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A retrospective study of electroencephalography burst suppression in children undergoing general anesthesia

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ABSTRACT

Importance: In children, anesthesia dosages are based on population pharmacokinetics and patient hemodynamics rather than patient-specific brain activity. Brain function is highly susceptible to the effects of anesthetics.

Objective: The primary objective of this retrospective pilot study was to assess the prevalence of electroencephalography (EEG) burst suppression—a sign of deep anesthesia—in children undergoing general anesthesia.

Methods: We analyzed EEG in patients aged 1–36 months who received sevoflurane or propofol as the primary anesthetic. Patient enrollment was stratified into two age groups: 1–12 months and 13–36 months. Burst suppression (voltage ≤ 5.0 mV, lasting > 0.5 seconds) was characterized by occurrence over anesthesia time. Associations with patient demographics and anesthetics were determined.

Results: In total, 54 patients (33 males and 21 females) were included in the study [age 11.0 (5.0–19.5) months; weight 9.2 (6.5–11.0) kg]. The total prevalence of burst suppression was 56% (30/54). Thirty-three percent of patients experienced burst suppression during the surgical phase. The greatest proportion of burst suppression occurred during the induction phase. More burst suppression event occurrences (18/30) were observed in the patient under sevoflurane anesthesia ($P = 0.024$). Virtually all patients who received propofol boluses had burst suppression ($P = 0.033$). More burst suppression occurred in patients with hypotension ($P < 0.001$). During the surgical phase, a younger age was associated with more burst suppression ($P = 0.002$).

Interpretation: EEG burst suppression was associated with younger age, inhalation anesthetics, propofol bolus, and lower arterial pressure.

KEYWORDS
Electroencephalography (EEG), Burst suppression, General anesthesia, Children

INTRODUCTION

In June 2016, the U.S. Food & Drug Administration issued a warning to the pediatric medical community that receiving anesthesia and sedation in children younger than 3 years old can cause adverse neurodevelopmental outcomes.[1] This warning about the neurotoxicity of anesthetics is based on compelling experimental evidence that immature animals receiving anesthesia showed subsequent cognitive and behavioral impairment. The risk of nervous system damage is related to the dose and duration of the anesthetics. The higher the dose of the anesthetic, the longer the anesthetized state lasts, and the higher the risk of damage.[2-6]

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In children, anesthesia dosages are based on pharmacokinetic models and hemodynamic monitoring, neither of which can monitor patient-specific brain responses to anesthetics. Therefore, some patients likely receive more anesthetics than surgery requires. Electroencephalography (EEG) has been useful to assess the effects of anesthesia on brain neural activity.[7] Burst suppression indicates deep anesthesia and is common during sevoflurane anesthesia in young children.[8-10] Burst suppression is recognized as periods longer than 0.50 s during which the EEG does not exceed approximately +5.0 mV.[11] The purpose of this pilot study was to retrospectively determine the prevalence of burst suppression in infants and young children under general anesthesia with propofol or sevoflurane as measured by Sedline EEG monitoring (Masimo Corporation, Irvine, CA), a portable 4-channel EEG designed for operating rooms with noise filtering, graphical display, and data storage to permit offline analysis of raw EEG. We also analyzed whether any demographic and anesthesia variables were associated with burst suppression.

METHODS

Ethical approval

The study protocol was approved by the Ethics Committee of Beijing Children's Hospital, Capital Medical University (2020-Z-033). The informed consent was waived due to the retrospective nature of the study. The study was registered with the Chinese Clinical Trial Registry under the number ChiCTR2000033427.

