Comparative evaluation of Bispectral Index and Narcotrend Index in children below 5 years of age

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Summary
Background: The use of electroencephalogram (EEG) monitoring devices for assessing the depth of hypnosis is most difficult in children under 5 years of age.
Methods: Forty five children aged 0–60 months were included in a prospective observational study. A direct comparison of the processed EEG variables Bispectral Index™ (BIS, version 3.4) and Narcotrend® Index (NI, version 2.0AF) was to be achieved by simultaneous recording. The ability of these parameters to differentiate between various clinical states was evaluated by using the prediction probability ($P_k$). Age-related effects on the BIS and NI were analyzed by dividing the children into three age groups: 0–6, 7–18 and 19–60 months.
Results: The preanesthesia, conscious children were differentiated from anesthetized patients by the BIS and NI with no overlap ($P_k = 1.0$). In the awake period the BIS was superior to the NI ($P_k$ to differentiate ‘end of anesthesia’ from ‘awakening’ was 0.97 vs 0.73 respectively; $P = 0.002$). Patients aged 7–18 months showed higher BIS and NI values in the course of anesthesia than the younger and older children ($P = 0.001$). On awakening, children aged 0–6 months showed the lowest mean BIS (n.s.) and NI ($P = 0.006$) values.
Conclusions: The BIS currently seems to be superior to the NI, but age-related processing algorithms of the raw EEG must be implemented in both BIS and NI in order to be useful in children younger than 5 years of age.

Keywords: anesthesia; monitoring; Bispectral Index; Narcotrend

Introduction
No neuromonitoring procedure has so far become generally accepted for observing anesthesia effects on the brain, which is the main target of anesthesia.

With the use of complex, multivariate analytical algorithms and simultaneous reduction of the data and adjustment of the size of electroencephalogram (EEG) equipment to operating-room conditions, computer-aided evaluation of the EEG opens up new possibilities of determining the depth of hypnosis during anesthesia. Besides the known problems of EEG monitoring of anesthesia in adults (e.g. different effects of hypnotics and opioids on the
EEG, interindividual variability, hysteresis), the continuous development of the central nervous system and thus age-related variance of the brain wave pattern in respect of basic frequency and amplitude in itself makes it doubtful whether the depth of hypnosis can be determined reliably in pediatric anesthesia (1,2).

Of the EEG-based indices currently available for determining the depth of hypnosis, the Bispectral Index (BIS) and the Narcotrend Index (NI) are considered the most suitable parameters for assessing different anesthetic states in adults (3). Both the BIS and the NI have already been used in various studies, including pediatric anesthesia, and these studies revealed age-related differences between infants and children in both the BIS and the NI (4–9). Although they are not transferable 1 : 1, both processed EEG variables indicate the hypnotic component of anesthesia as a dimensionsless value ranging from 100 (fully awake) to 0 (very deep hypnosis) (10). Both the BIS and the NI are constructed indices containing different EEG and electromyographic measurements whose exact calculation algorithm is not known. Besides the results of a frequency analysis and amplitude measurements, the calculation methods used include bispectral analysis for the BIS and EEG wave pattern recognition for the NI (11,12).

The main objective of the present study was to compare the ability of the BIS and the NI to differentiate between clinically determined states of anesthesia directly by using them simultaneously. The prediction probability of paired data was used as the primary outcome measure. As it was doubtful whether processed EEG parameters are useful for determining the depth of hypnosis in children under five because of the continuing growth and differentiation processes, the course of the BIS and NI was also to be compared within various age groups during anesthesia with sevoflurane.

