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Neonatal electroencephalography shows low sensitivity to anesthesia

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ABSTRACT

This study examined EEG under clinical anesthesia in neonates and infants, to clarify how growth affects EEG during anesthesia. Subjects comprised 62 neonates and infants. Patients were divided into four groups according to age: Group 1 (neonates), <1 month; Group 2, 1–2 months; Group 3, 3–5 months; and Group 4, 6 months to 2 years. Anesthesia was maintained with sevoflurane and fentanyl and/or caudal block. At four points of sevoflurane concentration (0.5%, 1%, 1.5%, and 2%), 90% spectral edge frequency (SEF90), burst suppression ratio (BSR), relative beta ratio (RBR) and approximate entropy (ApEn) were analyzed. In Group 4, SEF90, BSR, RBR and ApEn changes were dependent on the concentration of anesthesia, along with changes in sevoflurane concentration from 0.5% to 2% (from 14.3 (2.7) [mean (SD)] Hz to 8.2 (3.8) Hz, from 0.0 to 0.32 (0.36), from −1.58 (0.14) to −1.10 (0.15), and from 0.56 (0.25) to 0.24 (0.25) respectively; $p < 0.05$ each). Conversely, these processed EEG parameters in Group 1 showed little anesthesia-dependent change under sevoflurane concentrations between 0.5% and 2% (SEF90: 7.3 (1.2) Hz vs. 7.7 (2.1) Hz; BSR: 0.51 (0.20) vs. 0.62 (0.29); RBR: −1.00 (0.17) vs. −1.03 (0.27); ApEn: 0.32 (0.18) vs. 0.25 (0.14), respectively). The unique EEG features of neonates during anesthesia rapidly change to the usual anesthesia-dependent patterns seen in older children, with a boundary of 3–5 months old. In infants younger than 6 months old, neural network regulation reflected in EEG by anesthesia is weak.

1. Introduction

Clinically, electroencephalography (EEG) shows slowed and synchronous patterns with deepening anesthesia, with burst suppression patterns apparent under even deeper anesthesia, reflecting network regulation. Conversely, the neuron network system is functionally immature at birth. For instance, the slow endogenous spontaneous activity with large amplitude delta wave, mediated by N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl isoxazole-4-propionic acid (AMPA) receptors, is found in the immature human neocortex, which terminates with the maturation of functional gamma-amino butyric acid (GABA)-ergic inhibition [17,18,27]. Some patterns of spindle-bursts (tracé alternant), which resemble the burst suppression seen with high-dose anesthesia, also appear on EEG during emergence in early immature brain [5]. Moreover, myelination is known to become established during the first 2 years of life [12]. Because the synaptic connectivity through these neurotransmitters and the effective network connections are immature and unique in the developmental brain, the immature brains of the neonate and infant are expected to show different reactivity to anesthesia in comparison with adults.

In practical terms, anesthesia monitoring using methods such as the bispectral index (BIS) algorithm shows a wide variation in evaluation of EEG in infants and children. Age itself has been considered an important influencing factor [3]. Some investigations have suggested that the common methods of anesthesia monitoring may be valid in children above 2 years old [12]. Conversely, infants under 6 months old reportedly show fundamental differences in how EEG changes with emergence in comparison with older infants [4]. However, the availability and limitations of EEG indices have only been partially evaluated [11], as reports about EEG and EEG indices in neonates at different depths of anesthesia are rare. Details of how anesthesia levels change EEG patterns in neonates are not well known, and how age clinically affects EEG in neonates and infants under anesthesia remains unclear.

This study aimed to examine associations between neonatal growth and several processed EEG parameters during routine clinical anesthesia. Since most anesthetics exert effects on synaptic transmission mainly through inhibitory GABAergic receptors, and synaptic connectivity (particularly the GABAergic inhibition system) is thus immature and weak in this period, we hypothesized that changes in neural network regulation reflected in EEG under anesthesia are low in neonates and younger infants. We intended to examine EEG reactivity to anesthesia, particularly in infants

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younger than 6 months old, in comparison with EEG in older infants.

2. Methods

2.1. Subjects

The study was approved by the institutional review board at Aichi Colony Hospital, and complied with the regulations and ethical guidelines of the World Medical Association Declaration of Helsinki. We retrospectively analyzed EEG data for general anesthesia stored at Aichi Colony Hospital for the period 2003–2004. At Aichi Colony Hospital, informed consent for anesthesia was obtained in the general standard form, from which the consent for this study was simultaneously obtained from the parents. We included all cases, not arbitrarily, that met the criteria for this retrospective exploratory study. That is, children (age range, from 1 day to 2 years) were enrolled in this study, and patients were administered sevoflurane at a concentration from 0.5% to 2%. Cases were excluded from the study if neurological abnormalities were identified with the overall diagnosis for the patient. Preterm infants were not included, because EEG of premature infants have the different EEG patterns. No patients received any premedications. A total of 62 cases were included, approximately meeting the requirements for statistical significance with 0.05 alpha error and 0.1 beta error, based on power analysis regarding a 20% difference between groups as clinically relevant.

Children were divided into four groups according to age: Group 1 (neonates), <1 month old; Group 2, 1–2 months old (31–91 days, <3 months); Group 3, 3–5 months old (92–183 days, <6 months); and Group 4, 6 months to 2 years old (184–1095 days, younger than 3 years).