Patient enrollment

We reviewed our database of patients who underwent general anesthesia and simultaneous EEG recordings collected between September 1, 2019 and April 30, 2020. The inclusion criteria were as follows: (1) 1–36 months of age; (2) postmenstrual age (PMA) ≥ 37 weeks on the day of study; (3) anesthesia maintained with sevoflurane or propofol; and (4) no premedication. The exclusion criteria were as follows: (1) cardiac and emergency procedures; (2) structural brain or cranial malformations; (3) a history of abnormal EEG or severe neurologic disease; and (4) incomplete EEG recordings. All patients had intravenous (IV) access before anesthesia and received IV induction. After intubation, sevoflurane or propofol and remifentanil were initiated. IV opioids were converted to fentanyl equivalent (μg/kg). Due to expected age-dependent changes in EEG under general anesthesia, patient enrollment was stratified into two age groups: 1–12 months and 13–36 months.[12,13]

Data collection

EEG data were downloaded with MICT (Masimo Instrument Configuration Tool, Masimo Corporation, Irvine, CA) software and manually reviewed. Demographic information and physiological data were collected from the electronic medical records system (Docare, MedicalSystem Company). Four anesthesia phases were defined as follows: (1) induction: from the beginning of anesthesia administration to intubation; (2) preincision: from intubation to incision; (3) surgical phase: from incision to the last stitch; and (4) postsurgery: from the last stitch until the patient awakened enough to be extubated or had the laryngeal mask removed. Propofol boluses (yes/no) were recorded for the entire case. The severity of hypotension was classified based on prior studies as follows: mild—systolic arterial pressure (SAP) = 51–60 mmHg, mean arterial pressure (MAP) = 36–45 mmHg if 0–6 months, and SA*P* = 61–70 mmHg, MA*P* = 41–50 mmHg if > 6 months; moderate—SA*P* = 41–50 mmHg, MA*P* = 26–35 mmHg if 0–6 months, and SA*P* = 51–60 mmHg, MA*P* = 31–40 mmHg if > 6 months; and severe—SA*P* < 41 mmHg, MA*P* < 26 mmHg if 0–6 months, and SA*P* < 51 mmHg, MA*P* < 31 mmHg if > 6 months, lasting > 3 minutes.[14] Physiological (PHILIPS IntelliVue MP50, Germany) data represent average values during these phases.

Statistical analysis

The prevalence of burst suppression was reported for the entire anesthesia time as well as for each phase (i.e., induction, preincision, surgical, and postsurgery). Histograms and the Kolmogorov-Smirnov test were used to assess normality. Continuous variables are expressed as the mean ± standard deviation or median (interquartile interval), as appropriate. To assess the differences between the two groups, the *t* test was used for normally distributed continuous variables, whereas the Mann-Whitney *U* test was used for nonnormally distributed continuous variables. For categorical variables, the χ^2 test and Fisher's exact test were used. The Kruskal–Wallis test was used for multiple comparisons, and the Bonferroni correction was used to adjust the significance threshold for the post hoc comparisons. Statistics were performed using SPSS 19.0, and we selected a significance threshold of $P < 0.05$ for comparisons between groups.

RESULTS

Fifty-eight patients were identified. EEG recording files of 4 patients were incomplete or unavailable, resulting in 54 evaluable patients (Table 1). The patient's age and weight were 11.0 (5.0–19.5) months and 9.2 (6.5–11.0) kg, respectively. Fifty-six percent (30/54) of patients had burst suppression. There were no differences between patients with burst suppression and without burst suppression in age, sex, weight, or American Society of Anesthesiologists score. More burst suppression event occurrences (18/30) were observed in the patient under sevoflurane anesthesia ($P = 0.024$). Virtually all patients who received propofol boluses had burst suppression ($P = 0.033$). The occurrence

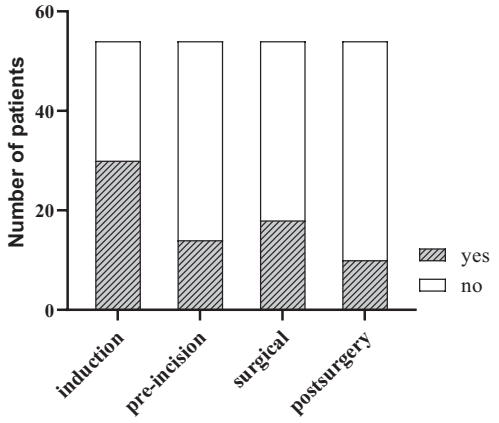

FIGURE 1 Number of patients with burst suppression during four phases. Induction phase: 30 patients experienced burst suppression. The occurrence of burst suppression was the highest. Preincision phase: 14 patients experienced burst suppression. Surgical phase: 18 patients experienced burst suppression. Postsurgery phase: 10 patients experienced burst suppression.

