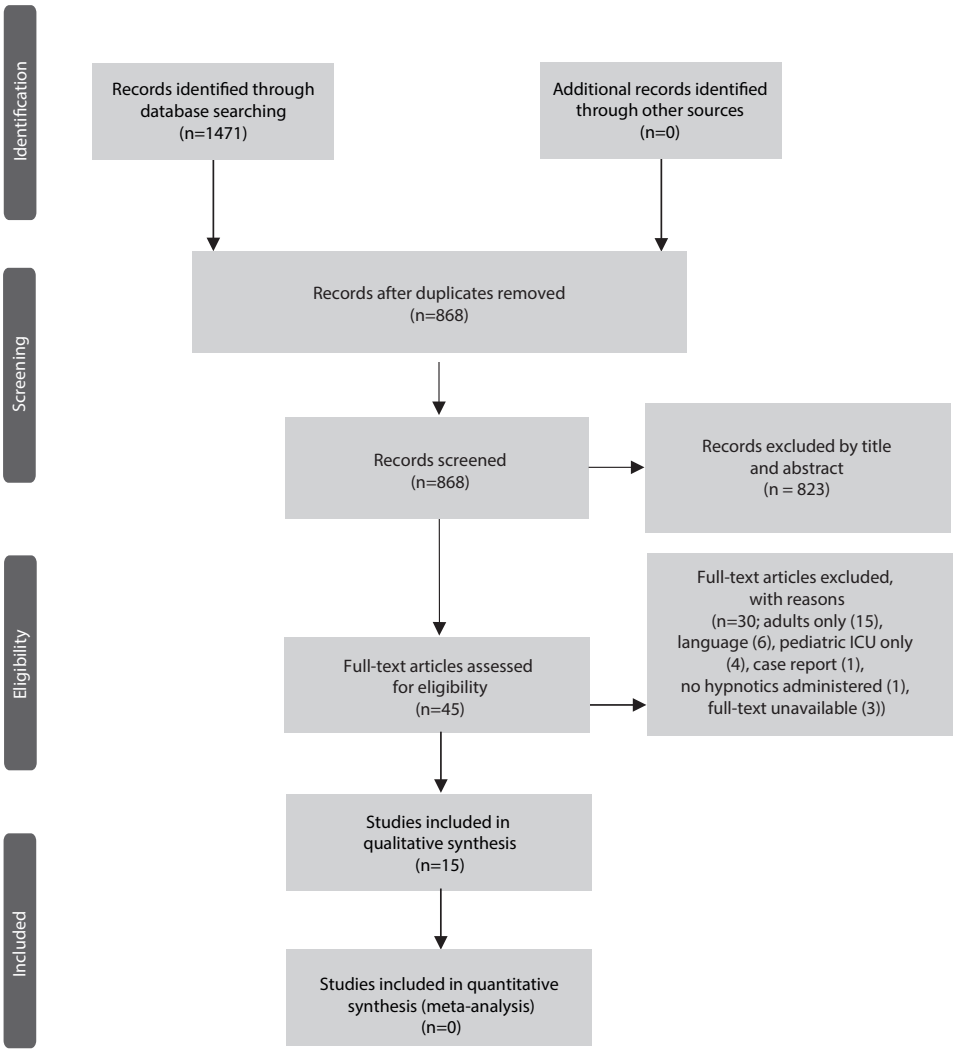

Figure 1. Screened manuscript according to the PRISMA flow diagram.

Propofol — Six studies described MLAEP during propofol anesthesia [17,18,21,23,25,28]. The effect of propofol on the components of the unprocessed MLAEP in children (with a mean age of 8.6 years) has been described by Kuhnle et al. [18]. They observed a dose related increase of latencies (Na, Pa, Nb and P1), and decreasing amplitudes, indicating that MLAEP could be a useful tool for monitoring the depth of hypnosis during propofol anesthesia in children.

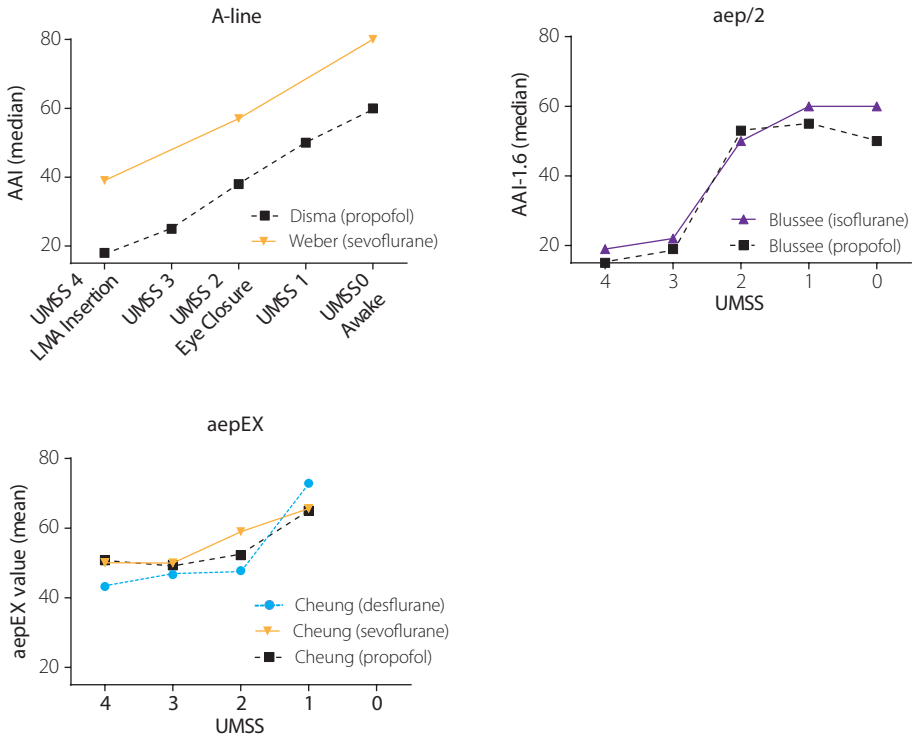

Figure 2. Index values from the A-line, aep/2 and aepEX monitor during different sedation levels and anesthetics administered. University of Michigan Sedation Scale (UMSS).

Three studies investigated the performance of an MLAEP based depth of hypnosis monitor, during propofol anesthesia, in children to detect the anesthetic depth as defined by the University of Michigan Sedation Scale (UMSS) [17,23,28]. Disma et al. demonstrated that the A-line monitor had a spearman's correlation of r=-0.82 ($p<0.0001$) in children 8 months to 7 years old receiving deep sedation for magnetic resonance imaging or esophagogastroduodenoscopy [17]. In older children (10–20 years), Blussé van Oud-Alblas et al. used a wake-up test during scoliosis surgery to evaluate the AEP monitor/2 (the successor of the A-line monitor), which resulted in a prediction probability (p_k) for the UMSS of 0.79 intra-operatively and 0.78 during emergence from anesthesia [23]. A prediction probability describes the proportion in which the monitor predicts the correct value of any chosen parameter, e.g. UMSS, dose of anesthetics. Its use has been a cornerstone in studies concerning monitoring the depth of hypnosis in children. In contrast to the study of Blussé van Oud-Alblas et al., a relatively low p_k value to predict

the UMSS of 0.64 for the aepEX monitor was observed by Cheung et al. [28]. The receiver operation characteristics (ROC) however, revealed an area under the curve (AUC) of 0.77 [28]. A recently published study by Blussé van Oud-Alblas et al. described a sigmoidal relationship between propofol serum concentration and AEP monitor/2 index values from a selection of the population from their previous published study [23,25]. They described the sigmoidal shape as steep for adolescents aging from 10 to 20 years, having a Hill coefficient of 6.85 [25]. This steep relationship was also noticeable between the aepEX PLUS monitor and propofol concentrations for children of 1 to 16 years, as predicted by the Propofol Paedfusor model, during the emergence period (propofol concentration of >2.0 mcg/mL) [28].

Table 2. Summary of manuscripts investigating the relationship between MLAEP and depth of hypnosis.

Study	Outcome	Results
Weber et al. 2004	p_k of AAI during awake versus LMA insertion (mean ± SE)	0.99 ± 0.00
	p_k of AAI during awake versus eye closure (mean ± SE)	0.77 ± 0.08
	p_k of AAI during eye closure vs LMA insertion (mean ± SE)	0.83 ± 0.07
Disma et al. 2007	Correlation between AAI and UMSS	r=-0.8237 (p<0.0001)
	Correlation between AAI and heart rate	r=0.2382 (p<0.05)
Blussé van Oud-Alblas et al. 2008	p_k of cAAI versus UMSS (mean ± SE)	0.90 ± 0.08
	p_k during induction of cAAI versus UMSS (mean ± SE)	0.84 ± 0.08
	p_k during emergence of cAAI versus UMSS (mean ± SE)	0.74 ±0.02
Blussé van Oud-Alblas et al. 2008	p_k during induction of cAAI versus UMSS (mean ± SE)	0.61 ± 0.1
	p_k during Wake-up test of cAAI versus UMSS (mean ± SE)	0.79 ± 0.05
	p_k during Emergence of cAAI versus UMSS (mean ± SE)	0.78 ± 0.03
Cheung et al. 2013	p_k aepEX versus UMSS (mean (95% CI))	0.64 (0.55 to 0.72)
	AUC (mean (95% CI))	0.77 (0.68 to 0.85)
Cheung et al. 2014	p_k of aepEX versus UMSS (mean (95% CI))	0.68 (0.44 to 0.92)
	AUC (mean (95% CI))	0.72 (0.62 to 0.82)
Cheung et al. 2018	p_k of aepEX versus UMSS (mean (95% CI))	0.68 (0.53 to 0.82)
	AUC (mean (95% CI))	0.89 (0.80 to 0.95)

Abbreviations: mid-latency auditory evoked potentials (MLAEP), prediction probability (p_k), A-line autoregressive index (AAI), laryngeal mask airway (LMA), University of Michigan sedation scale (UMSS), composite A-line ARX index (cAAI), area under the receiver operator characteristics curve (AUC)

Implementation of an AEP monitor/2 guided propofol anesthesia in children was described by Weber et al. and resulted in a 34% decrease in propofol consumption and a reduction of 8 minutes in emergence time, compared to standard practice [21].

Sevoflurane — MLAEP during Sevoflurane anesthesia were described by 7 papers. Feuerecker et al. described the effect of increasing steady state concentrations of sevoflurane on MLAEP in infants, schoolchildren and elderly [19]. The peak latency of Pa, Nb and P1 increased significantly with increasing MAC levels of Sevoflurane in all age groups. The mean MLAEP peak latency Nb at 2.3 vol% appeared earlier with increasing age, when comparing schoolchildren with infants (91.86ms ± 14.10 vs 74.71ms ± 10.15 $p<0.05$). The administration of sufentanil had no influence on the peak latencies for all age groups. Daunderer et al. also observed increased peak latencies when anesthesia was maintained with sevoflurane or isoflurane compared to the awake child [14]. However, they also found that the mean amplitude during steady state anesthesia was higher than during the awake state. No subgroup analysis for sevoflurane and isoflurane was performed.

The performance of the AAI during induction of anesthesia was evaluated by Weber et al. [20]. They used the p_k to evaluate the ability and accuracy of the AAI to distinguish between awake, the moment of spontaneous eye closure and the moment of laryngeal mask (LMA) insertion. Weber et al. found a p_k value of 0.99 (SE 0.00) for the AAI to distinguish between the awake state versus a clinical state of unconsciousness at LMA insertion. The awake state vs spontaneous eye closure resulted in a p_k value of 0.77 (SE 0.08). Ironfield et al. investigated the AAI-1.6 as a predictor of sevoflurane concentration in infants (0–1yr) and older children (2–11yr) [15]. The performance of the AEP monitor/2 and BIS were compared using prediction probability. To predict the level of anesthesia, index values during different end-tidal concentrations of sevoflurane (2.5%, 2.0% and 1.5%) and 1min pre-awakening were used. The mean p_k values for the AAI in both age groups were low (0.53 ± 0.14 (0–1yr) vs 0.53 ± 0.10 (2–11yr)). However, this study was terminated early, because of a fundamental shift in patient population. Therefore, only nine children were enrolled. The effect of MLAEP guided anesthesia on recovery after sevoflurane anesthesia was investigated by Liao et al. and Alvarez [13,16]. After discontinuation of sevoflurane Liao et al. found that the mean time to spontaneous movement was faster in de AAI group compared with the standard practice group (3.9 min ± 3.7 vs 6.1 ± 5.7, $p=0.02$). In addition, in the AAI group the mean time until fit for discharge was significantly shorter than in standard practice (60.5 ± 10.0 vs 66.8 ± 9.0, $p=0.03$) [16]. Alvarez et al. however, observed no such difference in recovery time when sevoflurane with N2O anesthesia was guided with the newer AEP monitor/2 [13]. They also did not found a difference

between the mean end-tidal sevoflurane concentration administered during anesthesia. Cheung et al. investigated the performance of the aepEX in distinguishing unconsciousness from consciousness using the UMSS [26]. In this study, the aepEX performed reasonably in terms of having a p_k value of 0.68 and AUC of 0.72.

Isoflurane — Another study by Blussé van Oud-Alblas et al. investigated the AEP monitor/2 during isoflurane anesthesia in children with a mean age of 6.2 years [24]. A p_k value of 0.74 during emergence from anesthesia was observed. Daunderer et al. administered isoflurane or sevoflurane during the maintenance of anesthesia in children [14]. They observed an increase in latencies after induction and a decrease after anesthetics were discontinued. Interestingly, they also found that the amplitude of the MLAEP was significantly higher during steady state compared during the awake state. However, no subgroup analysis was performed for children receiving isoflurane or sevoflurane during anesthesia maintenance.

Desflurane — The study of Cheung et al. was the only study investigating the MLAEP during desflurane anesthesia. They found that the aepEX monitor predicts the correct UMSS with a p_k value of 0.68, while it could discriminate between unconscious and conscious state with a AUC of 0.89 [27].

Age — Comparing children aging >4 years to <4 years old, Daunderer et al. found a statistically non-significant increase of all latencies of the MLAEP in the older group [14]. Feurecker et al. on the other hand demonstrated a significantly increased Pa, Nb and P1 at 1.3vol% sevoflurane between infants (2 months to 3 years) and elderly (75 to 89 years). At 2.3vol% sevoflurane, an increased Na (schoolchildren (6 to 14 years) versus infants) and Nb (schoolchildren versus infants and elderly versus infants) were observed [19]. The studies by Ironfield et al. and Cheung et al. investigated a commercially available MLAEP monitor and its performance (prediction probability and area under the ROC) between age groups of <1 year versus ≥ 1year [15] and <3 years versus 3 to 6 years versus ≥6 years [26,27]. No differences between the age groups were observed however in these studies. Table 4 summarizes studies concerning the effect of age on MLAEP.

Table 3. Summary of manuscripts investigating the relationship between mid-latency auditory evoked potentials and anesthetics or efficiency of anesthesia.

Study	Outcome	Results
Alvarez et al. 2004	Recovery time: controls vs cAAI vs BIS guided anesthesia respectively (s)	419 vs 411 vs 396 (p=0.993)
	Mean Et_{sevo}: controls vs cAAI vs BIS guided anesthesia (vol%)	1.71 vs 1.50 vs 1.87 (p=0.442)
Weber et al. 2005	Propofol requirement of cAAI vs control group (mg·kg-1·h-1: mean ± SD)	4.2 ± 1.7 vs 6.4 ± 1.3 (p< 0.01)
	Emergence time: cAAI vs control (minutes: mean ± SD)	5.1 ± 3.7 vs 13.2 ± 8.2 (p<0.01)
Daunderer et al. 2007	Latencies (Na, Pa, Nb, and P1) "Awake" vs "Intubation" or "Steady state"	Lower during "Awake" (p<0.05)
	Latencies (Na, Pa, Nb and P1) "Awake" vs "Extubation"	p>0.05
Ironfield et al. 2007	p_k of AAI versus Et_{sevo} of 0 to 1 year old (mean ± SE)	0.53 ± 0.14
	p_k of AAI versus Et_{sevo} of 2 to11 years old (mean ± SE)	0.53 ± 0.10
Feuerecker et al. 2011	Latency of Na vs MAC sevoflurane of 2 months to 3 years old	r=0.237 (p=0.163)
	Latencies vs MAC sevoflurane of 2 months to 3 years old (Pa, Nb and P1 respectively)	0.663, 0.783, 0.752 (p<0.0001 for all)
	Latency of Na vs vol% sevoflurane of 2 months to 3 years old	r=0.214 (p=0.208)
	Latencies vs vol% sevoflurane of 2 months to 3 years old (Pa, Nb and P1 respectively)	0.688, 0.768, 0.735 (p<0.0001 for all)
	Latency of Na vs MAC sevoflurane of 6 to 14 years old	r=0.523 (p=0.0003)
	Latencies vs MAC sevoflurane of 6 to 14 years old (Pa, Nb and P1 respectively)	0.734, 0.853, 0.868 (p<0.0001 for all)
	Latency of Na vs vol% sevoflurane of 6 to 14 years old	r=0.513 (p=0.0003)
	Latencies vs vol% sevoflurane of 6 to 14 years old (Pa, Nb and P1 respectively)	0.728, 0.845, 0.860 (p<0.0001 for all)
	Latencies (Na, Pa, Nb or P1) pre-opioid vs post-opioid application	p>0.05
Liao et al. 2011	Correlation between AAI and Et_{Sevo}	R^2=0.01 (p=0.01)
	Spontaneous movement: AAI vs control (min: mean ± SD)	3.9 ± 3.7 vs 6.1 ± 5 (p=0.02)
	Fit for discharge: AAI vs control (min: mean ± SD)	60.5 ± 10.0 vs 66.8 ± 9.0 (p= 0.03)

Table 3. *(Continued)*

Study	Outcome	Results
Kuhnle et al. 2013	Latencies (Na, Pa, Nb or P1) during serum propofol 0, 3, 6 and 9 $\mu g \cdot ml^{-1}$	$p<0.05$ (except Na: 3 vs 6 $\mu g \cdot ml^{-1}$)
Blussé van Oud-Alblas et al. 2019	Model to predict cAAI with serum propofol concentrations (mean (CV%))	E_0: 63.4 (14.9) E_{max}: 0.786 (6.1) γ: 6.85 (46.4)

Abbreviations: composite A-line ARX index (cAAI), seconds (s), end-tidal sevoflurane (Et_{Sevo}), volume percentage (vol%), prediction probability (p_k), minimum alveolar concentration (MAC), A-line autoregressive index (AAI)

DISCUSSION

Extensive systematic search and screening of the current literature resulted in only 15 relevant manuscripts concerning the use of MLAEP monitoring during anesthesia in children. Studies investigating the clinical performance of an MLAEP monitor as a depth of hypnosis monitor demonstrated a moderate to high correlation with the depth of hypnosis and an age-independent performance up to 14 years [14,15,17,19,20,23,24,26-28]. However, studies investigating the relationship between MLAEP and anesthetic drug dose show conflicting results [15,16,18,19].