Methods

The study was approved by the Ethics Committee of the University of Leipzig. After informed parental consent had been obtained, 45 pediatric patients under the age of 5 years, ASA physical status I or II, who were undergoing elective minor surgery (herniotomy, circumcision, hypospadias repair, ureteroneocystostomy) were included. Patients with neurological disorders, existing centrally acting medication, anemia or malignant hyperthermia disposition in their family history, and also premature-born infants, were excluded from the study. Anesthesia was induced in a standardized manner for all patients by facemask inhalation of 8% sevoflurane with a high fresh gas flow of 6 l min\(^{-1}\). Intubation was facilitated by an i.v. bolus of 2 mg kg\(^{-1}\) propofol. Anesthesia was maintained with sevoflurane in an air-oxygen mix (30–40% O\(_2\)) targeting normoventilation with an endtidal CO\(_2\) concentration of 4.6–5.8 kPa (35–45 mmHg). Endtidal sevoflurane concentration was adapted and i.v. fentanyl was applied according to clinical needs by an anesthetist blinded to BIS and NI monitoring. All the children received a weight-adapted intraoperative i.v. dose of either 20 mg kg\(^{-1}\) paracetamol or metamizol. After completion of all the surgical measures, the supply of sevoflurane was stopped and the fresh gas flow was increased from 3 to 6 l min\(^{-1}\). Once adequate spontaneous breathing had been established, extubation was carried out and the children were observed in the adjacent recovery room for 2 h.

EEG monitoring and data collection

An A-2000 Monitor (Aspect Medical Systems; Newton, USA) with the BIS version 3.4 and a Narcotrend Monitor (MT MonitorTechnik GmbH; Bad Bramstedt, Germany) with the NI version 2.0AF were used simultaneously. Electrodes (‘BIS Standard’; Aspect Medical Systems, USA and ‘blue sensor’; Medicotest, Denmark) were placed on the patient’s forehead as directed by the manufacturer. A skin preparation with ether was necessary for placing blue sensor electrodes only. Optimum electrode contact was checked by testing impedance for values <6 kOhm. To avoid unnecessary stress reactions in uncooperative, agitated patients, the electrodes were not applied until after loss of consciousness if the first attempt was unsuccessful. All EEG data were downloaded from the two devices and stored on a laptop computer. In addition, a hand-noted record was kept by a second anesthetist not involved in adjusting anesthesia depth. Besides the BIS and NI, heart rate, noninvasive blood pressure and endtidal sevoflurane...
concentration were recorded at different clinical states. The preoperative values (PRE) were recorded in the conscious child immediately before the facemask was applied. Loss of consciousness (LOC) was ascertained by testing loss of eyelash reflex every 3–5 s after spontaneous closing of the eyes during facemask inhalation of sevoflurane. Further, case milestones were determined by the operation: SKI = skin incision/start of operation; IOP = intraoperative steady state 15 min after skin incision; END = end of operation and stop of sevoflurane supply. The clinical correlates of the awakening period were assessed by the anesthetist blinded to EEG monitoring: FIR = first reaction of the patient and AWK = awakening (determined by first response to verbal command, phonation, or continuous purposeful movement).

Further analysis included the number of available EEG data at different clinical states and the times to loss of consciousness (start of sevoflurane exposure to loss of eyelash reflex), from the end of anesthesia to the first reaction and until awakening.

Statistics

In order to compare the ability of the BIS and NI to distinguish between the different clinical states, and their accuracy in doing so, the prediction probability ($P_k$) was used as described by Smith et al. (13). $P_k$ was calculated using an SPSS macro, SPSS for Windows, version 11.0 (SPSS Inc., Chicago, IL, USA). To ensure suitable conditions for comparing the performance of the two anesthesia depth indicators, the BIS and the NI were measured simultaneously for the same subjects and $P_k$ analysis was only based on the available paired data for the 45 patients. The $P_k$-values are stated with a confidence interval of 95% (95% CI) based on the calculation of the SE with Somers’ d. A $P_k$ value of 1.0 means that the parameter predicts the state correctly 100% of the time; whereas a $P_k$-value of 0.5 means that the prediction is no better than a fifty-fifty chance.

In the secondary analysis, age-related effects on the BIS and NI were analyzed by dividing the children into three age groups: 0–6, 7–18 and 19–60 months. Mean BIS and NI values at the different clinical states were compared with the Wilcoxon sign rank test, using only data from patients with paired values. For statistical comparisons between the age groups the Kruskal–Wallis test was used. A Bonferroni–Holm correction was made to adjust for multiple comparisons. $P$-values <0.05 were considered statistically significant.