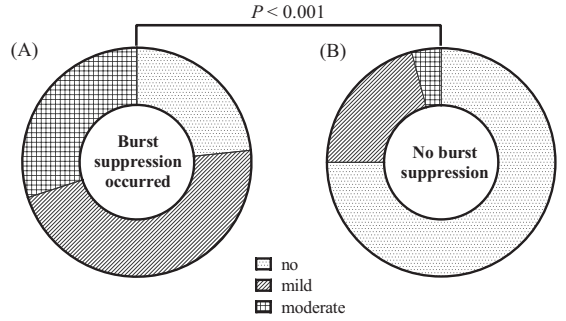

FIGURE 2 Prevalence of mild, moderate, and no hypotension in patients with and without burst suppression. (A) Prevalence of mild, moderate, and no hypotension in patients with burst suppression during anesthesia time. A total of 30 patients had burst suppression, 7 patients had no hypotension, 14 patients had mild hypotension, and another 9 patients had moderate hypotension. (B) Prevalence of mild, moderate, and no hypotension in the patient without burst suppression during anesthesia time. A total of 24 patients had no burst suppression, 18 patients had no hypotension, 5 patients had mild hypotension, and 1 patient had moderate hypotension. After χ^2 test, patients with hypotension were more likely to have burst suppression (77% *vs*. 25%, $P < 0.001$).

of burst suppression changed over anesthesia phases and was the highest during the induction phase (Figure 1). Accordingly, exposure to propofol boluses or induction anesthetics was associated with burst suppression. The remaining demographics and anesthesia factors did not differ significantly between patients with and without burst suppression.

During all phases, no severe hypotension was detected. In 30 patients with burst suppression, a total of 23 patients (77%) experienced mild hypotension ($n = 14$) and moderate hypertension ($n = 9$) during the anesthesia time (Figure 2A). In 24 patients without burst suppression, a total of six patients (25%) experienced mild hypotension ($n = 5$) and moderate hypertension ($n = 1$) during the anesthesia time (Figure 2B). More burst suppression occurred in patients with mild or moderate hypotension than in patients without hypotension ($P < 0.001$).

During the surgical phase, 33% (18/54) of patients had burst suppression, which was less than the overall incidence (Table 2). The patients with burst suppression were younger and had lower body weights than patients without burst suppression ($P = 0.002$, $P = 0.042$, respectively). More burst suppression occurrences (14/18) were observed in the patients aged 1–12 months old ($P = 0.024$). There was no significant difference in end-tidal sevoflurane concentration nor propofol infusion rate between patients with and without burst suppression during the maintenance phase (Table 3). Briefly, burst suppression during the surgical phase was associated with younger age.