Studies investigating the MLAEP waveform, observed increasing latencies and decreasing amplitudes when increasing the dose of anesthetics [18,19], while one study described an increased amplitude during anesthesia [14]. When investigating a commercially available MLAEP monitor, its relationship with the end-tidal sevoflurane showed a weak correlation [15,16]. Liao et al. found a r^2 of 0.03 for their linear regression model [16], while Ironfield et al. demonstrated a p_k value of 0.53 [15].

It might be expected that this weak correlation influences the performance of an MLAEP derived depth of hypnosis monitor. However, when analyzing the clinical performance of the A-line, AEP monitor/2 and aepEX monitor as a predictor for the UMSS during emergence, a p_k value ranging from 0.64 to 0.78 was observed during all commonly used anesthetics (propofol, isoflurane, sevoflurane, and desflurane) in children [23,24,26-28].

An even higher p_k value (0.99) was reported by Weber et al. to predict the awake state and movement of the patient during LMA insertion [20]. We can assume that an awake person has an UMSS ≤1 and that LMA insertion is a significant physical stimulus; thus, having an UMSS ≥3 when a patient does not react during LMA insertion. Figure 2 illustrates the

relationship between the index values and UMSS of each type of MLAEP monitor. The oldest MLAEP monitor, the A-line, showed a linear relationship with the UMSS, while the newer models, i.e. the AEP monitor/2 (which superseded the A-line) and the aepEX monitor, show a sigmoidal relationship. The sigmoidal relationship could suggest a binary behavior for the depth of hypnosis, i.e. consciousness and unconsciousness, instead of a gradual relationship. By performing a Receiver Operating Characteristics (ROC) analysis, Cheung et al. investigated the performance of the aepEX to detect conscious (UMSS ≤1) and unconscious (UMSS ≥2) patients [26-28]. They found an area under the curve (AUC) of 0.72–0.89, which implies that the aepEX is a reasonable device to distinguish between consciousness and unconsciousness.

Table 4. Summary of manuscripts investigating the effect of age on mid-latency auditory evoked potentials during anesthesia.

Study	Outcome	Results
Ironfield et al. 2007	p_k of AAI vs Et_{Sevo} (age: 0 to 1 years) (mean ± SE)	0.53 ± 0.14
	p_k of AAI vs Et_{Sevo} (age: 2 to11 years) (mean ± SE)	0.53 ± 0.10
Daunderer et al. 2007	Latencies (Na, Pa, Nb, P1) of <4yrs and >4 years	NS
Feuerecker et al. 2011	Latencies (Na, Pa, Nb and P1) "infants" vs "schoolchildren" during "Awake" or 1.3vol% or 2.6 vol% sevoflurane	Nb at 2.3 vol%; p<0.05 Na, Pa and P1; NS
Cheung et al. 2013	EC_{50} and AUC of aepEX vs UMSS (age: 1 to 3 vs 3 to 6 vs 6 to 16 years) during propofol anesthesia	NS
Cheung et al. 2014	EC_{50} and AUC of aepEX vs UMSS (age: 1 to 3 vs 3 to 6 vs 6 to 18 years) during sevoflurane anesthesia	NS
Cheung et al. 2018	EC_{50} and AUC of aepEX vs UMSS (age: 1 to 3 vs 3 to 6 vs 6 to 18 years) during desflurane anesthesia	NS

Abbreviations: prediction probability (p_k), A-line autoregressive index (AAI), endtidal sevoflurane (Et_{Sevo}), not significant (NS)

While the EEG matures in early adulthood, MLAEP mature in the first decade of life [10]. Regarding the applicability as a physiological monitoring parameter to assess the depth of hypnosis in anesthetized children, this could be a slight advantage of MLAEP when compared to the EEG. Six out of 15 studies investigated the effect of age on the MLAEP. Five studies comparing the MLAEP of children from different age groups with each other showed no significant differences in its latencies [14] and index values [15,26-28]. Only one study, by Feurecker et al., revealed increasing latencies with increasing age. This was however only apparent between infants and elderly patients [19], indicating the

consistency of the MLAEP as a parameter for assessing the depth of hypnosis in children of ages at least up to 14 years.

There are conflicting results concerning MLAEP guided anesthesia to improve the efficiency of the anesthetic regime. Weber et al. and Liao et al. demonstrated a faster recovery from anesthesia and less propofol requirement when anesthesia was guided by AAI or cAAI [16,21]. Alvarez et al. on the other hand could not demonstrate these benefits with cAAI guided anesthesia [13]. Although Alvarez et al. had a larger number of patients included in their study compared to Weber et al., essential details are lacking from their study since only a published abstract could be found.

In daily practice, application of a MLAEP monitor in children can be challenging. Manufacturers of these monitors usually supply an in-ear headphone with the device, which cannot be adequately placed in the small ear canal of a child. Published manuscripts try to circumvent this problem by securing the earpieces with tape or replacing the headphones with their own over-ear headphones [15,20,26-28].

The low voltage of the MLAEP waveform (a few hundred microvolts) makes it prone to noise and artefacts. This is especially evident when trying to measure MLAEP in young children when still awake or during the induction and emergence phase, making its clinical use challenging.

Very few studies concerning the use of MLAEP monitoring in children during anesthesia are conducted. This review yielded only 15 studies concerning this subject. Due to the diversity in defined outcome parameters and methodological differences, e.g. different anesthetics, pre-medication and type of monitor used, a comparative (meta)analysis was considered not meaningful. We therefore lack a statistically-founded recommendation in whether MLAEP monitoring is beneficial during anesthesia in children. This review however attempts to systematically exhibit the current available literature, so that the reader can make a well thought decision on whether MLAEP monitoring could benefit his or her anesthesia.

In conclusion, MLAEP analysis is a reasonable method to assess the depth of hypnosis in children during anesthesia. Furthermore, its reliability does not depend on the age of the child and the type of commonly used anesthetics. However, only a few studies investigated the performance of an MLAEP monitor as a depth of hypnosis monitor and conclusions for its reliability should be made with caution.

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Chapter 4

Evaluation of the aepEX™ monitor of hypnotic depth in pediatric patients receiving propofol-remifentanil anesthesia

Paediatr Anaesth. 2013;23(10):891-897.

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ABSTRACT

BACKGROUND: The aepEX Plus monitor (aepEX) utilizes a mid-latency auditory evoked potential-derived index of depth of hypnosis (DoH).

OBJECTIVE: This observational study evaluates the performance of the aepEX as a DoH monitor for pediatric patients receiving propofol–remifentanil anesthesia.

METHODS: aepEX and BIS values were recorded simultaneously during surgery in three groups of 25 children (aged 1–3, 3–6 and 6–16 years). Propofol was administered by target-controlled infusion. The University of Michigan Sedation Scale (UMSS) was used to clinically assess the DoH during emergence. Prediction probability (p_k) and receiver operating characteristics (ROC) analyses were performed to assess the accuracy of both DoH monitors. Nonlinear regression analysis was used to describe the dose-response relationships for the aepEX, the BIS, and propofol plasma concentrations (C_p).

RESULTS: The p_k for the aepEX and BIS was 0.36 and 0.21, respectively (p=0.010). ROC analysis showed an area under the curve of 0.77 and 0.81 for the aepEX and BIS, respectively (p=0.644). At half-maximal effect (EC_{50}), C_p of 3.13 $\mu g \cdot ml^{-1}$ and 3.06 $\mu g \cdot ml^{-1}$ were observed for the aepEX and BIS, respectively. The r2 for the aepEX and BIS was 0.53 and 0.82, respectively.

CONCLUSIONS: The aepEX performs comparable to the BIS in differentiating between consciousness and unconsciousness, while performing inferior to the BIS in terms of distinguishing different levels of sedation and does not correlate well with the C_p in children receiving propofol-remifentanil anesthesia.

Key words: Adolescent. Children, preschool. Consciousness Monitors. Evoked Potentials, Auditory/drug effects. Infant. Propofol

BACKGROUND

The aepEX Plus monitoring system (Medical Device Management Ltd., Essex, UK), designed to monitor the depth of hypnosis (DoH) in anesthetized patients, has recently become available in Europe. It is currently the only commercially available monitor, which processes mid-latency auditory evoked potentials (MLAEP). The computer analysis produces an index value called aepEX, which ranges from 0 to 99. MLAEP is a promising physiological variable to assess the DoH [1-3]. There are, however, few published studies concerning the use of the aepEX Plus (aepEX) as a DoH monitor in clinical anesthesia, and to our knowledge, these have only been conducted in the adult population [4-7]. In this observational study, we investigated the performance of the aepEX as a DoH device in pediatric patients anesthetized with propofol and remifentanil. Simultaneously Bispectral Index (BIS) data were collected as a means of reference.

METHODS

After obtaining Institutional Review Board approval (ErasmusMC, Rotterdam, the Netherlands, MEC2011-104, NL 35976.078.11), written informed consent was obtained from the patient's parents or guardians. Additionally, written assent was obtained from patients older than 12 years.

Seventy-five pediatric patients, scheduled for plastic, urological, orthopedic, or general surgery, were eligible for inclusion in the study. Patients were divided into three age groups of 25 patients aged 1–3, 3–6, and 6–16 years.

Patients were primarily excluded when they had clinically significant hearing impairments, EEG affecting conditions, taking EEG affecting drugs, needed admittance for the pediatric intensive care unit (PICU) and known allergies for propofol, sevoflurane and/or remifentanil.

After successful cannulation, a bolus of 0.5 $\mu g \cdot kg^{-1}$ remifentanil was given over 15 s followed by a continuous infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Propofol was administered by a target-controlled infusion (TCI) pump (Alaris PK Syringe Pump, CareFusion, Houten, the Netherlands) programed with the Propofol Paedfusor pharmacokinetic model [8,9] and was initially set at a target propofol concentration (C_p) of 6.0 $\mu g \cdot ml^{-1}$.

In case of inability to secure an i.v. access in the awake child, anesthesia induction was performed by mask with sevoflurane followed by i.v.-cannulation. Propofol-TCI and continuous remifentanil infusion were started as soon as possible. Subsequently, sevoflurane was stopped and washed out with high fresh-gas flow (10 l·min^{-1}).

The airway was secured by a laryngeal mask airway. Patients were connected to a semiclosed anesthetic circuit (Primus®, Draeger, Lübeck, Germany) and primarily allowed to breath spontaneously. In case of hypoventilation, mechanical ventilation was used to re-establish and maintain normocapnia.

The attending anesthesiologist could apply a localregional technique suitable for the type of surgery. Surgery was allowed to commence at least 10 min after the application of a local-regional technique. If needed, additional remifentanil could be given before intraoperative measurements were made.

Intraoperatively, the C_p were gradually decreased from 6.0μg·ml^{-1} to a minimum of 2.0 μg·ml^{-1} in steps of 0.5 μg·ml^{-1}. After each step, C_p were allowed to stabilize for at least 1min.

If the patient showed signs of inadequate depth of anesthesia, that is, tachycardia, tachypnea, sweating, involuntary movements, or hypertension, during the decrease in C_p, the C_p and/or remifentanil could be increased.

At the end of the procedure, remifentanil and propofol administration was discontinued, which marked the emergence. The University of Michigan Sedation Scale (Table 1) was applied to assess the patient's consciousness until a UMSS of 1 by a single researcher (Y.C.) [10].

All patients received standard anesthesia monitoring, consisting of ECG, pulse oximetry, noninvasive blood pressure measurement at 5-minute intervals, temperature, capnography, inspired and endtidal concentrations of oxygen and, in case of inhalation induction, inspired and endtidal sevoflurane concentration.

Table 1. University of Michigan Sedation Scale.

0	Awake/ Alert
1	Minimally Sedated: Tired/ sleepy, appropriate response to verbal conversation and/ or sounds.
2	Moderately Sedated: Somnolent/ sleeping, easily aroused with light tactile stimulation.
3	Deeply Sedated: Deep sleep, arousable only with significant physical stimulation.
4	Unarousable

aepEX- and BIS-monitoring

Before applying the DoH monitor sensors, the skin was swabbed with alcohol and abraded with Sensor Prep (Medical Device Management, Essex, UK). Attachment of the sensors was in accordance with the recommendations of the manufacturers. We attached the aepEX sensors on the left side and the BIS electrodes on the right side of the patient's head. At the midline, the BIS electrode was attached above the aepEX electrode. Sensor placement and skin preparation were repeated until the impedance was below the required value as indicated by the monitors. Prior to induction of anesthesia, no baseline data were collected for analysis.

aepEX monitoring and data processing

To evoke MLAEP, the aepEX produces 1ms short click sounds with an intensity of 90 dB at a frequency of 6.9 Hz, which were delivered via a pair of headphones (MDR-V150; Sony Europe, London, UK). These headphones made the monitor more suitable for our pediatric study population than the aepEX standard silicone earphones.

The aepEX algorithm calculates the MLAEP waveform by averaging 256 cortical responses (sweeps) to the applied click sounds. Due to a moving time-averaging technique, the aepEX value is updated every 0.3 s instead of (256 sweeps / 6.9 Hz) 37s.

We used the aepEX logger software (Medical Device Management, Essex, UK, version 1.3) to store aepEXvalues to a personal computer. Values contaminated with artifacts as flagged by the artifact detection routine of aepEX were excluded from further analysis.

BIS monitoring and data processing

We used a BIS Vista monitor (Aspect Systems International, de Meern, the Netherlands, software version 2.02) with smoothing rate set to 15s. Recordings were exported directly to a USB drive for subsequent offline analysis. Values having a signal quality lower than

50%, as reported by the BIS, were considered too heavily contaminated with artifacts and were discarded from further analysis.

DoH monitoring was performed throughout anesthesia until the patient regained consciousness. For analysis, index values of 10 s were averaged.

During emergence, index values just before every UMSS score were averaged to minimize interference by UMSS assessment. To prevent interobserver variability, one single researcher (Y.C.) collected all DoH-monitoring data and made all UMSS observations. The attending anesthesiologist was blinded for both monitors during the study.

Statistics

Continuous data were validated for normality by visual inspection in combination with the D'Agostino and Pearson omnibus normality test. Unless stated otherwise, variables were presented as mean (SD). Nonparametric analyses were performed with the Kruskal-Wallis test with Dunn's posthoc test for unpaired data, for example, differences between age groups, and Wilcoxon matched-pairs signed rank test for paired data, for example, differences between aepEX and BIS. Multiple testing of paired data was corrected with a posthoc Bonferroni's correction.

Nonlinear regression calculations were used to investigate the relationship between index values and C_p by fitting the data in an inhibitory sigmoid Emax model:

$$E = E_0 + \frac{(E_{max} - E_0)}{1 + 10^{(logEC_{50} - x)y}}$$

where E is the index value as shown by the DoH monitors, EC_{50} the C_p with half-maximal effect on the DoH monitors, *x* the C_p as indicated by the TCI pump and γ the Hillslope which was variable to optimize for the best fit. E_0 and E_{max} were constrained to 0 and 100. Only intraoperative DoH data were used for this analysis, as we could not let the C_p stabilize for one minute during the emergence period due to ethical reasons.