Results

Forty-five patients were recruited for the study. Demographic data and operative specifications are summarized in Table 1. As expected, there was a difference between the groups with regard to demographic data but also concerning the duration of anesthesia and the operation. Interestingly, there was no difference between the age groups in respect of the consumption of fentanyl per kg per hour. The same applied to the endtidal sevoflurane concentration during the course of anesthesia as used by the EEG-blinded anesthetist (3.3% ± 0.4% and 3.3% ± 0.5% at IOP respectively).

Seven children did not tolerate application of the EEG electrodes before administration of anesthesia. In the remaining children who were awake, with successfully positioned electrodes, prior to anesthesia, data acquisition was more difficult with the NI monitor than with the BIS monitor (39% vs 63% available data). The same applied to the number of available data in the awakening period (BIS–FIR = 98% and NI–FIR = 84%; BIS–AWK = 84% and NI–AWK = 60%). The performance of both monitors was excellent in anesthetized patients (100% available data at SKI, IOP and END).

The $P_k$-values of the paired data available for both EEG-derived variables are summarized in Table 2. Both devices differentiated fairly well between patients who were awake before the operation and those who had just lost consciousness (LOC) or were sufficiently anesthetized for surgery (SKI) ($P_k > 0.9$). The clinical states in the course of awakening were differentiated better by the BIS than by the NI (Figure 1). At a BIS value of 60, children under the age of 5 years have a 5% probability of awakening; in the case of the NI this probability is nearly 38%. Whereas the NI did not differentiate accurately enough between END and AWK in the patient population as a whole ($P_k = 0.73$), the result changed when the 0–6 month age group was excluded ($P_k = 0.93$).

For the children aged 7–18 months the mean BIS and NI at IOP values were significantly higher than

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for the younger and older patients, although all had received the same sevoflurane concentration. Besides the significant differences in the mean values there was great individual variance within one age group (Figures 2 and 3). The range of the EEG variables was greatest at LOC (BIS: 8–98; NI: 21–98). Mean BIS values were higher at LOC than NI values in the age groups 0–6 and 19–60 months (P < 0.05). In the age group 0–6 months the first reaction in the awakening phase occurred at a lower endtidal sevoflurane concentration (0.58% ± 0.23%) than in the age group 19–60 months (0.78% ± 0.21%; P < 0.05) and after a longer recovery period than in the age groups 7–18 and 19–60 months (see Table 1). Nevertheless, both the BIS values (P < 0.05) and the NI values (P < 0.01) at this point were still significantly lower in the age group 0–6 months than in the children in the other two age groups. On awakening, children aged 0–6 months showed the lowest mean BIS (n.s.) and NI (P = 0.006) values.

Table 1
Demographic data and operative specifications

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>0–6 months (n = 16)</th>
<th>7–18 months (n = 14)</th>
<th>19–60 months (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 ± 0.16</td>
<td>1.0 ± 0.28</td>
<td>3.1 ± 0.95</td>
<td></td>
</tr>
<tr>
<td>63 ± 11</td>
<td>76 ± 2</td>
<td>103 ± 7</td>
<td></td>
</tr>
<tr>
<td>5.9 ± 1.7</td>
<td>9.6 ± 1.3</td>
<td>15.0 ± 3.0</td>
<td></td>
</tr>
<tr>
<td>11 : 5</td>
<td>11 : 3</td>
<td>10 : 5</td>
<td></td>
</tr>
<tr>
<td>68 ± 29</td>
<td>92 ± 47</td>
<td>101 ± 71</td>
<td></td>
</tr>
<tr>
<td>44 ± 24</td>
<td>68 ± 43</td>
<td>65 ± 54</td>
<td></td>
</tr>
<tr>
<td>67 ± 31</td>
<td>83 ± 32</td>
<td>87 ± 41</td>
<td></td>
</tr>
<tr>
<td>18 : 46 ± 24 : 27</td>
<td>06 : 45 ± 06 : 05</td>
<td>10 : 49 ± 07 : 46</td>
<td></td>
</tr>
<tr>
<td>30 : 54 ± 29 : 57</td>
<td>11 : 32 ± 05 : 57</td>
<td>18 : 08 ± 12 : 25</td>
<td></td>
</tr>
<tr>
<td>4.5 ± 2.8</td>
<td>5.2 ± 3.8</td>
<td>5.5 ± 3.5</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean ± SD
LOC, loss of consciousness; END, end of operation; FIR, first reaction; AWK, awakening.

