Emergence Delirium in children and intraoperative Electroencephalogram Burst Suppression – findings from a prospective, observational study

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Abstract

Background Emergence-delirium is the most frequent brain dysfunction in children recovering from general anaesthesia, though the pathophysiological background remains unclear. The presented study analysed an association between emergence delirium and intraoperative burst suppression activity in the electroencephalogram, a period of very deep hypnosis during general anaesthesia. Methods In this prospective, observational cohort study at the Charité - university hospital in Berlin / Germany children aged 0.5 to 8 years old, undergoing planned surgery, were included between September 2015 and February 2017. Intraoperative bi-frontal electroencephalogram monitoring were recorded. Occurrence and duration of burst suppression periods were visually analysed. Emergence delirium was assessed with the Pediatric Assessment of Emergence Delirium Score. Results From 97 children being analysed within this study, 40 children developed emergence delirium, and 57 children did not. Overall 52% of the children displayed intraoperative burst suppression periods; however, occurrence and duration of burst suppression (Emergence delirium group 55% / 261+462sec vs. Non-emergence delirium group 49% / 318+531sec) did not differ in between both groups. Conclusions Our data reveal no correlation between the occurrence and duration of intraoperative burst suppression activity and the incidence of emergence delirium. Burst suppression occurrence is frequent; however, it does not seem to have an unfavourable impact on cerebral function at emergence from general anaesthesia in children.

Background

Postoperative delirium is the most frequent brain dysfunction in patients recovering from general anaesthesia, mainly seen in preschool children as well as in elderly patients (1, 2).

In preschool children, postoperative delirium occurs during emergence from anaesthesia during stay in the post-anaesthesiological care unit (emergence delirium) and presents with acute disorientation, crying, agitation and missing response to the surrounding (3). Emergence delirium (ED) in children is mostly self-limited and has a benign course; however, it increases the risk of self-injury and induces stress to the medical staff as well as to the caregivers. The implications to long-term outcomes in cognitive function in children is still under discussion.

Pediatric anaesthesiologists are concerned, since it has been proposed that anaesthetic agents may be neurotoxic to the developing brain (4, 5).

In children elevated concentrations of the anaesthetic agent Sevoflurane cause an increase of epileptiform discharges during anaesthesia induction (6). In a former EEG analysis - focusing on the period of anaesthesia induction in the same patients group presented here - we had shown that the occurrence of interictal, epileptiform discharges, is positively related to the development of ED (7). In a study from Martin and colleagues, analyzing multichannel EEG characteristics in 12 children, from whom 5 developed ED, ED was associated with arousal from an indeterminate state (low voltage / fast frequency EEG activity) and an increased frontal cortical functional connectivity (8). All these EEG characteristics - interictal, epileptiform discharges; indeterminate state; increased frontal cortical functional connectivity - are related to a cortical state of hyperexcitability.

On the other hand, elevated concentration of anaesthetic agents will induce deeper level of sedation and periods of Burst Suppression in the EEG during general anaesthesia. It has been proved, that periods of Burst Suppression and deep Index level of anaesthesia in elderly patients trigger postoperative delirium (9-12). In contrast in children, two studies analyzing Index level of anaesthesia and its relationship with the occurrence of ED did not find this correlation (13, 14). But a study focusing on intraoperative Burst Suppression periods and the correlation with ED in children is still failing.

The aim of this study is to analyses, if the occurrence / duration of Burst Suppression periods during general anaesthesia is related to the development of ED in children.

Methods

This prospective, observational cohort study (NCT02481999) was approved by our local ethics committee on 12 March 2015 (Ethik committee Charité, University Medicine of Berlin / Chairperson Prof. Dr. R. Seeland / EA2/027/15). Written informed consent of either parents or legal proxies was obtained according to the Declaration of Helsinki. We included children aged 0.5 – 8 years, undergoing elective surgery with a planned duration of ≥ 60min at our University hospital – Charité / Berlin. Between September 8, 2015 and February 22, 2017 parents or legal proxies of the child were approached by study staff members during stay in the preoperative evaluation center on the day prior to surgery. Exclusion criteria comprised any history of neurological or psychiatric diseases, any signs of delayed development in the child, isolation required because of multiresistant bacteria, inability of the parents to speak, read or understand the German language, as well as concurrent enrollment in another study. After obtaining written informed consent of the parents, 189 children participated in the study.

The *a priori* primary outcome was ED assessed during stay in the recovery room with the Pediatric Assessment of Emergence Delirium (PAED) Score (15). Values of at least 10 were considered as ED.