Evaluation of the predictive value of the DoH monitors for the UMSS was performed by calculating the prediction probability (p_k) as proposed by Smith et al. [11]. A custom spreadsheet macro, p_k MACRO, provided and described by them [11], was used for analysis. The p_k value ranges from 0.0 to 1.0 and is calculated from index values of at least three different UMSS scores. A value of 0.5 means that in 50% of the cases, the DoH monitor

correctly predicts the clinically observed UMSS. If the device predicts the UMSS 100% correctly, the p_k value would be 1.0. Values below 0.5 describe an inverse relationship.

To investigate the reliability of the monitors in distinguishing between consciousness and unconsciousness, dichotomized UMSS scores (UMSS >1 indicating unconsciousness, UMSS ≤1 indicating consciousness) were used to perform a paired receiver operating characteristic (ROC) analysis for both monitors. ROC analysis for each DoH monitor and age group was performed to calculate sensitivity and specificity. All ROC analyses were calculated using MEDCALC for Windows, version 12.3.0.0 (MedCalc Software, Mariakerke, Belgium). Other analyses were calculated by GRAPHPAD Prism 5 for Mac OS X, version 5.0d (GraphPad Software, San Diego, California, USA). P-values <0.05 were considered statistically significant.

RESULTS

We were able to complete the registration of aepEX and BIS values until awakening in 69 patients. In four patients (group 6–16), the C_p and/or remifentanil administration was increased. Data recording could not be completed due to technical or logistical difficulties in three, one, and two patients from groups 1–3, 3–6, and 6–16, respectively. In one patient (group 6–16), artifactfree aepEX values were only available during emergence. Two study patients (groups 1–3 and 6–16) received premedication and were excluded from further analysis. No patient received neuromuscular blocking agents.

For caudal blocks (n=61), ropivacaine 0.2% was administered at a dose of 1.0–1.25 ml·kg^{-1}, up to a maximum of 25 ml. In two patients, a penile block was performed with bupivacaine 0.5%, 0.2 ml·kg^{-1}. Peripheral loco-regional techniques were applied under ultrasound guidance, and volumes <5 ml of ropivacaine 0.2% were injected. Demographic data of the patients are shown in Table 2.

Figure 1 illustrates the means of the index values of both DoH monitors during the various measurement points.

Table 2. Baseline Characteristics of patients receiving propofol-remifentanil anesthesia.

	1–3 years (n=24)	3–6 years (n=25)	3–6 years (n=24)	1–18 years (n=73)
Mean age in months [IQR]	23 [14–34]	57 [43–72]	107 [74–176]	62 [14–176]
Weight in kg (mean ± SD)	12.00 ± 1.92	18.86 ± 4.01	33.19 ± 13.22	21.32 ± 11.85
Male/female	23/1	23/2	22/2	68/5
Mean duration of surgery in minutes [IQR]	87 [40-210]	87 [45-215]	87 [45-155]	87 [40-215]
Procedure				
Subumbilical	21 (88%)	25 (100%)	24 (100%)	70 (96%)
Upper extremity	3 (13%)	0 (0%)	0 (0%)	3 (4%)
Locoregional technique				
No block	2 (8%)	2 (8%)	2 (8%)	6 (8%)
Caudal block	21 (88%)	20 (80%)	20 (83%)	61 (84%)
Penile block	0 (0%)	1 (4%)	1 (4%)	2 (3%)
Ileoinguinal block	0 (0%)	2 (8%)	0 (0%)	2 (3%)
Axillary block	1 (4%)	0 (0%)	0 (0%)	1 (1%)
Sciatic and femoral block	0 (0%)	0 (0%)	1 (4%)	1 (1%)

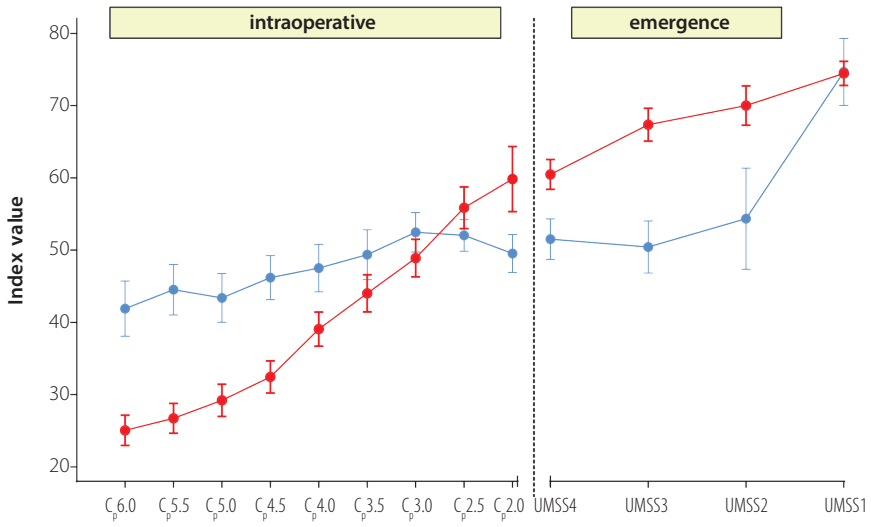

Figure 1. Mean aepEX (● blue) and BIS (● red) index values with 95% confidence intervals at different propofol concentrations (C_p) and UMSS scores of all groups.

Non-linear regression analysis revealed a median EC_{50} of 3.13 µg·ml^{-1} (IQR: 1.94–3.96) and 3.06 µg·ml^{-1} (IQR: 2.46–3.43) for the aepEX and BIS, respectively (p=0.949). Comparisons between different age groups within and between both monitors revealed no significant differences. Table 3 summarizes the results derived from the nonlinear regression analysis.

Paired comparison of p_k values was possible for 26 patients. The mean p_k value for the aepEX (Pk_{aepEX} 0.36; 95% CI: 0.28–0.45) was significantly higher than for the BIS (Pk_{BIS} 0.21; 95% CI: 0.17– 0.25) (p=0.010).

ROC analysis for patients at the start of the emergence compared with patients assigned to UMSS1 revealed an area under the curve (AUC) of 0.77 (95% CI: 0.68–0.85) and 0.81 (0.74–0.87) for the aepEX and BIS, respectively. Specificity was 2% and 16% for the aepEX and BIS, respectively, at 100% sensitivity. At 100% specificity, sensitivity was 14% and 15% for the aepEX and BIS, respectively (Figures 2 and 3).

Maximum sensitivity and specificity were, respectively, 77% and 71% for the aepEX and 66% and 93% for the BIS at index values of, respectively, >55 and >70. The results of the unpaired ROC analyses are illustrated in Figures 2 and 3.

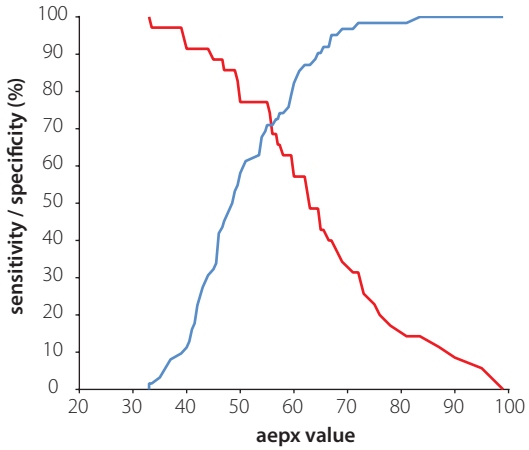

Figure 2. The sensitivity (● red) and specificity (● blue) of the aepEX monitor to detect consciousness (UMSS of 1) from various index values.

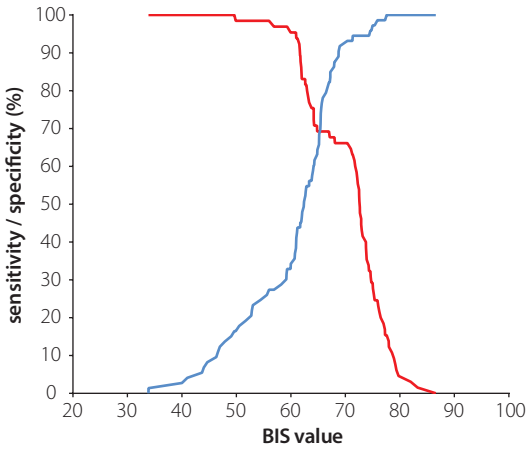

Figure 3. The sensitivity (● red) and specificity (● blue) of the BIS monitor to detect consciousness (UMSS of 1) from various index values.

DISCUSSION

This study is, to our best knowledge, the first to evaluate the applicability of the aepEX in pediatric surgical patients. We found that the aepEX performs comparable to the BIS in detecting UMSS ≤1. The aepEX was furthermore less related to C_p and performed inferior to the BIS in discriminating subtle differences in DoH.

Figure 1 illustrates the relationship between index values at different measurement moments. As opposed to the BIS, the aepEX was less affected by different C_p (see Figure 1), whereas at emergence from anesthesia,transition from unconsciousness to consciousness resulted in a significant increase in index values. This same response pattern of the aepEX was also reported in other studies, which were performed in adult patients [6,12]. Interestingly, the AEP monitor/2, which also processes MLAEP, has been reported to produce a comparable increase in index values at awakening [5,13-15].

The relatively constant aepEX value during maintenance and the abrupt increase at UMSS 1 suggests that the aepEX has a weak correlation with the actual C_p, but rather with the clinical endpoints consciousness vs unconsciousness. This weak correlation corresponds with the rather low r2 (0.53) of the nonlinear regression model. The observed r2 of the BIS is in agreement with the current literature [16-18] and suggests a more accurate prediction of BIS values at different C_p. The EC_{50} ranging from 2.46 to 3.43μg·ml^{-1} propofol for the BIS is comparable with published adult data (see Table 3) [17–20]. Rigouzzo et al.

demonstrated that the EC_{50} for the BIS was significantly higher in prepubertal patients than in postpubertal patients [16]. As we mostly had prepubertal patients, this effect, that is, decreasing EC_{50} with increasing age was not observed in our study.

Table 3. Half maximal effective concentrations derived from non-linear regression analysis of propofol on aepEX and BIS index values.

	1–3 years	3–6 years	6–18 years	1–16 years
aepEX				
EC_{50}* (median [IQR])	3.24 [1.34–3.93]	2.77 [2.24–3.93]	2.97 [2.01–5.88]	3.13 [1.94–3.96]
r^2 (mean ± SD)	0.49 ± 0.30	0.53 ± 0.36	0.57 ± 0.34	0.53 ± 0.33
BIS				
EC_{50} (median [IQR])	3.09 [2.34–3.66]	3.17 [2.94–3.61]	2.55 [2.35–3.30]	3.06 [2.46–3.43]
r^2 (mean ± SD)	0.78 ± 0.22	0.87 ± 0.10	0.83 ± 0.16	0.82 ± 0.17

* EC_{50}; Half maximal effective concentration in $\mu g \cdot ml^{-1}$.

P_k analysis revealed a Pk_{aepEX} value of 0.36 indicating an inverse correlation with the UMSS, in other words, the aepEX predicts 64% of the UMSS correctly. The BIS had a higher predictive value of 79% (p=0.010).

To our best knowledge, there are currently no published studies dealing with Pk_{aepEX} values in pediatric patients. Two recently published studies from our own research group reported a p_k value of 0.74 for the AEP monitor/2 calculated for 45 and 20 pediatric patients [13,14].

Struys et al. reported a p_k value of 0.89 for the MLAEP derived A-Line Index in 20 adult patients receiving propofol anesthesia [21]. The differences in the observed p_k values could, at least partially, be explained by differences in the applied study designs and the use of different DoH monitors.

Our own research group revealed a Pk_{BIS} of 0.74 and 0.75 in previous studies [13,14], which is close to our currently observed Pk_{BIS} value of 0.79.

Although p_k values of only 26 patients could be calculated in this study, the Pk_{BIS} of 0.79 seems to be in accordance with those in previously published pediatric studies; Pk_{BIS} of 0.74 and 0.75 [13,14].

We could not detect an age dependency for the EC_{50} (see Table 3) and p_k values. This could be a type II error because we had not performed a power analysis for these parameters. Using a precommercialized version of the aepEX, Doi et al. demonstrated that it does not correlate well with the C_p, whereas a sudden increase in aepEX values was observed when patients regained consciousness [12]. This behavior might suggest that the aepEX monitor does not measure a depth, but rather a clinical state (UMSS≥1). As the p_k value describes the accuracy to predict every UMSS, this could explain the rather lower Pk_{aepEX} value.

In a recent editorial, Sleigh questioned the model of 'depth of anesthesia' in favor of a simple on–off switchboard mechanism theory [22]. Although solely a theory, it seems to match our observations of the aepEX during propofol anesthesia.

Considering the aepEX's binary behavior, a (binary) ROC analysis could theoretically be more appropriate than a p_k analysis. Compared with our findings, Gajraj et al. observed at 100% specificity, a significantly higher sensitivity for the precommercialized aepEX monitor (14% vs 60%) and a comparable sensitivity for the BIS (15% vs 14%) [23]. At a sensitivity of approximately 85%, they reported a higher specificity compared with our findings for the aepEX (53% vs 85%) and BIS (45% vs 80%). In a previous study by our own group, the BIS had a sensitivity of 12%, 85%, and 100%, respectively, at 100%, 61%, and 9% specificity [13]. The discrepancy found between our study and Gajraj et al., could be explained by the large difference in age of the study populations. ROC analyses of the aepEX and BIS showed no significant differences in the AUC between the three age groups and the groups as a whole (p=0.644).

We did not analyze the relationship between the index values and C_p during emergence, due to the continuous decline of C_p at that moment. The 20 s averaged index values would therefore not represent one C_p, but rather a range.

Our study applied the Paedfusor pharmacokinetic model to calculate the expected C_p based on age and weight. C_p, however, is an indirect measurement of the propofol concentration at the effect site, the brains. For that reason, it would have been preferable to assess the DoH monitors with a TCI pump programed with a pediatric effect-site model. Unfortunately, no such model is commercially available at this moment. Our study population consisted only of pediatric patients receiving propofol with remifentanil anesthesia and, while the effect of remifentanil on the aepEX should be minimal [24], extrapolations to other combinations of anesthetics with opioids for children should be carried out cautiously.

Loco-regional anesthesia could have an effect on DoH. Davidson et al. demonstrated that a caudal block was associated with a five points decrease in BIS values compared with patients without a caudal block. The authors also pointed out that the clinical relevance of a decrease in five points is questionable [25].

In accordance with Absalom et al., who found no impact of aep monitoring on BIS values during propofol anesthesia, we assume that interference of aepEX- and BIS-monitoring is rather unlikely [26].

Having the headphones on did not give problems for UMSS assessment. The same headphones were used in a previously published study concerning the A-line monitor and UMSS, which also posed no problems in UMSS assessment [27].

We assumed that patients not known with hearing impairment would be suitable for aepEX monitoring. During our interaction with the patients, we did not observe any signs for hearing impairments and 69 patients were successfully scored with a UMSS of 1, which meant they had an adequate response to sound.

The investigator who collected the DoH data also made the UMSS assessments. This might lead to the possibility of a slight bias. We certainly would have preferred to let the UMSS assessments be carried out by another person. However, this was not possible for logistical reasons.

In conclusion, we have observed that in pediatric patients, under propofol-remifentanil anesthesia the aepEX performs comparably to the BIS in distinguishing consciousness from unconsciousness, while the aepEX is inferior to the BIS in detecting different UMSS. The aepEX was unaffected by age and, unlike the BIS, also C_p. The sudden increase in index values of the aepEX when patients regained consciousness comply with the intriguing hypothetic 'switchboard-theory' by Sleigh [22].

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Chapter 5

Evaluation of the auditory evoked potentials derived aepEX™ as a measure of hypnotic depth in pediatric patients receiving sevoflurane–remifentanil anesthesia

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ABSTRACT

BACKGROUND: The aepEX is a measure of depth of hypnosis (DoH), derived from processed mid-latency auditory evoked potentials.

OBJECTIVES: To evaluate the aepEX as a measure of DoH in children receiving sevoflurane–remifentanil anesthesia.

METHODS: aepEX and bispectral index (BIS) were recorded simultaneously in 75 children, (1–3, 3–6, and 6–18 years), receiving sevoflurane at endtidal concentrations (Et_{sevo}) between 1.5 and 0.5 MAC. The Et_{sevo} at which the aepEX and BIS had a value of 50 (EC_{50}aepEX and EC_{50}BIS) was calculated by nonlinear regression analysis. The accuracy of aepEX and BIS to predict the DoH was assessed by prediction probability (p_k) and receiver operating characteristics (ROC) analysis.

RESULTS: Seventy-four children were included for analysis. The EC_{50}aepEX (2.68%) and EC_{50}BIS (2.10%) were comparable; the same accounts for the EC_{50}aepEX of the different age groups and the EC_{50}aepEX and EC_{50}BIS of corresponding age groups. The EC_{50}BIS in children aged 1–3 years was lower than in the older age groups ($p<0.05$). P_k values of the aepEX (0.32, CI 95% 0.08–0.56) and BIS (0.47, CI 95% 0.19–0.75) were comparable. The area under the ROC curve was 0.72 (CI 95%: 0.62–0.82) and 0.67 (CI95%: 0.56– 0.77) for the aepEX and BIS, respectively (p=0.54). Optimal cutoff values were >60 (aepEX) and >68 (BIS), with corresponding specificities 91%, CI 95%: 80–97% (aepEX) and 66%, CI 95%: 52–77% (BIS).