2.2. Procedure and data acquisition

Anesthesia was induced by the inhalation of sevoflurane, then maintained using sevoflurane and fentanyl and/or caudal block with an adequate dosage of rocuronium for muscle relaxation. Mono-polar output signals from electrodes FP_1 (with the left ear lobe [A1] as the reference electrode) on an EEG monitor (EEG telemeter; GE Marquette, Tokyo, Japan) equipped with analog output (50 μV/1 V) were filtered at 0.5–50 Hz (time constant set to 0.3 s), and digitalized using an A/D converter REX5054B (PCMCIA card; Ratoc, Osaka, Japan), with a precision of 12 bits and 512 Hz. Signals were recorded using BSA version 3.22 software (Bispectrum Analyzer) developed by Hagihira throughout anesthesia [7]. Overshoot noise or spike noise, caused by events such as electric cautery, can be detected by this "BSA software". Finally, we manually checked the noise in the EEG records, before analysis. Contact impedance of each electrode was measured routinely before recording EEG with an impedance meter, and electrode impedance was confirmed to be <5000 Ω.

We saved the data on anesthetic concentrations in exhalation gas from a gas-monitoring device (Capnomac-ultima, Datex, Finland) using personal data-logging software (GasMon) developed by Hagihira, every 10 s. At four time points of different anesthetic end-expiratory concentrations (0.5%, 1%, 1.5% and 2%), corresponding EEG signals were retrospectively extracted for detailed analysis. Each time point was chosen when the targeted anesthetic end-expiratory concentration (equilibrium points of 0.5%, 1%, 1.5% and 2%) was maintained for 10 min.

2.3. Data processing

EEG signals were analyzed offline using BSA software and MATLAB software version 6.5.1 (MathWorks, MA, USA). Signals lasting 1 min without artifacts were used for analysis, and were divided to epochs of 2-s length. BSA software also calculated burst suppression ratio (BSR; with burst suppression defined as an EEG voltage amplitude <5 μV sustained for >0.5 s, the time in a suppressed state is measured and reported as the fraction of the epoch in which the EEG is suppressed, then averaged over 60 s), 90% spectral edge frequency (SEF90; the frequency below which 90% of EEG power is located) and relative beta ratio (RBR; the log ratio of power in the two empirically derived frequency bands, log $[P_{30-47\,Hz}/P_{11-20\,Hz}]$) from the averaged power spectra in the preceding 1-min period.

Approximate entropy (ApEn) of EEG was retrospectively calculated offline on a personal computer using MATLAB software employing the previously published VisualBasic algorithm described by Bruhn et al. [2,8]. The three parameters for ApEn calculation were set at the same levels as in earlier studies to achieve optimal performance for EEG approximate entropy. That is, epoch size (N) was fixed at 1024 data (m) points (2-s EEG epoch), length of compared runs of data (m) was 2, and the noise level (r) was set as 20% of the standard deviation (SD) for the 1024 samples. ApEn was averaged during these 1-min data samples.

2.4. Statistical analysis

Electroencephalographic changes between 0.5% and 2% sevoflurane anesthesia were examined using the paired t-test. Effects of sevoflurane concentration and age on EEG were analyzed by two-way analysis of variance (ANOVA) with repeated measures, where one repeated measured influence factor was the sevoflurane concentration ('within-subjects effect'), and one between factor was age group ('between-subjects effect'). When a difference was observed between the age groups, the Scheffe's F test was used for multiple comparisons. Values of $p < 0.05$ were considered statistically significant. Data are expressed as mean and SD. Statistical comparisons were analyzed using StatView version II software (SAS Institute, NC, USA).

3. Results

Table 1 shows background information for patients, including the disease and the duration of anesthesia and surgery in each group. Caudal block was used together with general anesthesia in 11 cases. Mean (SD) fentanyl dosage used for anesthesia was 10.7 (4.2) μg kg^{-1}.

Table 2 shows electroencephalographic changes between 0.5% and 2% sevoflurane anesthesia in each group. In Group 4, obvious changes were seen in SEF90, BSR, RBR and ApEn along with changes in sevoflurane concentration from 0.5% to 2% (from 14.3 (2.7) Hz to 8.2 (3.8) Hz, from 0.0 to 0.32 (0.36), from −1.58 (0.14) to −1.10 (0.15), and from 0.56 (0.25) to 0.24 (0.25) respectively; $p < 0.05$ each). On the other hand, these processed EEG parameters in neonates (Group 1) and infants <3 months old (Group 2) showed few changes under sevoflurane concentrations between 0.5% and 2%.

The respective changes in EEG processed parameters (SEF90, RBR, BSR and ApEn) with increasing concentrations of sevoflurane (0.5–2%) in the four different age groups are shown in Fig. 1. Sevoflurane concentration significantly influenced all EEG processed parameters, according to repeated-measures ANOVA ($p < 0.05$). Concerning the influence of age on EEG, significant differences were seen in SEF90, RBR and BSR ($p < 0.05$).

In Fig. 2, relationships between the EEG parameters (SEF90, RBR, BSR and ApEn) and age, with the different sevoflurane concentrations, are superimposed for every EEG parameter. For patients younger than about 100 days, SEF90 seemed low even under light anesthesia with 0.5% sevoflurane. Furthermore, RBR was large in