Table 2
P-values (95% CI) of Bispectral Index (BIS) and Narcotrend Index (NI)

<table>
<thead>
<tr>
<th>Clinical states</th>
<th>BIS</th>
<th>NI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRE vs LOC</td>
<td>0.95 (0.87–1.00)</td>
<td>0.92 (0.82–1.00)</td>
<td>0.628</td>
</tr>
<tr>
<td>PRE vs SKI</td>
<td>1.00 (-)</td>
<td>1.00 (-)</td>
<td>–</td>
</tr>
<tr>
<td>END vs FIR</td>
<td>0.82 (0.74–0.90)</td>
<td>0.74 (0.62–0.86)</td>
<td>0.155</td>
</tr>
<tr>
<td>END vs AWK</td>
<td>0.97 (0.93–1.00)</td>
<td>0.73 (0.58–0.88)</td>
<td>0.002</td>
</tr>
<tr>
<td>FIR vs AWK</td>
<td>0.75 (0.63–0.87)</td>
<td>0.59 (0.44–0.74)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

Only paired data are included.
PRE, preoperative awake; LOC, loss of consciousness; SKI, skin incision; END, end of operation; FIR, first reaction; AWK, awakening.

Discussion

When interpreting the results of this study it is essential to consider the influence of age on the growth and differentiation processes of the central nervous system. The various age groups differ considerably with regard to the number, distribution and function of the receptors, transmitter production and reuptake mechanisms and the interlinking of the individual neurons (14). The electrophysiological correlates of the morphological and functional peculiarities of the infant central nervous system (CNS) with the EEG of adults are to be found in different basic rhythms and amplitudes (15). In our study, we demonstrated a peak of high BIS and NI values, despite high anesthetic concentrations, in patients aged 7–18 months compared with the younger and older children. Interestingly, this coincides with a peak of greater receptor expression around the first year of life (14) and the highest EEG amplitude in children aged 9–18 months (100–200 Hz). Our results concerning the existence of an age-related peak of high BIS and NI values in children aged 0.5–1.5 years are supported by a recently published report by Davidson et al. (16), who demonstrated that the calculated sevoflurane concentrations required to achieve midscale values of entropy and BIS were highest in the 1–2-year age group and lower in the age groups 0–1, 2–4 and 4–12 years. The development of the infant CNS is not, therefore, just

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a linear process and this has to be taken into account when dividing children into age groups in EEG studies.

The $P_k$ analysis shows that the BIS differentiates between the clinical states ‘end of operation’ (END) vs ‘first reaction’ (FIR) and ‘end of operation’ (END) vs ‘awakening’ (AWK), figured as probability curves with error bars around the 50% probability. The steeper the curve, the better is the distinction between the clinical states. At a BIS value of 60 there is a 5% probability that the child is awake; in the case of the NCT this probability is nearly 38%.

The $P_k$ analysis shows that the BIS differentiates between the clinical states of the awakening phase better than the NI. The inadequate differentiation between the states FIR and AWK with the NI ($P_k = 0.59$) is because of the fact that the values were already very high at FIR, so the overlap of values at these two states is also greater with the NI than with the BIS. However, the NI is also much less able to differentiate between still anesthetized and awake patients than the BIS ($P_k = 0.73$ vs 0.97). This
does not correspond to the $P_k$ of 0.95 determined by Weber et al. (17) for the NI in children aged between 1 and 11 years. This may be explained by the influence of the 0–6 month age group: 64% inaccurate classification of the awake state with NI values <30. In view of a basic rhythm of 3–4 Hz and amplitudes between 10 and 50 μV this result may be not surprising. Caution is repeatedly recommended when interpreting EEG data in the 0–6 month age group (5,16), and exclusion of this age group from the $P_k$ analysis correspondingly results in a similar $P_k$ of 0.93.