CONCLUSIONS: In this study with children receiving sevoflurane anesthesia, the aepEX outperformed the BIS in distinguishing unconsciousness from consciousness. Both indices performed equally bad in differentiating different levels of DoH.

Keywords: Adolescent; Child; Child, Preschool; Consciousness Monitors; Evoked Potentials, Auditory; Drug Effects; Infant; Sevoflurane

BACKGROUND

Monitoring the depth of hypnosis (DoH) in pediatric surgical patients is both necessary and challenging. All currently available EEG-derived DoH monitors are primarily designed for use in adult patients. The EEG of a child has different characteristics than the adult EEG, the younger the child, the more pronounced the differences. Therefore, the use of EEG-derived DOH monitors is not recommended in children younger than two years [1].

Another approach to monitoring DoH is the analysis of mid-latency auditory evoked potentials (MLAEP) [2]. A potential advantage of MLAEP over the EEG in terms of their applicability as a measure of DoH in children is, that the differences between children and adults appear to be less pronounced [3].

The recently marketed aepEX Plus monitor (Medical Device Management Ltd., Essex, UK) processes midlatency auditory evoked potentials (MLAEPs) resulting in the so-called aepEX index, representing a measure of depth of hypnosis (DoH).

In this prospective observational study, we evaluated the performance of the aepEX monitor to detect the DoH in children of different age groups receiving sevoflurane–remifentanil anesthesia. bispectral index (BIS) recordings were simultaneously collected and compared to the aepEX as a means of reference.

METHODS

After IRB approval (ErasmusMC, Rotterdam, the Netherlands, MEC 2011-104, NL 35976.078.11) and written informed consent of the parents and patients older than 12 years were obtained, pediatric patients aged between 1 and 18 years and scheduled for elective plastic, urological, orthopedic, or general surgery were eligible for inclusion in this study. 75 patients were stratified for age into three groups of 25 (1–3, 3–6, and 6–18 years). Clinically significant hearing impairments, EEG affecting conditions, use of EEG affecting drugs (premedication included), need for admittance to the pediatric intensive care unit, and/or known allergies for sevoflurane and/or remifentanil served as primary exclusion criteria.

For induction of general anesthesia, it was first attempted to obtain and secure peripheral intravenous access. A slow bolus of 0.5 $\mu g \cdot kg^{-1}$ remifentanil was administered over 15 s followed by a continuous infusion of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, followed by propofol (3–5 $mg \cdot kg^{-1}$)

or sevoflurane (without nitrous oxide) by mask. If intravenous access could not be obtained under awake conditions, anesthesia induction was performed by mask with sevoflurane, followed by i.v. access and remifentanil as described above. A laryngeal mask airway was used to secure the airway. Patients were connected to a semi-closed anesthetic circuit (Primus, Draeger, Lubeck, Germany) and primarily allowed to breathe spontaneously. In case of hypoventilation (endtidal CO_2 >6.0 kPa), mechanical ventilation was used to re-establish and maintain normocapnia (endtidal CO_2 of 4.5–6.0 kPa).

If possible, patients received locoregional blocks for both intra- and postoperative pain relief. Peripheral low volume loco-regional techniques were applied under ultrasound guidance, using ropivacaine 0.2%. For caudal blocks, plain ropivacaine 0.2% was used at a volume of 1.00–1.25 ml·kg^{-1}. For penile nerve blocks, bupivacaine 0.5% 0.2 ml·kg^{-1} was administered. If local regional techniques were not an option, remifentanil was increased to 0.3–0.4 µg·kg^{-1}·min^{-1}. Furthermore, i.v. paracetamol 15 mg·kg^{-1} and i.v. diclofenac 2 mg·kg^{-1} were given.

Et_{sevo} was initially adjusted to 3.9%, equivalent to 1.5 MAC values [4], in a mixture of oxygen and air, and subsequently decreased by steps of 0.5% at least every 5 min to a minimum of 1.8% to maintain an adequate DoH during the surgical procedure. A further decrease to 1.3% (0.5 MAC) was achieved at the start of wound closure.

Et_{sevo} and/or remifentanil could be increased if the attending anesthesiologist had reason to suspect inadequate depth of anesthesia, i.e., tachycardia, tachypnea, sweating, involuntary movements, or hypertension.

At the end of the procedure, sevoflurane and remifentanil administration was discontinued and the fresh gas flow was set to 10 lmin1, which marked the start of the emergence period. The University of Michigan Sedation Scale [5] (UMSS, see Table 1) was used to assess the DoH until a score of ≤1 was reached.

All patients received standard anesthesia monitoring consisting of ECG, pulse oxymetry, noninvasive blood pressure measurement, temperature, capnography, and inspired and endtidal concentrations of oxygen and sevoflurane.

aepEX and BIS monitoring

The skin on the forehead was first swabbed with alcohol and abraded with Sensor Prep (Medical Device Management, Essex, UK). Then, the aepEX sensors were attached on the left side and the BIS electrodes on the right side of the patient's head according to the manufacturers' recommendations. The aepEX sensor was attached just below the BIS electrode at the center of the forehead.

To not distress the child unnecessarily, no baseline data of both DoH monitors were collected from the patients prior to the induction of anesthesia.

In patients who had an i.v.-induction with propofol, intraoperative aepEX and BIS measurements were postponed for 15 min after the last bolus of propofol.

Intraoperatively, values from both DoH monitors were collected at least 5 min after every decrease in Et_{sevo} during the emergence period values recorded just before every UMSS score were used for analysis. Analyses were performed with averaged index values of 10s.

To prevent interobserver variability, one single researcher (Y.C.) collected all DoH-monitor's data and made the UMSS assessments. During the whole study-period, the attending anesthesiologist was blinded to the screens of both DoH monitors.

Table 1. University of Michigan Sedation Scale.

0	Awake/alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation, and/or sounds.
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation.
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation.
4	Unarousable.

aepEX monitoring and data processing

The aepEX delivers click sounds with a duration of 1 ms, an intensity of 90 dB, and a frequency of 6.9 Hz through a pair headphones to provoke MLAEPs. As the standard earplugs are unsuitable for small children, we connected the aepEX to a commercially available over-the-ear headphone (MDR-V150; Sony Europe, London, UK).

The aepEX algorithm calculates the MLAEP waveform by averaging 256 cortical responses (sweeps) to the applied click sounds. The aepEX value is updated every 0.3 s by moving

time average technique. aepEX values were recorded to a personal computer using the AEPEX LOGGER software (Medical Device Management, version 1.3). Values that were marked by the aepEX's artifact detection protocol were manually excluded from further analysis.

BIS monitoring and data processing

The BIS VISTA monitor (Aspect Systems International, de Meern, the Netherlands, software version 2.02) was used. The smoothing rate was set to 15 s, and BIS values were exported directly to a USB drive. BIS values having a signal quality of <50% were manually discarded from subsequent analysis.

Statistics

To investigate the relationship between DoH index values and Et_{sevo}, the data were fitted in an inhibitory sigmoid E_{max} model:

$$E = E_0 + \frac{(E_{max} - E_0)}{1 + 10^{(logEC_{50} - x)y}}$$

E is the index value as shown by the DoH monitors; EC_{50} represents the Et_{sevo} with half-maximal effect on the DoH monitors, *x* the Et_{sevo} and γ the variable Hillslope, to optimize for the best fit. E_0 and E_{max} were constrained to 0 and 100, representing the range of the DoH monitors. The EC_{50} of every individual patient was calculated separately and summarized according to whether the data were (non)parametric (median or mean). Only intraoperative DoH data were used for this analysis.

Prediction probabilities (p_k) for the DoH monitors were calculated according to the method described by Smith et al. [6], using the custom spreadsheet macro, p_k-MACRO, provided by the authors. The p_k value describes how good a DoH index predicts the clinical DoH of a patient. It ranges from 0.0 to 1.0 and is calculated from index values of at least 3 different clinical DoH stages, in our study the UMSS. If a monitor always predicts the correct UMSS, the p_k is 1.0. p_k values below 0.5 describe an inverse relationship between the index and the UMSS, which is the same as 1.0 p_k. A DoH monitor with a p_k of 0.5 predicts only 50% of the clinically observed UMSS of the patient correctly, which is no better than chance.

We also performed paired and unpaired receiver operating characteristic (ROC) analyses and calculated the corresponding area under the curve (AUC) to evaluate the monitors' performance in distinguishing between unconsciousness (UMSS >1) and consciousness (UMSS ≤1). The optimal combination of the sensitivity and specificity was defined as 'max (Sensitivity + Specificity –1).' ROC analyses were calculated using MEDCALC for WINDOWS, version 12.7.0.0 (MedCalc Software, Mariakerke, Belgium). Other analyses were calculated

by GRAPHPAD PRISM 5 for Mac OS X, version 5.0d (GraphPad Software, San Diego, CA, USA). Continuous data, for example, p_k and EC_{50}, were tested for normality by the D'Agostino & Pearson omnibus normality test and visual inspection. Unpaired nonparametric data were analyzed with the Kruskal-Wallis test combined with Dunn's posthoc analysis, for example, EC_{50} of the different age groups. The Wilcoxon matched-pairs signed rank test was applied to analyze paired nonparametric data, for example, EC_{50} and p_k of the same groups, and if appropriate with Bonferroni correction for multiple testing. Parametric data were analyzed with paired or unpaired t tests combined, in case of multiple tests with Bonferroni correction.

Variables were presented as mean (SD) unless otherwise stated. P-values <0.05 were considered statistically significant.

RESULTS

Complete datasets, suitable for subsequent analysis, could be obtained in 69 of 75 patients. Patient characteristics are given in Table 2. One patient (group 1–3 years) received midazolam preoperatively and was primarily excluded from the study. An increase in sevoflurane during intraoperative measurements was not needed in any patient. Propofol was administered in three patients (group 3–6 years) during emergence due to extreme agitation (n=2) and laryngospasm (n=1). In one patient (group 3–6 years), conversion to laparoscopy after the initial operation, during which all intraoperative measurements were completed, required tracheal intubation. Another patient (group 6–16) pulled off the electrodes during emergence. As only data from the emergence period were corrupted and/or missing, intraoperative data from these five patients were still included for further analyses.

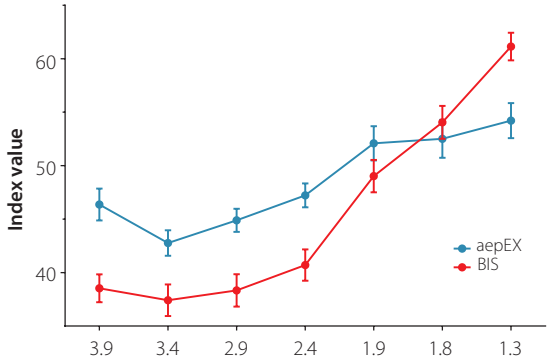

Figure 1. Mean aepEX (● blue) and bispectral index (● red) values with standard error of the mean at different endtidal sevoflurane concentrations (Et_{sevo}) of all groups.

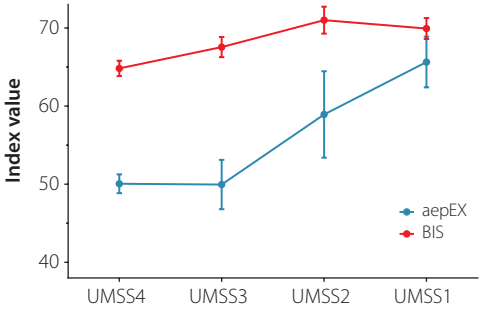

Figure 2. Mean aepEX (● blue) and bispectral index (● red) values with standard error of the mean at different university of Michigan Sedation Scale scores of all groups.

The EC_{50}aepEX (2.68%; CI 95%: 2.24–3.86%) and the EC_{50}BIS (2.10%; CI 95%: 1.35–3.19%) were not significantly different (p=0.065, after correction for multiple testing). The EC_{50}BIS in the youngest patient group (1–3 years was higher) was higher than in older patients (p<0.05), whereas the EC_{50}aepEX was not age dependent. For details, see Table 2 and Figure 1.

Due to artifact contamination of the MLAEP data during emergence, paired p_k analysis was possible in 10 patients only. P_k values for the aepEX (PkaepEX) and BIS (PkBIS) were respectively 0.32 (CI 95%: 0.08–0.56) and 0.47 (CI 95%: 0.19–0.75) (p=0.23). See also Figure 2. The paired ROC analysis showed an AUC of 0.72 (CI 95%: 0.62–0.82) and 0.67 (CI 95%:0.56–0.77) for the aepEX and BIS, respectively (p=0.54). At 100% sensitivity, the aepEX and BIS had respectively a specificity of 2% and 0%, while at 100% specificity, the sensitivity was respectively 31% and 21%. Maximum sensitivity and specificity for the aepEX were at 64% (CI 95%: 46– 79%) and 91% (CI 95%: 80–97%), respectively, at a cutoff index value of >60. The BIS had a maximum sensitivity and specificity of respectively 70% (CI95%: 57– 81%) and 66% (CI 95%: 52–77%) at an index value >68. The AUC of the different age groups with the same monitor and AUC of same age groups with different monitors were not different.

Table 2. Patient characteristics.

	1–3 years (n=24)	3–6 years (n=25)	6–18 years (n=25)	1–18 years (n=74)
Mean age in months [Range]	20 [13–29]	54 [38–66]	137 [77–188]	71 [13–188]
Weight in kg (mean ± SE)	11.3 ± 0.4	18.6 ± 0.7	43.0 ± 2.9	24.6 ± 1.9
Male/female, no	23/1	22/3	22/3	67/7
Mean duration of surgery in minutes [Range]	82 [32–184]	71 [15–147]	66 [20–183]	73 [15–184]
Procedures, no (%)				
Subumbilical	19 (79%)	23 (92%)	24 (96%)	66 (89%)
Upper extremity	5 (21%)	1 (4%)	1 (4%)	7 (10%)
Combination of subumbilical and upper extremity	0 (0%)	1 (4%)	0 (0%)	1 (1%)
Locoregional technique, no (%)				
Axillary block	0 (%)	0 (0%)	1 (4%)	1 (1%)
Caudal block	15 (63%)	18 (72%)	12 (48%)	45 (61%)
Epidural catheter	0 (0%)	0 (%)	1 (4%)	1 (1%)
Ileoinguinal block	0 (0%)	4 (16%)	4 (16%)	8 (11%)
Dorsal nerve of penis block	0 (0%)	1 (4%)	0 (0%)	1 (1%)
Popliteal block	0 (0%)	0 (0%)	1 (4%)	1 (1%)
Pudendal nerve block	1 (4%)	0 (0%)	0 (0%)	1 (1%)
Radial nerve block	1 (4%)	0 (0%)	0 (0%)	1 (1%)
Supraclavicular block	1 (4%)	0 (0%)	0 (0%)	1 (1%)
Infiltration by surgeon	1 (4%)	1 (4%)	1 (4%)	3 (4%)
Femoral and popliteal block	0 (0%)	0 (0%)	1 (4%)	1 (1%)
Femoral and sciatic block	0 (0%)	0 (0%)	2 (8%)	2 (3%)
Ilioinguinal and pudendal nerve block	1 (4%)	1 (4%)	0 (0%)	2 (3%)
No block	4 (17%)	0 (0%)	2 (8%)	6 (8%)

DISCUSSION

In this study of children under sevoflurane–remifentanil anesthesia, the aepEX and the BIS perform comparably in terms of p_k and AUC, whereas the aepEX outperforms the BIS with respect to its specificity at optimal cutoff values.

This is, to our best knowledge, the first pediatric study to examine the pharmacodynamic relationship between sevoflurane and the aepEX. We observed a tendency of decreasing EC_{50}aepEX with age, however not statistically significant, and a significantly higher EC_{50}BIS for children aged 1–3 years compared to the two older age groups (see Table 3). McCann et al. [7] reported an EC_{50}BIS of 1.48% sevoflurane in oxygen/nitrous oxide mix in children with a mean age of 3.3 years. In terms of MAC equivalents, this is 0.74, which lies close to the EC_{50}BIS of 2.10% (0.8MAC) in our study.

Table 3. Half-maximal effective concentrations derived from nonlinear regression analysis of sevoflurane on aepEX and BIS index values.

	1–3 years	3–6 years	6–16 years	1–18 years
aepEX				
EC_{50}[a] (median [IQR])	2.29 [1.20–5.50]	2.73 [1.82–3.40]	2.11 [1.41–3.27]	2.68 [1.63–3.91]
r^2 (mean ± SD)	0.34 ± 0.33	0.70 ± 0.33	0.49 ± 0.34	0.51 ± 0.36
BIS				
EC_{50} (median [IQR])	2.56 [2.10–3.62]*	2.04 [1.33–2.27]	1.74 [1.15–2.34]	2.10 [1.45–2.62]
r^2 (mean ± SD)	0.72 ± 0.22	0.54 ± 0.31	0.70 ± 0.19	0.65 ± 0.26

[a]EC_{50}: Half-maximal effective concentration in endtidal volume%.