DISCUSSION

In this pilot study, burst suppression events occurred in 56% of children 1–36 months of age undergoing surgery using sevoflurane or propofol and remifentanil infusion maintenance anesthesia. The prevalence was similar to data reported by Koch et al,[15] who observed that 52% of children had burst suppression during general anesthesia. We demonstrated a significant difference in the prevalence of burst suppression between sevoflurane and propofol anesthesia (72% *vs*. 41%). Some previous studies observed that sevoflurane and propofol had different mechanisms of action on the brain and effects on EEG; propofol predominantly produces slow delta and alpha oscillations, while sevoflurane produces evenly distributed effects from the slow oscillation range through the alpha range;[16-18] thus we hypothesis that different mechanisms of action lead to different incidences of burst suppression in children. Furthermore, the propofol and sevoflurane could reduce cerebral blood flow (CBF),[19] and a study showed that sevoflurane could reduce CBF in children younger than 6 months, meanwhile, a significant decrease in MAP was observed which was associated with a significant variation in CBF velocity, this population is more sensitive to MAP decrease than older children because of a lower limit of cerebral autoregulation, and this limit may be 38 mmHg with sevoflurane anesthesia.[20] Beyond the range of autoregulation, CBF becomes more pressure-dependent. The lower the blood pressure, the lower the CBF, and the brain becomes ischemic.[21] Cerebral hypoxic and ischemic are associated with burst suppression.[22,23] According to the classification criteria of hypotension in our study, the limit MAP of 38 mmHg can be considered mild hypotension. Similarly, we observed that patients with hypotension experienced more burst suppression events throughout the entire anesthesia time, possibly because when cerebral autoregulation was impaired, the lower blood pressure had a more profound effect on decreasing cerebral perfusion, leading to burst suppression. The patients who received propofol boluses had more possibilities to develop burst

TABLE 1 Demographics and anesthesia factors in patients with burst suppression and without burst suppression during total anesthesia phases

Factors	All Patients (*n* = 54)	With burst suppression (*n* = 30)	Without burst suppression (*n* = 24)	*P*
Age (months)	11.0 (5.0–19.5)	12.5 (2.8–20.0)	10.0 (5.3–20.3)	0.862[†]
1–12	30 (56)	15 (50)	15 (63)	0.358[‡]
13–36	24 (44)	15 (50)	9 (37)	
Weight (kg)	9.2 (6.5–11.0)	9.6 (5.3–11.0)	9.0 (8.0–11.0)	0.479[§]
Sex				
Male	33 (61)	18 (60)	15 (62)	0.851[‡]
Female	21 (39)	12 (40)	9 (38)	
ASA score				
ASA I	17 (31)	8 (27)	9 (37)	0.394[‡]
ASA II	37 (69)	22 (73)	15 (63)	
Induction drugs				
Propofol (mg/kg)	1.7 ± 0.5	1.7 ± 0.5	1.7 ± 0.5	0.840[§]
Fentanyl (μg/kg)	1.3 ± 0.5	1.3 ± 0.6	1.4 ± 0.5	0.649[§]
Muscle relaxant given	52 (96)	30 (100)	22 (92)	1.000[‡]
Airway management				
Endotracheal tube	47 (87)	28 (93)	19 (79)	0.221[‡]
Laryngeal mask	7 (13)	2 (7)	5 (21)	
Maintenance				
Sevoflurane	25 (46)	18 (60)	7 (29)	0.024[‡]
Propofol	29 (54)	12 (40)	17 (71)	
Propofol bolus	9 (17)	8 (27)	1 (4)	0.033
Anesthesia time (min)	135 (103–185)	155 (108–224)	116 (89–163)	0.337[†]

Data are presented as *n* (%) or median (interquartile range) or mean ± SD. ASA, American Society of Anesthesiologists. [†]Mann-Whitney *U* test. [‡]χ^2 tests and Fisher exact tests. [§]Student's *t* test.

TABLE 2 Demographics and anesthesia factors in patients with and without burst suppression during surgical phase

Factors	All Patients (*n* = 54)	With burst suppression (*n* = 18)	Without burst suppression (*n* = 36)	*P*
Age (months)	11.0 (5.0–19.5)	5.0 (2.0–14.5)	14.5 (6.5–23.0)	0.002[†]
1–12	30 (56)	14 (78)	16 (44)	0.024[‡]
13–36	24 (44)	4 (22)	20 (56)	
Weight (kg)	9.2 (6.5–11.0)	6.7 (5.0–9.9)	9.9 (8.5–11.6)	0.042[§]
Sex				
Male	33 (61)	10 (56)	23 (64)	0.578[‡]
Female	21 (39)	8 (44)	13 (36)	
ASA score				
ASA I	17 (31)	3 (27)	14 (37)	0.127[‡]
ASA II	37 (69)	15 (73)	22 (63)	
Airway management				
Endotracheal tube	47 (87)	17 (94)	30 (83)	0.403[‡]
Laryngeal mask	7 (13)	1 (6)	6 (17)	
Maintenance				
Sevoflurane	25 (46)	12 (67)	13 (36)	0.034[‡]
Propofol	29 (54)	6 (33)	23 (64)	

Data are presented as *n* (%) or median (interquartile range). ASA, American Society of Anesthesiologists. [†]Mann-Whitney *U* test. [‡]χ^2 tests and Fisher exact tests was used. [§]Student's *t* test.