Secondary outcomes, related to frontal EEG recordings were depth of anaesthesia and burst suppression duration.

Oral premedication with midazolam was administered in all children. Children were anaesthetised with either Propofol or Sevoflurane as decided by the anaesthesiologist in charge. Standard monitoring included non-invasive blood pressure, electrocardiogram and pulse oximetry. Patients received i.v. Propofol (assessed as mg kg^{-1} body weight) or mask induction / maintenance with Sevoflurane (assessed as endtidal concentrations et Vol %). Dosage of Sevoflurane and Propofol was given according to clinical needs and chosen by the anaesthesiologist in charge. Remifentanil was administered as analgesic agent during the induction period in all children, according to clinical needs. If muscle relaxation was needed, Cis-atracurium was administered, adapted to body weight. Before end of surgery, children received Metamizol or Paracetamol and / or Piritramid as analgesia medication. Some children also received regional anaesthesia. The complete anaesthetic procedure and medication were outside of the studies scope.

ED assessment

ED was assessed according to the PAED Score. From admission to the recovery room until discharge, the PAED score was determined 1min after extubation, at arrival in the recovery room, 5min, 10min, 15min, 30min, 45min, and 60min during stay in the recovery room and at discharge from the recovery room by a member of the study staff sitting next to the child. Values $\geq$ 10 were considered emergence delirium (15). The “Faces Legs Activity Cry Consolability Pain Scale” was used to determine pain events (16). Richmond Agitation Sedation Scale score was used to assess the level of consciousness (17). PAED score was only included in the analysis if the Richmond Agitation Sedation Scale score was above -2 and if it was unlikely that pain was triggering agitated behavior. If inadequate behavior during stay in the recovery room improved after pain-medication, these periods of agitated behavior were not classified as ED. If a member of the study team was unable to take the PAED score in the recovery room, these corresponding children were excluded from further evaluation.

EEG recording and analysis

Bi-frontal EEGs were obtained with the Narcotrend Monitor (MT Monitor Technik, Bad Bramstedt, Germany). EEG was recorded continuously from baseline before start of anaesthesia until the end of stay in the recovery room. After skin preparation with alcohol four electrodes (Ambu BlueSensor, Bad Nauheim Germany) were placed on the patients’ forehead at positions Fz, F7 and F8, with a reference at Fp2. The impedances were kept below 8kOhm, differences between electrodes were less than 2kOhm. During the EEG recording, event markers comprising “start of anaesthesia”, “intubation”, “operation” and “extubation” and “recovery room” were placed. “Start of anaesthesia” was defined as the time-point when the anaesthesiologist began to administer the anaesthetic agent, i.e., either Sevoflurane, Propofol or a mixture of both. “Intubation” was defined as the time point, when the anaesthesiologist in charge began to intubate the child. “Operation” indicated a time point within 15 min to 30 min after intubation of stable surgery and anaesthesia, without severe pain events or intraoperative bolus application of Propofol. “Extubation” was defined as the time point, when the anaesthesiologist in charge extubated the child.

Visual EEG analysis (EEG viewer software: 50µV-100µV and 1s/div) was performed from the time point of “start of anaesthesia” until “extubation”. Raw EEG was analysed by an expert (S. K., neurologist with specialization in clinical neurophysiology and EEG) blinded to the outcome ED, the medication patients received and further clinical data. The presence of Burst Suppression periods was validated by a second expert (C.P. pediatric neurologist with specialization in electroencephalography in children). Short periods (< 5 min within the total anaesthesia procedure) with artifacts (muscle, eyelid, and electricity) were excluded from any further analysis. If persistent artifacts or repeating artifacts were seen, these EEGs were excluded from further analysis.

Burst Suppression periods were assessed by visual inspection of the raw EEG (EEG viewer software: 50µV and 1s/div). Burst Suppression segments were included if duration of isoelectric line exceeded 2 seconds. Duration of intraoperative Burst Suppression was calculated from start of the first isoelectric line segment until the end of the last isoelectric line. Isoelectric line is classified as an EEG activity below 5µV (18). Additionally, we calculated the duration of the isoelectric line activity by distracting the time duration of the intermittent burst activity. Duration of the isoelectric line is the sum of all periods of isoelectric line presented in the raw EEG.

Statistical Analysis

The present study was designed as a prospective, observational study. Statistical analysis was performed using SPSS, version 23, copyright SPSS, Inc., Chicago, IL 60606, USA. Data are presented as means ± SD, in case of unbalanced data distribution as medians (IQR 25/75) or as frequencies (%). For nominal data, statistical analysis was performed by Chi-square test from Pearson. Numerical data were analysed using the Mann-Whitney-U test for non-parametric data. To determine the impact of age, anaesthetic medication, burst suppression and depth of anaesthesia on the incidence of ED, we performed a univariate logistic regression. Odds Ratio with 95% confidence intervals and corresponding p-values were calculated for each risk factor. Statistical significance was assumed at $p<0.05$.