*Significantly different from age groups 3–6 and 6–18 years ($p<0.05$).

It might be regarded as a shortcoming of our study that we excluded the emergence period from the pharmacodynamic analysis. During the emergence period, a high fresh gas flow of 10 l·min^{1} was applied to achieve a rapid washout of sevoflurane. As a consequence, it was technically impossible to reliably link Et_{sevo} to the aepEX and the BIS.

Due to the high incidence of artifacts and the fact that the jackknife method for the p_k analysis requires index values related to at least three different UMSS scores, computation of a p_k analysis was possible in no more than 10 patients. Our observed pkaepEX of 0.32 implies an inverse relation with the UMSS; that is, it can predict the correct UMSS in 68%. The BIS had an even worse prediction probability of 53%, which is just a little better than

pure chance. We did not observe a difference between the pkaepEX and pkBIS; however, the possibility of a type II error should be considered. In a study of adult patients, Kurita et al. [8] observed a pkaepEX (with a precommercialized version aepEX monitor) and a pkBIS of respectively 82% and 81%. Unfortunately, they did not report their method of analgesia and whether any premedication was administered, which makes it difficult to compare their results to ours.

In a recent study [9] we examined the performance of the aepEX in children receiving propofol–remifentanil anesthesia and showed a comparable specificity of 2% (vs 2% of the current study) for the aepEX and a higher specificity of 16% (vs 0% of the current study) for the BIS at 100% sensitivity. At 100% specificity, the sensitivities are 31% and 21% for the aepEX and BIS monitor, respectively, which are higher than what we had previously observed with propofol (14% and 15% for the aepEX and BIS, respectively). The AUC of the BIS during propofol–remifentanil anesthesia was higher than observed in our present study (0.81 vs 0.67), while the AUC of the aepEX appears to be comparable in both studies (0.77 vs 0.72). The comparable AUC of the aepEX during sevoflurane and propofol anesthesia may imply that it is less susceptible to the different pharmacodynamics of these hypnotics.

Possible effects of remifentanil on the aepEX and the BIS should be considered. Schraag et al. [10] could show that remifentanil had no effect on MLAEPs. Guinard et al. reported the same for the BIS [11]. We could not find any reason why these findings should not account for this study as well.

For intraoperative measurements, we targeted at different Et_{sevo}. Figure 1 shows the overall trend of aepEX and BIS values at different Et_{sevo}. During the emergence period, we related the UMSS to the values of both monitors (see Figure 2). Although not significant, we observed a slight decrease in the aepEX at the beginning of the emergence period compared to the intraoperative values related to Et_{sevo} 1.3% from 55 to 50 units. A possible explanation for this unexpected phenomenon could be that the aepEX was also influenced by surgical stimuli, despite the local regional technique given. Interestingly, the BIS did not show the same behavior.

In conclusion, we have observed that, in children receiving sevoflurane–remifentanil anesthesia, the aepEX had a better specificity than the BIS in distinguishing unconscious from conscious children at their optimal cutoff values. As the sensitivity and specificity vary at different cutoff values, it depends on the chosen cutoff values whether the aepEX

should be favored above the BIS. With respect to their ability to distinguish between different levels of hypnotic depth, both indices performed equally bad.

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Chapter 6

Monitoring Depth of Hypnosis: Mid-Latency Auditory Evoked Potentials Derived aepEX in Children Receiving Desflurane-Remifentanil Anesthesia

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ABSTRACT

BACKGROUND: The aepEXplus monitoring system, which uses mid-latency auditory evoked potentials to measure depth of hypnosis, was evaluated in pediatric patients receiving desflurane-remifentanil anesthesia.

METHODS: Seventy-five patients, 1–18 years of age (stratified for age; 1–3, 3–6, 6–18 years, for subgroup analyses), were included in this prospective observational study. The aepEX and the bispectral index (BIS) were recorded simultaneously, the latter serving as a reference. The ability of the aepEX to detect different levels of consciousness, defined according to the University of Michigan Sedation Scale, investigated using prediction probability (p_k), and receiver operating characteristic (ROC) analysis, served as the primary outcome parameter. As a secondary outcome parameter, the relationship between end-tidal desflurane and the aepEX and BIS values were calculated by fitting in a nonlinear regression model.

RESULTS: The p_k values for the aepEX and the BIS were, respectively, 0.68 (95% CI, 0.53–0.82) and 0.85 (95% CI, 0.73–0.96; p=0.02). The aepEX and the BIS had an area under the ROC curve of, respectively, 0.89 (95% CI, 0.80–0.95) and 0.76 (95% CI, 0.68–0.84; p=0.04). The maximized sensitivity and specificity were, respectively, 81% (95% CI, 61%–93%) and 86% (95% CI, 74%–94%) for the aepEX at a cutoff value of >52, and 69% (95% CI, 56%–81%) and 70% (95% CI, 57%–81%) for the BIS at a cutoff value of >65. The age-corrected end-tidal desflurane concentration associated with an index value of 50 (EC_{50}) was 0.59 minimum alveolar concentration (interquartile range: 0.38–0.85) and 0.58 minimum alveolar concentration (interquartile range: 0.41–0.70) for, respectively, the aepEX and BIS (p=0.69). Age-group analysis showed no evidence of a difference regarding the area under the ROC curve or EC_{50}.

CONCLUSIONS: The aepEX can reliably differentiate between a conscious and an unconscious state in pediatric patients receiving desflurane-remifentanil anesthesia.

BACKGROUND

Monitoring the depth of hypnosis (DoH) in anesthetized patients provides the anesthesiologist with significant additional information, enabling one to adjust the dose of anesthetic agents more adequately, according to the needs of the patient. DoH monitoring in children has been shown to result in the use of lower doses of anesthetic drugs and a faster recovery [1-3]. Bearing in mind the ongoing discussion about potential neurotoxic effects of anesthetic drugs on the developing brain, this technology can help prevent anesthetic drug overdosing, adding safety to the conduct of pediatric anesthesia.

Mid-latency auditory evoked potentials (MLAEP) can be utilized to measure the DoH during anesthesia [4-7]. The developmental time of MLAEP extends through the first decade of life [8], as opposed to the raw electroencephalogram (EEG), which is not mature before early adulthood. MLAEP are therefore a potentially more useful parameter to assess the DoH than EEG in children.

The aepEXplus monitor (aepEX) is a commercially available DoH monitor that utilizes MLAEP. In previous studies, the performance of the aepEX was evaluated in children during propofol and sevoflurane anesthesia [9,10]. Desflurane, due to its low blood-gas partition coefficient, has a unique pharmacokinetic profile, which, from a clinical perspective, can best be described as "fast in-fast out." Desflurane is a challenging drug for DoH monitors because they have to calculate their DoH indices in a clinical setting characterized by fast changes in hypnotic drug target concentration.

The current study was conducted to assess the performance of the aepEX monitor in children during desfluraneremifentanil anesthesia. For means of reference, bispectral index (BIS) values were also recorded simultaneously.

The primary objective of this prospective observational study was to assess the ability of the aepEX to detect the return of consciousness during emergence from anesthesia. Our secondary objective was to assess the relationship between the aepEX and different end-tidal desflurane concentrations.

METHODS

This article adheres to the applicable STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guideline. The study was reviewed and approved on May 12, 2011 by the Institutional Review Board of the Erasmus MC, Rotterdam, the Netherlands (MEC 2011–104, NL 35976.078.11) and registered in the Dutch trial register before inclusion of the first patient (http://www.trialregister.nl/trialreg/admin/ rctview.asp?TC=2983, NTR2983, principal investigator: Y. M. Cheung, date of registration: July 12, 2011). Written informed consent was obtained from the participants' parents or guardians. According to the Dutch law, additional written informed assent was collected from children ≥12 years of age.

Patients scheduled in the Erasmus MC, Sophia children's hospital for elective general, urologic, plastic, or orthopedic surgery were eligible for inclusion. The entire cohort of 75 patients was stratified for age into 3 groups of 25 children each (group 1: 1–3 years; group 2: 3–6 years; and group 3: 6–18 years) to detect possible age-related effects. Exclusion criteria consisted of known allergies to any medication in the study protocol (remifentanil, desflurane, sevoflurane, and/or propofol), the presence of a clinically significant hearing impairment, the use of medication (eg, premedication, antiepileptics), having a condition affecting the EEG (to prevent bias), and a planned postoperative admittance to the pediatric intensive care unit.

Conduct of Anesthesia

After arrival at the operating room, an intravenous cannula was inserted and remifentanil 0.5 $\mu g \cdot kg^{-1}$ was administered over 15 seconds followed by a continuous infusion of 0.1 $\mu g \cdot kg^{-1} \cdot minute^{-1}$. General anesthesia was induced with propofol 3.0–5.0 $mg \cdot kg^{-1}$.

When it was not possible to obtain intravenous access in the awake child, induction was performed with sevoflurane by facemask, after which an intravenous access was obtained in the anesthetized child. Immediately after an intravenous cannula was in place, remifentanil was administered according to the same scheme as in awake children. After insertion of a laryngeal mask, airway desflurane was slowly washed in to an end-tidal desflurane concentration (Et_{des}) of approximately 1 minimum alveolar concentration (MAC), adjusted for age [11].

Once the airway was secured, locoregional analgesia was given whenever possible and appropriate. Ropivacaine 0.2% was used for low-volume ultrasound-guided peripheral locoregional techniques and caudal blocks. Penile nerve blocks were performed with

bupivacaine 0.5%. When locoregional analgesia was not an option, for whatever reason, remifentanil was increased to a dose of 0.3–0.4 $\mu g \cdot kg^{-1} \cdot minute^{-1}$ during the surgery.

During anesthesia, all patients were monitored with our standard equipment, which consists of electrocardiogram, pulse oximetry, noninvasive blood pressure measurement, temperature, capnography, and inspired and end-tidal concentrations of oxygen, sevoflurane, and desflurane.

aepEX and BIS Monitoring

After induction of general anesthesia, the skin on the forehead was swabbed with alcohol and abraded with Sensor Prep (Medical Device Management, Essex, United Kingdom) to decrease the impedance to a low enough level to allow for both aepEX and BIS monitoring. aepEX and BIS electrodes were then attached, respectively, on the left and right sides of the patient's forehead according to the manufacturer's recommendation. A commercially available over-the-ear headphone (MDR-V150; Sony Europe, London, United Kingdom) was connected to the aepEX because standard earplugs are unsuitable for small children. aepEX index values were transferred to a personal computer at 5-second intervals using the aepEX's logger software (version 1.3, Medical Device Management, Essex, United Kingdom). aepEX data labeled with "artefact," as shown by the aepEX logger software, were excluded from subsequent analysis.

The BIS Vista monitoring system (version 2.02, Aspect Systems International, de Meern, the Netherlands) was used, with a smoothing rate of 15 seconds. BIS data were directly transferred at 1-second intervals to a USB stick plugged into the monitor. BIS values with a signal quality <50%, as indicated by the BIS signal quality index, were excluded from subsequent analysis.

Data collection for study purposes started 15 minutes after administration of propofol or when the end-tidal sevoflurane concentration, in the case of an inhalation induction, was 0% as measured by our anesthesia machine (Primus, Draeger, Lübeck, Germany). Patients were primarily allowed to breathe spontaneously during the surgical procedure. In case of hypoventilation (end-tidal CO_2 >6.0 kPa), mechanical ventilation was used to reestablish and maintain normocapnia (end-tidal CO_2 of 4.5–6.0 kPa). During the surgical procedure, Et_{des} was initially titrated to 1.5 MAC and decreased every 3 minutes by 1 vol% to a minimum of 0.7 MAC, corrected for age. According to Taylor and Lerman [11], we defined 1 MAC as 8.7%, 8.6%, 8.0%, and 7.5% for children 1–3, 3–5, 5–12, and ≥12 years of age. At the start of wound closure, Et_{des} was decreased to 0.5 MAC. After completion of the

surgical procedure, the administration of desflurane was discontinued, and the fresh-gas flow was set to 10 L·minute^{-1} using 100% oxygen.

During the emergency period, the DoH was assessed according to the University of Michigan Sedation Scale (UMSS) [12] until the patient had a UMSS ≤1. The UMSS consists of 5 levels, including "awake/alert," "minimally sedated," "moderately sedated," "deeply sedated," and "unarousable," which correspond, respectively, to a UMSS of 0, 1, 2, 3, and 4.

Data analyses were performed with the average index value over 10 seconds before the intended time points as described previously.

Statistical Analysis

Primary Outcome — The relationship between the index values and different DoH (UMSS) were analyzed by calculating the prediction probability value (p_k), which was described by Smith et al. [13] A p_k value and the area under the curve (AUC) derived from a receiver operating characteristic (ROC) analysis are both measures of the discriminative ability of a predictor; to set it more precisely, p_k is a generalization of the AUC. ROC analyses can only be performed with dichotomous outcome parameters, whereas p_k also allows assessment of the discriminative power of a predictor when there are >2 states. A p_k of 1.0 corresponds with a DoH monitor that always predicts the correct UMSS. If a DoH monitor predicts the correct UMSS in only 50% of the cases, then it will have a p_k of .5. A p_k<.5 describes an inverse relationship. An inverse relationship will be expressed as $1 - p_k$ for a better understanding. P_k values were only computed when ≥3 different UMSS values were observed because computing this for only 2 different values would be the same as a ROC with its corresponding AUC. For each individual patient, the p_k value would be computed, after which the mean p_k value for its corresponding age group would be calculated.

ROC analyses and its corresponding AUC were performed to investigate the predictive capabilities of the DoH monitor to distinguish consciousness from unconsciousness using MedCalc for Windows, version 5.6.1 (MedCalc Software, Mariakerke, Belgium). The cutoff index value at which both the sensitivity and the specificity was the highest was defined as the maximized combination. For analysis, we defined consciousness and unconsciousness as a UMSS of, respectively, ≤1 and ≥2.

Secondary Outcome — aepEX and BIS data were fitted in a nonlinear regression model to analyze the relationship between index values and different Et_{des}. An inhibitory sigmoid E_{max} model was used for this purpose:

$$E = E_0 + \frac{(E_{max} - E_0)}{1 + 10^{(logEC_{50} - x)y}}$$

E_0 and E_{max} are, respectively, the minimum and maximum value of the index values, which were 0 and 100. The EC_{50} is the Et_{des} at which an index value of 50 was reached on the DoH monitors. *E* is the predicted index value during the administration of an Et_{des} of *x*, whereas γ is the Hillslope, which was variable to optimize the best fit for this model. The EC_{50} of each individual patient was first computed after which the median of the corresponding group was calculated.

Continuous data were tested for normality by visual inspection and the D'Agostino & Pearson omnibus normality test. To compare the EC_{50} between the aepEX and BIS (of the cohort and different age groups), the Wilcoxon matched-pairs signed rank test was used. When comparing the EC_{50} among different age groups, a Kruskal-Wallis test was used. P_k values of the aepEX and BIS (of the cohort and different age groups) were compared with a paired *t* test, while p_k values among different age groups were analyzed with an unpaired *t* test. These tests were computed and analyzed with GraphPad Prism for Windows, version 6.04 (GraphPad Software, San Diego, CA). The method of DeLong et al. [14] was applied for analysis of the (paired) AUC between the aepEX and BIS monitor. The comparison of the AUC of different age groups was made according to the method of Hanley and McNeil [15]. All analyses among or within the 3 age groups were corrected for multiple testing with the Bonferroni correction, except for the KruskalWallis test, for which Dunn's post hoc analysis was applied.

Descriptive analyses were performed with IBM SPSS Statistics for Windows, version 21.0 (IBM Corp, Armonk, NY). Variables were presented as mean ± standard deviation unless stated otherwise. P-values <.05 were considered statistically significant.

A sample size of 25 children per age group and the defined age groups correspond to similar published studies concerning DoH monitors [6,16,17]. Previous studies have assumed that a reliable p_k value can be computed with a sample size of >20 patients [18-20].

RESULTS

Between December 2012 and September 2014, a total of 75 patients were included, of whom 7 had to be excluded secondarily due to the following reasons: administration of premedication (n=1, group 2), tracheal intubation (n=1, group 1), and ventilation difficulties before or during the data collection (n=4, group 1; n=1, group 3). Details concerning baseline characteristics of the patient are shown in Table 1.

During the wash-in period of desflurane, 28 patients (n=11, group 1; n=8, group 2; n=9, group 3) had difficulties maintaining normocapnia, despite mechanical ventilation. In these patients, a further increase of desflurane was avoided, and intraoperative measurements were started at an end-tidal desflurane concentration <1.5 MAC. In another 3 patients (n=1, group 1; n=2, group 2), the target MAC of 1.5 could not be reached due to an unexpected short surgical procedure. Furthermore, we were unable to collect data until a UMSS of 1 was reached in 3 patients (n=2, group 2; n=1, group 3) due to patient agitation during emergence. In 1 patient (group 3), the aepEX could not compute any index values due to excessive artifact contamination of the signal. From this patient, only BIS values from the emergency period were available for analysis.