Viewed as a whole, the means of the EEG parameters over the course of anesthesia corresponded to the values obtained by monitoring adults. Nevertheless, at each time there are BIS and NI values outside the range for the particular clinical correlate. The individual scatter of the means of the BIS and NI is greatest at LOC. Besides a time lag in EEG processing [as recently described by Pilge et al. (18)] it is possible that loss of eyelash reflex was not recorded exactly to the second and plays a role here. Interestingly, the mean NI values in all the age groups already correspond to the values for anesthesia, whereas the mean BIS values at LOC are around 65. As the values were measured directly at loss of eyelash reflex and not as a mean within a time window, this cannot be attributed to the faster EEG processing and data output of the NI monitor, as the update rate is 1 s for the BIS and 5 s for the NI. It is possible that initial desynchronization with the occurrence of increased beta waves at the induction of anesthesia (19) is responsible for this phenomenon, as a ‘beta ratio’ is a calculated subparameter for the BIS (11). Figures 2 and 3 also show that the spread of the individual values for BIS and NI at the times FIR and AWK decreases as the age of the children increases. A greater spread of values in younger age groups has already been described by Davidson et al. (16) for BIS and entropy. Wodey et al. (20) explain this wide range of BIS values directly by the effect of age on the EEG and demonstrate that the EEG bispectrum is strongly related to the child’s age. This may also explain why the BIS is currently superior to the NI in younger age groups.

Another finding of this study is the different performance of the two EEG devices in children under 5 years of age when awake or regaining consciousness. When assessing values derived before the operation it must be taken into account that the NI monitor does not show any values in the first few minutes after the start of measurement.

Figure 3
Time course of the Narcotrend Index (NI) in different clinical states and corresponding mean endtidal sevoflurane concentrations in the three different age groups. The solid black lines indicate mean NI values, and each dot represents an individual NI value in the investigated clinical state. The grey line represents the measured endtidal sevoflurane concentration with a numerical statement of the mean. LOC, loss of consciousness; IOP, intraoperative steady state; END, end of operation; FIR, first reaction; AWK, awakening.
(manufacturer’s user manual). Rapid induction of anesthesia causing little stress is therefore one reason for the small number of values recorded preoperatively. However, in the awakening period the NI monitor also displays an alert term ‘>30 Hz’ or ‘EMG’ more often than the BIS monitor, and this resulted in fewer NI values. A high rate of missing NI values has already been described by Weber et al. for preanesthesia awake children and by Schneider et al. for adult patients in recovery of consciousness phases (8,21). The BIS therefore seems to be more resistant to artifacts and more useful in daily anesthesia practice. One explanation may be the higher input impedance of the BIS monitor (50 vs 10 MOhm) or the higher sampling rate and resolution of the BIS (16 bits at 256 samples vs 12 bits at 128 samples per second).

Our study has certain limitations. Although the BIS value is influenced more by the particular software version than by the sensor used it is still conceivable that use of the older BIS Standard Sensor (instead of the now more usual XP Sensor) influenced the measurements we obtained. Moreover, new software and hardware upgrades are now available for both EEG-based indices. As some of the algorithms or modifications of these are secret, it is not possible to predict their value for use in pediatric anesthesia. It also has to be taken into account that the measurements in this clinical study were not standardized to the same sevoflurane and fentanyl concentrations at the selected clinical correlates. Except at the time ‘TOP’, all the data for sevoflurane reflect nonsteady-state concentrations, as no steady state can be equilibrated over at least 10 min in the dynamic phases of anesthesia investigated by us. Furthermore, we have to consider that opioids affect arousal and both BIS and NI by reducing nociceptive stimulus in the course of anesthesia (22). However, as the BIS and NI were recorded simultaneously, the influence of fentanyl is the same for both EEG parameters.

In conclusion, a direct comparison by means of prediction probability and based on the performance of the two EEG devices showed the BIS monitor to be superior to the NI monitor for children under 5 years of age. Besides the enormous natural inter-individual variance there are remarkable age-related differences in the processed EEG-derived variables even within the first 5 years of life. This requires age-related processing algorithms of the EEG, and both BIS and NI must be adapted better to the patient’s age. A large database comprising both raw and processed pediatric EEGs should therefore be established.

Acknowledgements

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