The statistical analysis plan was made prior to data assessment. To calculate the sample size needed, we postulated an ED incidence of 10.5% (from a pilot study in our department 2013 (NCT02358278), resulting in a 10.5% incidence of ED in children aged 0-14 years) and an increased risk to develop ED with an increase in depth of anaesthesia and the occurrence of burst suppression periods. 470 patients were initially planned to be included in this study. An interim analysis was planned (after approximately 1/3 – 1/2 of the total planned sample size) with recalculation of the initial sample size calculation, to adopt the study procedure, when the initial assumptions would differ strongly. At the interim analysis the ED incidence rate were distinctly higher. We re-run the sample size calculation taking into account the new incidence rate of 41%. Initially, the study was planned for an odds ratio of 1.6 with an ED incidence rate of 10.5% and a R^2 of the other covariates of 0.2 resulting into a sample size of 470 children with a power of 80%. Considering the new incidence rate of 41% and without changes of the other parameters, we achieve a power of 80% with 97 children and an odds ratio of 2.1.

Results

A total of 412 children were screened at the preoperative evaluation center. 189 children have been included in this prospective observational study. Finally, intraoperative EEG data analysis could be performed from “start of anaesthesia” until “extubation” in 97 children (Figure s1, Flow chart).

From these 97 children 40 (41%) children developed Emergence delirium (ED group) and 57 (59%) did not (Non-ED group). Patients' characteristics are presented in Table 1. ED patients were significantly younger of age (P = 0.042).

51.5% (n=50) of all children developed Burst Suppression periods during anaesthesia procedure, while the remaining 48.5% (n=47) did not. Burst Suppression started within ~ 4min after "start of anaesthesia" (223 sec (IQR 123 to 412), and ended ~ 11min after "start of anaesthesia" (676 sec (IQR 417 to 1413)). Burst Suppression duration was 294 ± 502 sec and isoelectric line duration was median 179 ± 375 sec.

Occurrence and duration of Burst Suppression as well as duration of isoelectric line did not differ between ED patients and Non ED patients (Table 2).

Calculation of univariate logistic regression for confounders considered as risk factors triggering ED [age (months), anaesthetic agent given at induction / maintenance (Sevoflurane vs. Propofol), anaesthesia duration (min), and EEG suppression (occurrence, duration (sec)] only age (P = 0.046) and anaesthesia duration (P = 0.025) showed a significant association (Table 3).

Discussion

Discussion

We show that occurrence and duration of Burst Suppression in children aged 0.5 – 8 years is not associated with the incidence of ED. Overall, Burst Suppression occurred in about 52% of all children aged 0.5 – 8 years, appearing mainly within the first ~ 4 min after application of the anaesthetic agents at start of anaesthesia.

Delirium is the most frequent brain dysfunction seen after anaesthesia procedures, mainly occurring in elderly patients and preschool children (19). In elderly patients it has been shown, that periods of Burst Suppression and deep Index level of anaesthesia is related to postoperative Delirium (9-12), however, in two studies analyzing Index level of anaesthesia in children a relationship with the occurrence of ED was not found (13, 14).

Faulk and colleagues were examining 400 children aged 1 – 12 years, scheduled for dental procedures. Deep hypnosis was defined as a level of BIS Index reading of less than "45". They did not find a correlation between deep hypnosis and the occurrence of ED (13).

Frederick and colleagues, undertaking a randomized controlled trial including 40 children aged 2-8 years, randomized in a low-normal group (BIS Index values 40-45) versus high-normal group (BIS-Index values

55-60), found no significant effect of deep versus light anaesthesia and the incidence of ED (14).

The underlying hypothesis that deep Index levels of anaesthesia in children might be related to ED, were not confirmed. This is in line with our data, where we found that the occurrence and duration of Burst Suppression activity was not related to ED in children. Burst suppression segments in the EEG are characterized by an isoelectric line interrupted by burst of a-activity, indicating a very deep state of unconsciousness with a marked reduction in brain metabolism (20). The occurrence of Burst Suppression during general anaesthesia in elderly patients is positively correlated to the incidence of postoperative delirium, hence one might propose, that elderly patients struggle to restore preoperative brain metabolism level. In contrast, in children neuronal hyperexcitability – as seen by occurrence of interictal, epileptiform discharges during anaesthesia induction or increased frontal connectivity during emergence of general anaesthesia – has been related to ED (7, 8). These striking differences in EEG activity related to delirium in children compared with elderly patients extends into its clinical presentation, where delirious children present with crying, agitation, disorientation and altered response to their surroundings, whereas elderly patients present primarily with a hypoactive form of delirium.