Data during emergence were available in 45 patients in which ≥3 UMSS values could be observed. The quality of the EEG signal was sufficient to compute 13 p_k values for the aepEX and 37 for the BIS. A paired *t* test was possible in 12 p_k data pairs, resulting in a p_k value of 0.68 (95% CI, 0.53–0.82) for the aepEX and 0.85 (95% CI, 0.73–0.96) for the BIS (p=0.02). Because only 12 pairs of p_k values were available for analysis, a subsequent age-group analysis was abandoned.

The maximized combination of sensitivity and specificity of the aepEX was 81% (95% CI, 61%–93%) and 86% (95% CI, 74%–94%) at an index value >52. This was for the BIS at an index value of >65, during which the sensitivity was 69% (95% CI, 56%–81%) and the specificity 70% (95% CI, 57%–81%). A detailed relationship between index value and sensitivity and specificity are plotted in Figures 1 and 2.

Paired comparisons of the AUC of the aepEX and BIS monitor showed no evidence for a difference between the entire cohort or the different age groups. Details are shown in Table 2. We also found no evidence of a difference when comparing AUCs of the 3 age groups with each other after correction for multiple testing.

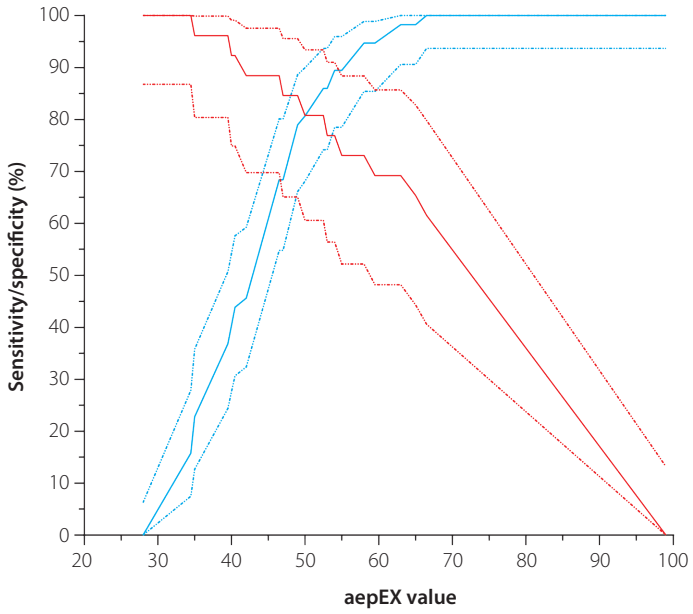

Figure 1. aepEXplus monitor's (aepEX) receiver operating characteristic. Sensitivity (solid red lines) and specificity (solid blue lines) at different aepEX cutoff values with their respective 95% CIs (dotted red and blue lines).

Table 1. Baseline Characteristics.

Characteristics	1–3 y (n=20)	3–6 y (n=24)	6–18 y (n=24)	Entire Cohort (n=68)
Female, no. (%)	1 (5)	2 (8)	7 (29)	10 (15)
Age, median [range] (mo)	22 [12–35]	54 [37–70]	139 [73–210]	74 [12–210]
Weight, median (IQR) (kg)	12 (10–15)	17 (15–21)	44 (26–59)	17 (14–26)
Procedure, no. (%)				
Upper extremity	3 (15)	3 (13)	5 (21)	11 (16)
Subumbilical	17 (85)	20 (83)	19 (79)	56 (82)
Upper and lower extremity	0 (0)	1 (4)	0 (0)	1 (1)
Locoregional analgesia technique, no. (%)				
Caudal	17 (85)	16 (67)	9 (38)	42 (62)
Brachial plexus	1 (5)	2 (8)	2 (8)	5 (7)
Lumbosacral plexus	0 (0)	2 (8)	10 (42)	12 (18)
Epidural	0 (0)	1 (4)	0 (0)	1 (1)
None	2 (10)	3 (13)	3 (13)	8 (12)

Abbreviation: IQR, interquartile range.

A total of 569 aepEX values qualified for subsequent analysis (having no artifacts), while the BIS provided 632 index values with a signal quality of >50%. These values are plotted in Figure 3, describing the relationship between the index values of both DoH monitors during different Et_{des} and UMSS.

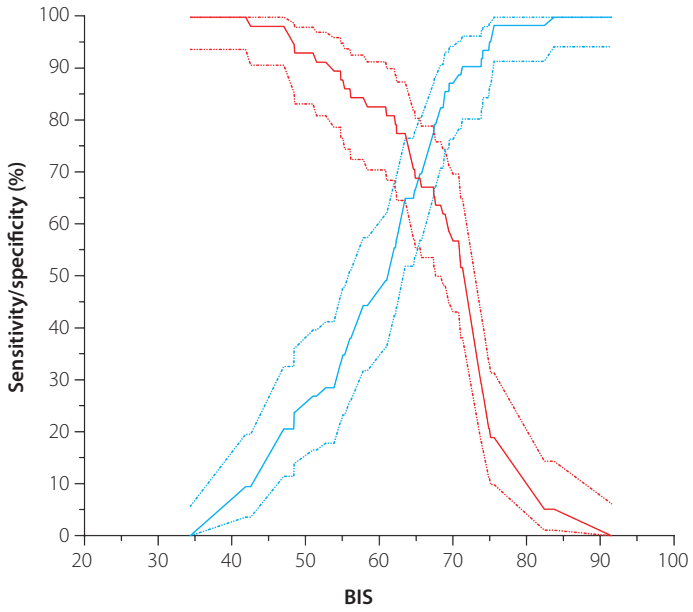

Figure 2. Bispectral index's (BIS) receiver operating characteristic. Sensitivity (solid red lines) and specificity (solid blue lines) at different BIS cutoff values with their respective 95% CIs (dotted red and blue lines).

Table 2. Receiver Operator Characteristics Analysis of the aepEX and BIS Monitor.

Age Group	AUC of the aepEX (Mean: 95% CI)	AUC of the BIS (Mean: 95% CI)	P-value
Group 1	0.76 (0.55–0.90)	0.63 (0.42–0.81)	.31[a]
Group 2	0.95 (0.79–1.00)	0.84 (0.64–0.95)	.05[a]
Group 3	0.99 (0.85–1.00)	0.98 (0.84–1.00)	.87[a]
Entire cohort	0.89 (0.80–0.95)	0.76 (0.68–0.84)	.04

Abbreviations: aepEX, aepEXplus monitor; AUC, area under the curve; BIS, bispectral index; CI, confidence interval.
[a] Uncorrected p-value for multiple testing.

The age-corrected EC_{50} for the aepEX (EC_{50}aepEX) was 0.59 MAC (interquartile range: 0.38–0.85; n=57) and for the BIS (EC_{50}BIS) 0.58 MAC (interquartile range: 0.41–0.70; n=63). Eleven EC_{50}aepEX could not be computed due to software limitations (unable to converge data; n=2, group 1; n=1, group 2; n=1, group 3), too few intraoperative data (n=1, group 1; n=1, group 2; n=1, group 3), and data with too many artifacts (n=3, group 2; n=1, group 3).

Software limitations accounted for 2 missing EC_{50}BIS (n=1, group 1; n=1, group 3) and 3 for having too few intraoperative data (n=1, group 1; n=1, group 2; n=1, group 3). Both monitors had a comparable r^2: 0.62 (95% CI, 0.54–0.71) for the aepEX and 0.69 (95% CI, 0.63–0.76) for the BIS. The Kruskal-Wallis tests comparing the EC_{50} among different age groups also showed no evidence of a difference (p=0.27 for the aepEX and p=0.12 for the BIS). Paired comparison (n=57) between the EC_{50}aepEX and EC_{50}BIS resulted in a p-value of 0.69. The same comparison for age groups 1, 2, and 3 revealed p-values of, respectively, 0.38, 0.14, and 0.84.

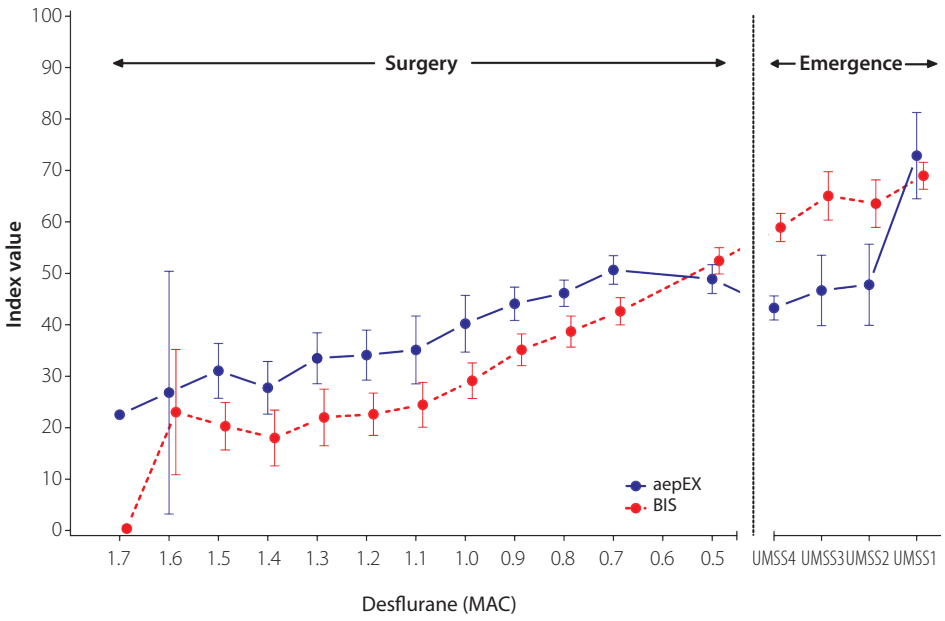

Figure 3. Trend of aepEXplus monitor (aepEX) and bispectral index (BIS). Mean index values of the aepEX (solid lines) and BIS (dashed lines) with their respective 95% CIs related to different end-tidal desflurane concentrations and University of Michigan Sedation Scale (UMSS) values. MAC indicates minimum alveolar concentration.

DISCUSSION

Our study demonstrates that the aepEX monitor differentiates between unconscious and conscious pediatric patients with a 10% higher sensitivity and specificity than the BIS monitor. As opposed to this finding, the aepEX performs inferiorly to the BIS to correctly predict different UMSS. We found no evidence of an age-related difference in performance of the aepEX, suggesting that the aepEX performs equally in all patients from 1 to 18 years of age.

The results of this study are consistent with our findings from the previous study investigating the aepEX in children during propofol and sevoflurane anesthesia [9,10]. This finding implies that the aepEX monitor also performs equally during different commonly used anesthetics in children, that is, propofol, sevoflurane, and desflurane.

As proposed by Smith et al., [13] the p_k approach to measure the performance of an anesthetic depth indicator is aimed to include different levels of anesthetic depth in the analysis. We could, however, only measure 2 levels of anesthetic depth in the majority of our patients, which is probably attributable to the properties of desflurane, for example, its low blood-gas partition coefficient. Nonetheless, we found evidence of the superiority of the BIS over the aepEX in discriminating different UMSS levels.

The concept that consciousness has levels has been accepted for decades. Many different clinical observational scales have been designed, validated, and used to assess the level of consciousness, among them the Observer's Assessment of Alertness/Sedation scale and the UMSS. All of these scales assume that DoH is graded and that, beginning with a fully awake subject, each step of the scale reflects a "lower level of consciousness," or, in the context of anesthesia research, "depth of hypnosis." By now we are still not sure about the true underlying mechanism(s) of our mental states named consciousness and unconsciousness. Regarding unconsciousness, it is even possible that the concept of "hypnotic depth" is not correct at all, in other words, that we are either conscious or unconscious [21]. Therefore, we also performed an ROC analysis as an alternative approach to quantify the monitors' performance. An ROC analysis requires only 2 different states ("conscious" and "unconscious") for analysis. Beside this, it also gives a more clinically applicable result, that is, a clear cutoff value with its corresponding sensitivity and specificity. In our current study, we found that when choosing the maximal sensitivity and specificity, the aepEX is superior to the BIS. Choosing the clinically most relevant combination of the sensitivity and specificity of the monitors depends on personal preferences regarding the most important monitoring target. When prevention

of intraoperative awareness is of paramount importance, a DoH monitor with a higher sensitivity is favorable. However, if the sensitivity is chosen too high, the resulting low specificity would render the monitor useless (Figures 2 and 3).

By definition, the EC_{50} is the drug concentration needed to achieve 50% of the drug's maximum effect. In our current study, we fitted our intraoperative data in a nonlinear regression model to compute the EC_{50}. However, the EC_{50} can also be measured by recording the end-tidal desflurane concentration while maintaining an index value of 50. Fletcher et al. [17] performed such a study by maintaining a BIS of 60 during pediatric scoliosis surgery under desflurane anesthesia. The end-tidal concentration desflurane needed to maintain a BIS of 60 can be described as an EC_{60} for the BIS monitor. Although an EC_{60} is different from an EC_{50} and our study designs are not comparable, we found a similar MAC of 0.58. Caution is needed when comparing both studies; despite the aforementioned, their EC_{60} comes close to the EC_{50}BIS we observed.

Although processed EEG and MLAEP have strong relationships with consciousness level, we should not solely rely on computed DoH index values. A recent study by Schneider et al. [22] supports this concept. They demonstrated that the combination of the BIS monitor with other standard monitoring parameters, for example, heart rate and blood pressure, resulted in a p_k of 1.0 to detect the return of consciousness in adult patients, emphasizing the importance of observing the patient as a whole.

Almost all patients in our study received additional locoregional analgesia before the surgical procedure, most often a caudal block. Davidson et al. [16] demonstrated that a caudal block resulted in a decrease in BIS value of 5 points. The effect of a caudal block on the aepEX has not yet been studied. Although remifentanil decreases the MAC of volatile anesthetics, the DoH seems to be unaffected by it, which was demonstrated by Schraag et al and Guignard et al. [23,24]. Both studies observed no effect of remifentanil on the aepEX and BIS index values, and we assume that this also applies for our study.

Other studies have revealed a p_k BIS value of .82 and .89, which is similar to our observed p_k value of .85 [25,26]. However, these results were observed in the adult population and concerned p_k values detecting different end-tidal desflurane concentrations or eye opening after general anesthesia. Because our observed p_k BIS value is not comparable to other studies and only 13 paired p_k values could be computed in our study, interpretations of the p_k values of the aepEX and BIS are limited.

The age stratification applied in this study was designed to match similar studies for comparison purposes. However, concerns can be made due to the broad range of group 3 (6–18 years of age). Because the MLAEP is still developing until the first decade of life [8], this group consisted of children with developing MLAEP and fully developed MLAEP pathways. However, because the development of the MLAEP is a continuous process, we would at least expect to find a difference between group 1 (fully undeveloped MLAEP) and group 3 (MLAEP in final development combined with fully developed MLAEP) if an age-dependent performance for the aepEX exists. It would be interesting to compare group 3 with adult data, but unfortunately no such comparable study was published.

Our study population consisted predominantly of male children. However, we believe it is unlikely that this factor affected our study.

In conclusion, our current study observed that the aepEX monitor could reliably differentiate unconsciousness from consciousness in pediatric patients during remifentanil-desflurane anesthesia combined with a locoregional technique.

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Chapter 7

General discussion

Many different scales and measurement methods have been developed to assess the anesthetic depth in the past few decades [1]. In general, the depth of anesthesia was measured by the response of the patient to a stimulus (tactile/pain or sound). This requires the patient to respond physically (movement) or verbally. Verbal response however, is not possible when the trachea of the patient is intubated or a laryngeal mask inserted. Furthermore, neuromuscular relaxing agents abolish movement of striated muscles and analgesics attenuate pain sensation. Without a reliable response from the patient to reflect his or her current depth of hypnosis, these scales are difficult if not impossible to interpret when balanced anesthesia is applied.

What is the current opinion regarding depth of hypnosis monitoring in children?

Depth of hypnosis monitoring devices are expected to be more dependable in these situations, since these circumvent the requirement of a (vocal) motor response from the patient to a stimulus. Despite the lack of evidence for it, monitoring is traditionally used with the intention to prevent intraoperative awareness in children, as was demonstrated in our survey amongst ESPA members.

Despite the fact that there is literature available supporting a faster emergence phase when anesthesia was guided by a depth of hypnosis monitor, due to more efficient dosing of anesthetics, this was considered a less important reason to use such a monitor in children. Avoiding possible side effects of the anesthetic agents by decreasing the dose administered, was expected to an important reason to use depth of hypnosis monitoring in children, especially considering the current discussion regarding neurotoxicity to the developing brain of the child. However, this argument was considered the least important according to our the ESPA members as well.

Our research also revealed that anesthesiologists doubt about whether use of these devices can prevent intraoperative awareness in children. This was their main reason not to use it. Even ESPA members who did use hypnosis monitoring in children had their reservations towards its reliability in younger children and/or the type of anesthetic(s) used. This was illustrated by the less frequent use of hypnosis monitoring devices in younger children and when anesthesia was maintained by volatile anesthetics. Inadvertently, these two items were also ranked as the most important requirements of a hypothetical ideal depth of hypnosis monitor to overcome.