TABLE 3 End-tidal sevoflurane concentration, propofol and remifentanil infusion rate in patients with and without burst suppression during surgical phase

Anesthetics	With burst suppression (n = 18)	Without burst suppression (n = 36)	P
Sevoflurane maintenance (n = 25)	12	13	
End-tidal sevoflurane (%)	2.38 ± 0.42	2.52 ± 0.78	0.722
Remifentanil rate [μg/(kg · min)]	0.33 ± 0.02	0.32 ± 0.02	0.316
Propofol maintenance (n = 29)	6	23	
Propofol rate [μg/(kg · min)]	167.18 ± 2.26	166.81 ± 5.87	0.898
Remifentanil rate [μg/(kg · min)]	0.33 ± 0.02	0.33 ± 0.03	0.953

Values are presented as n or mean ± SD. P value was calculated using Student's t test.

suppression, which may be attributed to the administration of high doses of propofol to achieve deeper anesthesia and adapt the level of nociceptive stimulation during surgery. Administration of an additional propofol bolus, either before or after intubation, can result in either enhancement of the slow oscillation or the conversion of the slow oscillation into burst suppression.[7,24] Overall, propofol boluses, use of sevoflurane, and lower arterial pressure during anesthesia were associated with burst suppression events.

Most patients experienced burst suppression during the induction phase (Figure 1). There was no significant difference in age between the patients with burst suppression and those without burst suppression during the induction phase. Patients were more likely to develop burst suppression after rapid injections of intravenous induction anesthetics. Therefore, if we analyzed the overall factors of all four phases, it could obscure the difference in age between the patients with burst suppression and those without burst suppression during the surgical phase, which is a phase with relatively appropriate anesthesia. When the patients were stratified by the burst suppression occurrence of the surgical phase, the prevalence of burst suppression was 33% and less than the total incidence. In other words, some patients experienced burst suppression only during the induction phase. During the surgical phase, there were significant differences in age and weight between the patients with burst suppression and without burst suppression, and patients aged 1–12 months experienced more burst suppression events. These changes could be explained by several structural and functional neurobiological factors associated with age. Neurodevelopmental processes that occur throughout childhood, including thalamocortical development, may underlie age-dependent changes in electroencephalogram power and coherence during anesthesia.[25] We suggest that patients under 1 year old with an immature brain are more vulnerable to the effects of the anesthetic. The mechanisms underlying burst suppression are currently poorly understood. Recent modeling studies suggest that a decrease in cerebral metabolic rate, coupled with the stabilizing properties of ATP-gated potassium channels, leads to the characteristic epochs of suppression.[26] In summary, the rapid administration of a higher dose of anesthetics has a more profound effect on the brains of children, which should be avoided as much as possible. During anesthesia maintenance, younger patients have a greater chance of experiencing burst suppression events.

Our pilot study was not designed to evaluate determinants of burst suppression on EEG or powered to adjust for confounding with secondary analyses. As a result, the relationship between burst suppression and perioperative factors must be explained very carefully, as they may suffer from type 1 errors and confounding. For example, burst suppression could be due to an increased depth of anesthesia from propofol boluses, thus causing hypotension. We need more samples for regression analysis in future studies.

In summary, in all anesthesia phases, burst suppression events are common in children, especially when hypotension and propofol boluses occur during general anesthesia using sevoflurane for maintenance anesthesia. During the surgical phase, younger age is associated with burst suppression events.

CONFLICT OF INTEREST

All authors declare that they have no competing interests.

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