Besides having doubts towards the reliability of a depth of hypnosis monitor, the lack of a consensus in how to interpret its index values also persists according to our survey. The thoughts of our respondents however, are mostly based on the BIS monitor, since 77% of the "Users" used a BIS monitor to assess the depth of hypnosis in children. This makes the results difficult to extrapolate to all depth of hypnosis monitors available. A probable downside of using the BIS monitor in children is that the spontaneous EEG, from which the BIS monitor computes its index values, matures through middle age [2]. Kanazawa et al. demonstrated that young patients (20 to 30 years) had lower BIS values compared to middle-aged (31 to 65 years) or elderly (66 to 80 years) patients during 1 minimum alveolar concentration (MAC) of sevoflurane and desflurane anesthesia [3]. This might suggest that the BIS monitor is less reliable in the youngest of our patients.

What is currently known concerning MLAEP in children during anesthesia?

The MLAEP on the other hand, matures earlier in life [4]. Reviewing the available literature concerning MLAEP monitoring peri-operatively yielded only 15 studies who met our lenient inclusion criteria, including a few from our own research group. Except for the studies from this thesis, all of them were conducted with MLAEP based monitors which are no longer commercially available or were experimental setups. In accordance with the adult population, the overall MLAEP waveform of children showed increasing latencies and decreasing amplitudes with increasing anesthetics given [5-8]. Also, its performance to detect different states of consciousness seems to be reasonable in children [9-15]. Whether a MLAEP based hypnosis monitor will decrease the rate of unintentional intraoperative awareness has not been studied.

Published studies investigating the effect of depth of hypnosis monitoring on unintentional perioperative awareness show conflicting results and are conducted in the adult population [16,17]. The incidence of unintentional intraoperative awareness in children is estimated to be 0.74%, which is much higher compared to adults having an incidence of 0.1 to 0.2% [17,18]. However, Blusse van Oud-Alblas et al. reported that the children who experienced true awareness in their study (n=6) did not seem to be traumatized [19], but taking into account that 50% of the patients develop long-term psychological effects after enduring accidental awareness, a reliable depth of hypnosis monitor (even for children) seems still to be needed [18].

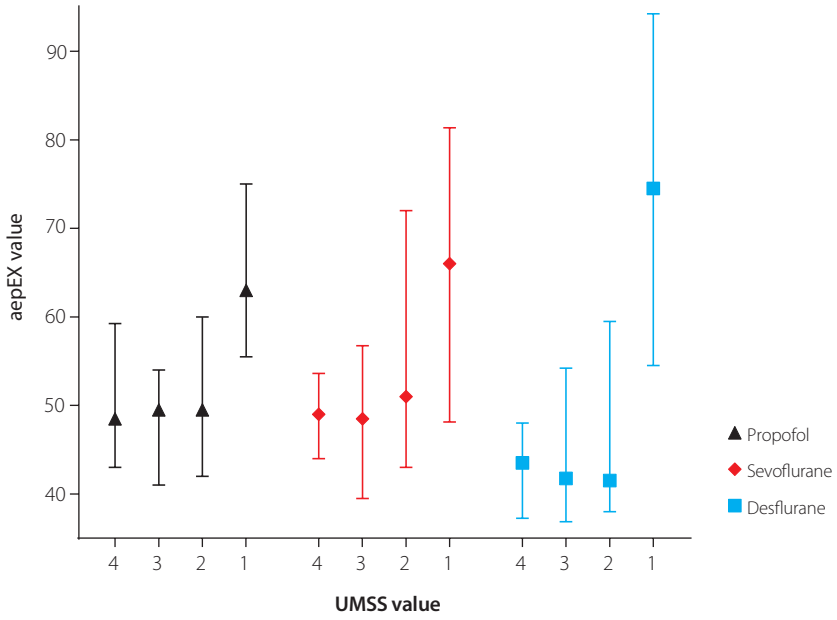

Figure 1. Median and interquartile range of aepEX values during different UMSS values.

How does a MLAEP monitor perform in children during anesthesia?

In this thesis we evaluated the performance of the aepEX monitor, currently the only commercially available MLAEP based depth of hypnosis monitor, in measuring the depth of hypnosis during anesthesia in children. Using the BIS monitor as a reference, the aepEX seems to perform worse in differentiating different UMSS levels (prediction probability values) during propofol, sevoflurane and desflurane anesthesia. However, detecting the conscious (UMSS ≤1) and unconscious (UMSS >1) states by the aepEX monitor was superior to the BIS monitor during desflurane anesthesia, while being comparable with each other during propofol and sevoflurane anesthesia.

When aepEX values against different UMSS scores were plotted in a graph, a sudden sharp increase was consistently observed during different kinds of anesthetics when an UMSS of 1 was reached (Figure 1).

On the other hand, the BIS monitor showed a more gradual increase over the different UMSS values (Figure 2). When compared to the BIS values, the sudden increase in median aepEX values resulted in a greater difference between values during an UMSS >1 and UMSS of 1. This relationship between the different levels of consciousness and aepEX

index values could make its interpretation in clinical practice less ambiguous for the assessment of the depth of hypnosis in children.

Subgroup analysis showed comparable results for the different age groups for both monitors, indicating that both monitors were just as reliable for the different age groups. However, a recent study by Scuisco et al. found higher mean BIS index values for toddlers aging 13 months to 36 months compared to infants (1 month to 12 months) or children (37 months to 144 months) [20]. The study investigated the effect of age on BIS, response entropy and state entropy indexes. Anesthesia was given with sevoflurane. However, the dose of sevoflurane was "adjusted in response to clinical signs" and no reproducible protocol was described. This could probably explain our different findings concerning the effect of age on the BIS index values.

There seems to be a lower correlation between the aepEX values and dose of anesthetics administered compared to the BIS values. Both show a negative correlation but, the aepEX values were less linear with the concentration anesthetics administered. However, the clinical relevance to predict the correct concentration of anesthetic administered is questionable for a depth of hypnosis monitor. This is especially true during administration of volatile anesthetics, during which the end-tidal concentration is measured by any standard modern-day anesthesia machine. For volatile anesthetics the administered dose is generally guided by its minimum alveolar concentration (MAC) value. The MAC is defined as the concentration vapor needed within the alveoli during which 50% of the patients do not move in response to a surgical stimulus. While the absence of movement despite a significant stimulus, i.e. surgical stimulus, indicates an adequate depth of hypnosis for surgery (comparable to an UMSS of 4), 1 MAC value describes that only 50% of the patients has reached this level of depth. Therefore, believing that the MAC is a measure of depth of hypnosis for the individual patient is a misconception.

This thesis has described the thoughts, opinions and (mis)understandings of anesthesiologists about the use of depth of hypnosis monitoring in children during anesthesia. We described the performance of the aepEX monitor during anesthesia in children, demonstrating that it has a reasonable accuracy to detect consciousness from unconsciousness and that it is feasible for different age groups.

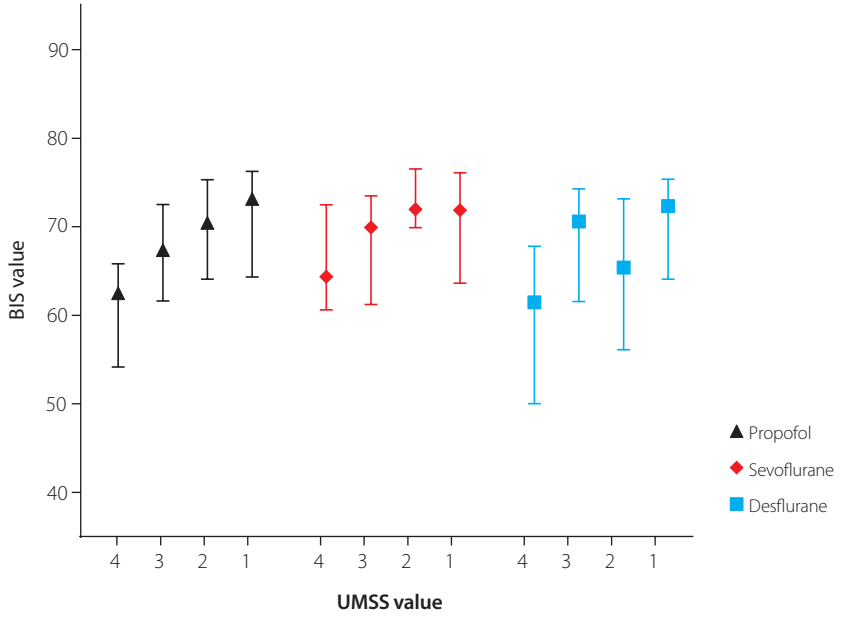

Figure 2. Median and interquartile range of BIS values during different UMSS values.

FUTURE PERSPECTIVES

A few questions remain after this thesis. Anesthesia is not administered in a uniform method and different combinations of anesthetics and analgesics (systemic or locoregional) are used. The effect of combining anesthetics on a MLEAP based hypnosis monitor still remains to be answered. Also, its value in prevention of unintentional intra-operative awareness in children remains to be elucidated.

As the aepEX index monitor can detect the return of consciousness no more than only reasonably, it is not the ideal depth of hypnosis monitor in children. Further investigation searching for an even more reliable monitor continues, and the answer might still be found in the spontaneous EEG. Density spectral array (DSA) is a method to display the spontaneous EEG in a graph by color-coding the intensity of different brainwave frequencies, i.e. gamma, beta, alpha, theta, delta and slow waves [21]. Compared to EEG based hypnosis monitors, the EEG in a DSA is less processed by a computer algorithm and therefor the interpretation depends less on what the algorithm computes, i.e. index value. Understanding the EEG and the effect of different anesthetics on it, might help to assess the state of the brain more accurately and therefore improving anesthesia technique.

However, this means anesthesiologists need to have appropriate knowledge concerning EEG recordings and its interpretation, just like capnography, plethysmography, and electrocardiography. The brain remains to be one of the most important target organs in anesthesia. Since this detailed knowledge about the unprocessed EEG is at present not a part of the general skill set of anesthesiologists, we should consider to add this to the curriculum of anesthesiology training programs.

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Summary

Chapter 1 explains the concerns about unintentional awareness during anesthesia and the potential role for a depth of hypnosis monitor to prevent this. The concerns regarding neurotoxicity in children receiving anesthesia, as shown in animal studies, might also be averted by a reliable hypnosis monitor. Different variables of the brain can be used to assess the depth of hypnosis (DoH), from which the electroencephalogram (EEG) is the most commonly used. An alternative could be the mid-latency auditory evoked potentials (MLAEP), which could have an advantage in children since it matures earlier in life compared to the EEG.

In **chapter 2** we assessed the thoughts of practicing anesthesiologists about the use of depth of hypnosis monitors in children. We developed an online survey and invited the members of the European Society for Paediatric Anaesthesiology to participate in this survey to share their thoughts regarding the use, applicability and reliability of hypnosis monitoring in children. The survey achieved a response rate of 30% (n=168) and a total of 138 completed surveys were included for further analysis. Sixty-eight respondents used hypnosis monitoring in children (users) and 70 did not (non-users). Sixty-five percent of the users reported that prevention of intra-operative awareness was their main reason to apply hypnosis monitoring. Among the non-users, the most frequently given reason (43%) not to use hypnosis monitoring in children was the perceived lack of reliability of the devices used in children. Hypnosis monitoring is used with a higher frequency during propofol anesthesia than during inhalation anesthesia. Hypnosis monitoring is furthermore used more frequently in children >4 years than in younger children. An ideal hypnosis monitor should be reliable for all age groups and any (combination of) anesthetic drug. We found no agreement in the interpretation of monitor index values and subsequent anesthetic interventions following from it. We concluded that the prevention of intraoperative awareness appears to be the most important reason to use hypnosis monitoring in children and the perceived lack of reliability of hypnosis monitoring in children is the most important reasons not to use it. No consensus currently exists on how to adjust anesthesia according to hypnosis monitor index values in children.

The brain is considered as the major target organ of anesthetic agents. Despite that, a reliable means to monitor its function during anesthesia is lacking. Several depth of hypnosis monitoring devices are available and most of them are EEG derived. In children the EEG develops until adulthood, while MLAEP, which are known to be sensitive to anesthetic agents, mature during the first decade of life. MLAEP might therefore be a

more reliable parameter to measure the state of the brain during anesthesia in pediatric patients. The literature concerning MLAEP based hypnosis monitoring during anesthesia in children are set out in **chapter 3**. This chapter reviews the current literature and demonstrates that MLAEP analysis is a reasonable method to assess the depth of hypnosis in children during anesthesia. Furthermore, its reliability does not depend on the age of the child and the type of commonly used anesthetics.

The aepEX Plus monitor (aepEX) utilizes the mid-latency auditory evoked potentials and is currently the only commercially available MLAEP based hypnosis monitor. In **chapter 4** the performance of the aepEX as a depth of hypnosis monitor for pediatric patients receiving propofol-remifentanil anesthesia was evaluated. aepEX and BIS values were recorded simultaneously during surgery in three groups of 25 children (aged 1 to 3, 3 to 6 and 6 to 16 years). Propofol was administered by target-controlled infusion. The University of Michigan Sedation Scale (UMSS) was used to clinically assess the DoH during emergence. Prediction probability (p_k) and receiver operating characteristics (ROC) analyses were performed to assess the accuracy of both DoH monitors. Nonlinear regression analysis was used to describe the dose-response relationships for the aepEX, the BIS, and propofol plasma concentrations (C_p). The study revealed a p_k of 0.36 and 0.21 for the aepEX and BIS, respectively (p=0.010). ROC analysis showed an area under the curve of 0.77 and 0.81 for the aepEX and BIS, respectively (p=0.644). At half-maximal effect (EC_{50}), C_p of 3.13 $\mu g \cdot mL^{-1}$ and 3.06 $\mu g \cdot mL^{-1}$ were observed for the aepEX and BIS, respectively. The r^2 for the aepEX and BIS was 0.53 and 0.82, respectively. Therefore, the aepEX seems to perform comparable to the BIS in differentiating between conscious and unconscious states, while performing inferior to the BIS in terms of distinguishing different levels of sedation. It also does not correlate well with the C_p in children receiving propofol-remifentanil anesthesia.

In **Chapter 5** we have evaluated the aepEX as a measure of DoH in children receiving sevoflurane-remifentanil anesthesia. aepEX and BIS were recorded simultaneously in 75 children, (1 to 3, 3 to 6, and 6 to 18 years), receiving sevoflurane at end-tidal concentrations (Et_{sevo}) between 1.5 and 0.5 MAC. The Et_{sevo} at which the aepEX and BIS had a value of 50 (EC_{50}aepEX and EC_{50}BIS) was calculated by nonlinear regression analysis. The accuracy of aepEX and BIS to predict the DoH was assessed by p_k and ROC analysis. Seventy-four children were included for analysis. The EC_{50}aepEX (2.68%) and EC_{50}BIS (2.10%) were comparable; the same accounts for the EC_{50}aepEX of the different age groups and the EC_{50}aepEX and EC_{50}BIS of corresponding age groups. The EC_{50}BIS in children aged 1 to 3 years was lower than in the older age groups ($p<0.05$). P_k values of the aepEX (0.32, CI 95% 0.08–0.56) and BIS (0.47, CI 95% 0.19–0.75) were comparable. The area under the ROC curve was 0.72 (CI 95%: 0.62–0.82) and 0.67 (CI 95%: 0.56– 0.77) for the aepEX

and BIS, respectively (p=0.54). Optimal cut-off index values were >60 (aepEX) and >68 (BIS), with corresponding specificities of 91%, CI 95%: 80–97% (aepEX) and 66%, CI 95%: 52–77% (BIS). In this study with children receiving sevoflurane anesthesia, the aepEX outperformed the BIS in distinguishing unconsciousness from consciousness. Both indices performed equally badly in differentiating different levels of DoH.

The performance of the aepEX monitor is again evaluated in **chapter 6**. Only this time in pediatric patients during desflurane-remifentanil anesthesia. Seventy-five patients, 1 to 18 years of age (stratified for age; 1 to 3, 3 to 6, 6 to 18 years, for subgroup analyses), were included in this prospective observational study. The aepEX and the BIS were recorded simultaneously, the latter serving as a reference. The ability of the aepEX to detect different levels of consciousness, defined according to the University of Michigan Sedation Scale, was investigated using p_k, and ROC analysis, served as the primary outcome parameter. As a secondary outcome parameter, the relationship between end-tidal desflurane and the aepEX and BIS values were calculated by fitting in a nonlinear regression model. The p_k values for the aepEX and the BIS were, respectively, 0.68 (95% CI: 0.53–0.82) and 0.85 (95% CI: 0.73–0.96; p=0.02). The aepEX and the BIS had an area under the ROC curve of, respectively, 0.89 (95% CI: 0.80–0.95) and 0.76 (95% CI, 0.68–0.84; p=0.04). The maximized sensitivity and specificity were, respectively, 81% (95% CI: 61%–93%) and 86% (95% CI: 74%–94%) for the aepEX at a cut-off value of >52, and 69% (95% CI: 56%–81%) and 70% (95% CI: 57%–81%) for the BIS at a cut-off value of >65. The age-corrected end-tidal desflurane concentration associated with an index value of 50 was 0.59 MAC (interquartile range: 0.38 to 0.85) and 0.58 MAC (interquartile range: 0.41 to 0.70) for, respectively, the aepEX and BIS (p=0.69). Age-group analysis showed no evidence of a difference regarding the area under the ROC curve or EC_{50}. The aepEX appears to reliably differentiate between a conscious and an unconscious state in pediatric patients receiving desflurane-remifentanil anesthesia.

Our findings in this thesis are discussed and put in perspective in **chapter 7**. There seems to be a need for a reliable depth of hypnosis monitoring in children and the most commonly used hypnosis monitors are lacking in this as perceived by a large portion of anesthesiologists participated in our survey. There is also a lack of consensus in how to use and interpret these devices during anesthesia in children. While the literature demonstrated that the use of MLAEP as a variable to assess the DoH seemed promising, the currently only commercially available MLAEP based DoH monitor appears to be only reasonably reliable in distinguishing between the conscious and unconscious states in children during different anesthesia. Future research concerning DoH monitoring might want to focus on less processed EEG, letting the anesthesiologist him-/herself interpreting

the state of the brain during anesthesia, while preventing confounded computer algorithms. Anesthesiologists should therefore consider to revise their training program by implementing teaching about the unprocessed EEG during anesthesia.

Samenvatting

Hoofdstuk 1 bespreekt de problemen rondom onbedoelde wakkere patiënten tijdens de anesthesie en de potentiele rol van een hypnose diepte monitor om dit te voorkomen. De zorgen over neurotoxiciteit bij kinderen die onder narcose gaan, waarvoor aanwijzingen zijn in dierenstudies, zou mogelijk voorkomen kunnen worden door een betrouwbare hypnose diepte monitor. Verschillende variabelen van het brein kunnen worden gebruikt om de diepte van hypnose te meten, waarvan het elektro-encefalogram (EEG) het meest gebruikt wordt. Een alternatief hiervoor zouden de mid-latency auditory evoked potentials (MLAEP) kunnen zijn. Deze zijn mogelijk betrouwbaarder bij kinderen, omdat ze eerder volledig ontwikkeld zijn dan het EEG.

In **hoofdstuk 2** evalueren wij de gedachten van praktiserende anesthesiologen over het gebruik van hypnose diepte monitoring bij kinderen. De leden van de European Society for Paediatric Anaesthesiology waren uitgenodigd om een door ons ontworpen online enquête in te vullen, zodat zij hun ideeën over het gebruik, toepasbaarheid en betrouwbaarheid van hypnose diepte monitoring bij kinderen met ons te delen. De enquête werd ingevuld door 30% (n=168) van de respondenten, waarvan er in totaal 138 enquêtes volledig waren ingevuld en werden gebruikt voor verdere analyse. Acht-en-zestig respondenten gebruikten hypnose diepte monitoren bij kinderen (users) en 70 gebruikte dit niet bij kinderen (non-users). Vijf-en-zestig procent van de users meldden dat het voorkomen van onbedoelde intra-operatieve bewustzijn hun belangrijkste reden was om een dergelijke monitor toe te passen. Onder de non-users was hun beleving van de slechte betrouwbaarheid van een hypnose diepte monitor de meest gegeven reden (43%) om deze niet te gebruiken bij kinderen. Hypnose monitoren werden vaker ingezet tijdens anesthesie met propofol dan met dampvormige anesthetica. Verder werden hypnose monitoren vaker gebruikt bij kinderen >4 jaar dan jongere kinderen. Er werd geen consensus gevonden over hoe men een hypnose monitor dient te interpreteren en eventueel hoe hierop te reageren. We concluderen dat het voorkomen van onbedoelde intra-operatieve bewustzijn de meest belangrijke reden blijkt te zijn om een hypnose diepte monitor te gebruiken en dat juist het gevoel van gebrek aan betrouwbaarheid van een hypnose diepte monitor bij kinderen de meest belangrijke reden is om deze niet te gebruiken. Er is op dit moment geen consensus over hoe de anesthesie aan te passen op basis van een hypnose monitor index waarden bij kinderen.

Het brein wordt gezien als een van de belangrijkste doelorgaan voor de anesthetica. Desondanks dat ontbreekt er een betrouwbare methode om de functie van dit orgaan te monitoren tijdens de anesthesie. Een aantal hypnose diepte monitoren zijn beschikbaar en de meerderheid ervan gebruikt het EEG hiervoor. Bij kinderen ontwikkelt het EEG verder tot en met in de volwassenheid, terwijl het MLAEP, waarvan bekend is dat het gevoelig is voor anesthetica, volledig ontwikkeld is gedurende de eerste 10 levensjaren. Daardoor zou het MLAEP mogelijk een betrouwbaardere variabele kunnen zijn om de status van het brein te meten tijdens anesthesie bij kinderen. De beschikbare literatuur over MLAEP gebaseerde hypnose diepte monitoring tijdens anesthesie bij kinderen worden uiteengezet in **hoofdstuk 3**. Dit hoofdstuk beoordeelt de huidige literatuur en laat zien dat MLAEP-analyse een redelijke methode is om de diepte van hypnose bij kinderen tijdens anesthesie te meten. Verder lijkt de betrouwbaarheid ervan niet afhankelijk te zijn van de leeftijd en de verschillende veelgebruikte anesthetica.

De aepEX Plus monitor (aepEX) gebruikt mid-latency auditory evoked potentials en is op dit moment de enige commercieel beschikbare MLAEP gebaseerde hypnose diepte monitor. In **hoofdstuk 4** wordt de prestatie van de aepEX als hypnose diepte monitor geëvalueerd bij kinderen die propofol-remifentanil anesthesie krijgen. aepEX en BIS waarden werden simultaan opgeslagen tijdens de operatie van drie groepen van 25 kinderen (leeftijd 1 tot 3, 3 tot 6 en 6 tot 16 jaar). Propofol werd toegediend middels target-controlled infusion. De University of Michigan Sedation Scale (UMSS) werd gebruikt om de klinische diepte van hypnose te objectiveren gedurende de uitleiding van de narcose. Prediction probability (p_k) en receiver operating characteristics (ROC) analyses werden gebruikt om de nauwkeurigheid van beide monitors te evalueren.

Non-lineaire regressieanalyse werd gebruikt om de relatie tussen de plasmaconcentratie propofol (C_p) en het effect op de aepEX en BIS monitor te beschrijven. Het onderzoek toont een p_k van 0.36 en 0.21 voor respectievelijk de aepEX en BIS monitor (p=0.010). ROC analyse laat een oppervlakte onder de curve zien van 0.77 en 0.81 voor respectievelijk de aepEX en BIS (p=0.644). Op de helft van het maximale effect (EC_{50}), was de C_p voor de aepEX en BIS respectievelijk 3.13 $\mu g \cdot mL^{-1}$ en 3.06 $\mu g \cdot mL^{-1}$. De r^2 voor de aepEX en BIS waren respectievelijk 0.53 en 0.82. Hieruit lijkt de aepEX vergelijkbaar te presteren met de BIS monitor in het differentiëren tussen "wakkere" en "slapende" patiënt, terwijl het slechter presteert in het onderscheiden van verschillende niveaus van sedatie ten opzichte van de BIS. De aepEX correleert ook matig met de C_p in kinderen onder propofol-remifentanil anesthesie.

In **hoofdstuk 5** hebben wij de aepEX geëvalueerd als een maat voor de diepte van hypnose bij kinderen die sevofluraan-remifentanil anesthesie kregen. aepEX en BIS waarden werden simultaan verzameld van 75 kinderen (1 tot 3, 3 tot 6 en 6 tot 18 jaar), die een endtidal sevofluraan (Et_{sevo}) concentratie kregen tussen 1,5 en 0,5 MAC. De Et_{sevo} waarop de aepEX en BIS waarde 50 was (EC_{50}aepEX en EC_{50}BIS) werd berekend middels non-lineaire regressieanalyse. De betrouwbaarheid van de aepEX en BIS om de diepte van hypnose te voorspellen werd beoordeeld met p_k en ROC analyse. Vier-en-zeventig kinderen waren geïncludeerd voor analyse. De EC_{50}aepEX (2.68%) en EC_{50}BIS (2.10%) waren vergelijkbaar; hetzelfde gold voor de EC_{50}aepEX van de verschillende leeftijdsgroepen en tussen de EC_{50}aepEX en EC_{50}BIS van dezelfde leeftijdsgroepen. De EC_{50}BIS was lager voor de kinderen van 1 tot 3 jaar vergeleken met de oudere leeftijdsgroepen ($p<0.05$). P_k waarden voor de aepEX (0.32, CI 95% 0.08–0.56) en BIS (0.47, CI 95% 0.19–0.75) waren vergelijkbaar. De oppervlakte onder de ROC curve waren respectievelijk 0.72 (CI 95%: 0.62–0.82) en 0.67 (CI 95%: 0.56–0.77) voor de aepEX en BIS ($p=0.54$). De optimale afkap punten voor de index waarden waren >60 (aepEX) en >68 (BIS), met daarbij de corresponderende specificiteit van 91%, CI 95%: 80–97% (aepEX) en 66%, CI 95%: 52–77% (BIS). In dit onderzoek met kinderen die sevofluraan-remifentanil anesthesie kregen, overtrof de aepEX de BIS monitor in het onderscheiden van bewusteloze en bewuste patiënten. Beide monitoren presteren even slecht in het differentiëren van verschillende niveaus van hypnose diepte.

De prestaties van de aepEX monitor wordt opnieuw geëvalueerd in **hoofdstuk 6**. Dit keer bij pediatrische patiënten die desfluraan-remifentanil anesthesie ondergaan. Vijf-en-zeventig patiënten, van 1 tot 18 jaar (gestratificeerd op leeftijden, 1 tot 3, 3 tot 6 en 6 tot 18 jaar, voor subgroep analyse), werden geïncludeerd in dit prospectief observationeel onderzoek. De aepEX en BIS waarden werden simultaan verzameld, waarvoor de BIS als referentie werd gebruikt. Het vermogen van de aepEX om verschillende niveaus van hypnose diepte te meten, gedefinieerd volgens de University of Michigan Sedation Scale, werd onderzocht door middel van p_k en ROC analyse en diende als de primaire uitkomst maat. Als secundaire uitkomst maat werd de relatie tussen endtidal desfluraan en de aepEX en BIS waarden gebruikt, welke berekend werd door middel van non-lineaire regressieanalyse. De p_k waarden van de aepEX en BIS waren respectievelijk 0.68 (95% CI: 0.53–0.82) en 0.85 (95% CI: 0.73–0.96; $p=0.02$). De aepEX en BIS hadden een oppervlakte onder de ROC curve van respectievelijk, 0.89 (95% CI: 0.80–0.95) en 0.76 (95% CI, 0.68–0.84; $p=0.04$). De maximale combinatie van sensitiviteit en specificiteit waren respectievelijk 81% (95% CI: 61%–93%) en 86% (95% CI: 74%–94%) voor de aepEX met een afkapwaarde van >52, en 69% (95% CI: 56%–81%) en 70% (95% CI: 57%–81%) voor de BIS met een afkapwaarden van >65. De endtidal desfluraan concentratie (gecorrigeerd voor leeftijd)

waarbij de index waarde 50 was, was voor de aepEX 0.59 MAC (interkwartielafstand: 0.38 tot 0.85) en voor de BIS 0.58 MAC (interkwartielafstand: 0.41 tot 0.70; p=0.69). Analyse van de verschillende leeftijdsgroepen laat geen verschil zien voor de oppervlakte onder de ROC curve en EC_{50}. De aepEX lijkt betrouwbaar te differentiëren tussen bewust en bewusteloosheid bij pediatrische patiënten die desfluraan-remifentanil anesthesie krijgen.

Onze bevindingen van dit proefschrift worden besproken en in perspectief gebracht in **hoofdstuk 7**. Er lijkt vraag te zijn voor een betrouwbare hypnose diepte monitor voor kinderen, wat volgens een groot deel van de anesthesiologen, die deel hadden genomen in onze enquête, ontbreekt bij de gangbare hypnose diepte monitoren. Er ontbreekt ook een consensus over hoe een hypnose diepte monitor gebruikt dient te worden en hoe deze geïnterpreteerd moet worden bij kinderen tijdens anesthesie. Hoewel de literatuur laat zien dat MLAEP een veel belovende variabele is om de diepte van hypnose te meten, lijkt de op dit moment enige commercieel beschikbare MLAEP gebaseerde hypnose diepte monitor slechts maar redelijk te kunnen differentiëren tussen bewuste en bewusteloze pediatrische patiënten tijdens anesthesie met verschillende anesthetica. Toekomstige onderzoeken op het gebied van hypnose diepte monitoring zouden zich mogelijk moeten concentreren op minder bewerkte EEG, zodat de anesthesioloog zelf de conditie van het brein kan beoordelen tijdens de anesthesie zonder dat deze beïnvloed wordt door een computer algoritme. Anesthesiologen zouden daarom moeten overwegen om het curriculum uit te breiden met kennis over het onbewerkte EEG tijdens anesthesie.

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List of Publications

Cheung YM, Scoones GP, Stolker RJ, Weber F.
Monitoring Depth of Hypnosis: Mid-Latency Auditory Evoked Potentials Derived aepEX in Children Receiving Desflurane-Remifentanil Anesthesia.
Anesthesia Analgesia. 2018 Jun 28. Published Ahead-of-Print

Cheung YM, Scoones G, Stolker RJ, Weber F.
Use, applicability and reliability of depth of hypnosis monitors in children – a survey among members of the European Society for Paediatric Anaesthesiology.
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Cheung YM, Scoones GP, Stolker RJ, Weber F.
Evaluation of the auditory evoked potentials derived aepEX™ as a measure of hypnotic depth in pediatric patients receiving sevoflurane-remifentanil anesthesia.
Paediatric anaesthesia. 2014;24(7):760-5.

Cheung YM, Scoones GP, Hoeks SE, Stolker RJ, Weber F.
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Paediatric anaesthesia. 2013;23(10):891-7.

Cheung YM, Lange MM, Buunen M, Lange JF
Current technique of laparoscopic total mesorectal excision (TME): an international questionnaire among 368 surgeons.
Surgical Endoscopy. 2009 dec; 23 (12): 2796-2801.

Curriculum Vitae

Yuen Cheung was born on the 19th of December 1982 in Emmen, the Netherlands. He graduated in 2001 from his secondary school, the Kaj Munk College in Hoofddorp. In 2003 he enrolled for his medical training at the Erasmus University of Rotterdam after which he started as a PhD student at the department of anesthesiology under supervision of dr. Frank Weber and prof. dr. Robert Jan Stolker, investigating mid-latency auditory evoked potentials in children during anesthesia. Just before the clinical data sets for this thesis were complete, he started the anesthesiology training in 2013 at the Erasmus MC in Rotterdam (prof. dr. Robert Jan Stolker). During his period of training, data acquisition for this thesis was completed and he got married with Jennifer Lai. At the end of his anesthesia training in 2018, he continued as a fellow intensive care medicine at the OLVG in Amsterdam. About a year ago Yuen became the father of Aimee and recently started working as an anesthesiologist at the HMC in The Hague.

PhD Portfolio

Name PhD student:	Y.M. Cheung
Erasmus MC Department:	Anesthesiology
PhD period:	2011 - 2019
Promotor:	Prof. dr. R.J. Stolker
	Prof. dr. F. Weber

PhD TRAINING

General courses

- BROK ("Basiscursus Regelgeving Klinisch Onderzoek") – Erasmus University
- Biostatistics for clinicians – Erasmus University
- Regression analysis for clinicians – Erasmus University
- CPO mini-course: Methodology of patient orientated research and preparation for subsidy application – Erasmus University
- Evidence Based Medicine – Erasmus MC

Presentations

- NVA wetenschapsdag 2013, Zeist (the Netherlands) (oral)
- ErasmusMC wetenschapsdag anesthesiologie 2014, Rotterdam (the Netherlands) (oral)

(Inter)national conferences

- Nederlandse Vereniging voor Anesthesiologie: wetenschapsdag 2013, Zeist (the Netherlands)
- Erasmus Master Class in Anesthesia and Perioperative Care 2014, Rotterdam (the Netherlands)
- Nederlandse Vereniging voor Anesthesiologie: anesthesiologendagen 2015, Maastricht (the Netherlands)
- Nederlandse Vereniging voor Anesthesiologie: anesthesiologendagen 2016, Maastricht (the Netherlands)
- Nederlandse Vereniging voor Anesthesiologie: anesthesiologendagen 2017, Maastricht (the Netherlands)
- Amercian Society of Anesthesiologists: Anesthesiology 2017, Boston (United States of America)
- European Society of Intensive Care Medicine: LIVES 2019, Berlin (Germany)

Other

- Research meetings department of pediatric anesthesiology (2014)

Teaching

- Weekly journal club during anesthesia training
- Annual symposia during anesthesia training: "Magnesium and Anesthesia. What is it good for?"
- Lectures for anesthesia nurses in training
- Lecture for medicine students