Additionally, we found that children display Burst Suppression periods to a lower extent during general anaesthesia procedures (52%) compared with adults and older patients (aged 62 $\pm$ 14 years; 89%) (12). Our finding is supported by a study showing, that the risk to develop intraoperative Burst Suppression activity is increasing with age (21).

Limitations

In our study, children receiving a mask induction with Sevoflurane were significantly younger compared with children receiving an i.v. induction with Propofol, due to standard operating procedure in our clinic, trying to avoid children's discomfort during anaesthesia induction. Since younger age as well as Sevoflurane anaesthesia has been described to cause ED, this may have biased our results. However, Non-ED versus ED-group did not show a significant difference between anaesthetic agent used for induction or maintenance.

Conclusion

Intraoperative burst suppression activity in the EEG is not associated to ED in young children. Burst Suppression activity is a characteristic EEG feature of a pathological, profoundly inactivated brain, but despite its pathological character, this does not render to the occurrence of ED in children.

Abbreviations

ED Emergence delirium

EEG Electroencephalography / Electroencephalogramm

Declarations

Ethics approval and consent to participate: This prospective, observational cohort study (NCT02481999) was approved by our local ethics committee on 12 March 2015 (Ethik committee Charité, University Medicine of Berlin / Chairperson Prof. Dr. R. Seeland / EA2/027/15).

Consent for publication: Written informed consent of either parents or legal proxies was obtained according to the Declaration of Helsinki.

Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: Claudia Spies received material support by Narcotrend-Gruppe, MT Monitortechnik GmbH, Maienbaß 27, 24576 Bad Bramstedt. The authors declare no further competing interests.

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Authors' contributions: SK, SyK and CS conceived and designed the experiments. SK, AMS and LR performed the experiments. SK, AMS, LR, JR, CP, SyK and AF analysed the data. SK and CS contributed to the materials/analysis tools. SK and JR wrote the paper. All authors read and approved the final manuscript.

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Tables

Table 1 Patients' Characteristics for children with Emergence Delirium and children without Emergence Delirium. Values are median (IQR range), number (propotion) or mean ± SD.

	Non-ED Group (n=57)	ED Group (n=40)	P value
Age [months]	58 (15.75 / 78	22 (13 / 60)	0.042
Weight (kg)	17 (9.7 / 22)	11 (9.3 / 22)	n.s.
Height (cm)	107.5 (80 / 131)	86 (81.5 / 119.5)	n.s.
ASA Score (I / II / III) (%)*	46 / 11 / 0 (81 / 19 / 0)	32 / 7 / 1 (80 / 17,5 / 2,5)	n.s.
Gender male / female (%)	35 / 22 (61 / 39)	25 / 15 (62,5 / 37,5)	n.s.
Procedures (%) Cleft-lip-palate; Oral / neck surgery	6 (11)	13 (33)	n.s.
Inguinal hernia / Circumcision / Orchidopexy / Cystoscopy	15 (26)	8 (20)	n.s.
Otorhinolaryngology surgery	7 (12)	4 (10)	n.s.
Intraabdominal surgery / long procedures (>60min)	14 (25)	9 (23)	n.s.
Limb surgery / short procedures (< 60min)	15 (26)	6 (15)	n.s.
Midazolam premedication (mg/kg body weight)	0.64 ± 0.17	0.67 ± 0.18	n.s.
Induction Agent Sevoflurane / Propofol / mixed (%)	12 / 23 / 22 (21 / 41 / 39)	9 / 13 / 18 (22,5 / 32,5 / 45)	n.s.
Maintance Agent Sevoflurane / Propofol / mixed (%)	38 / 18 / 1 (67 / 32 / 2)	27 / 13 / 0 (67,5 / 32,5 / 0)	n.s.
Anaesthesia duration (min)	102 ± 71	146 ± 113	n.s.

Table 1 Patient characteristics for children without emergence delirium (Non ED group) and children with ED (ED group). Age (p=0.042) differed significantly between NonED group vs. ED group (Mann-Whitney-U Test). *ASA: American Society of Anesthesiologists.

Table 2 EEG suppression for children with Emergence Delirium and children without Emergence Delirium. Values are number (propotion) or mean ± SD.

	Non-ED Group (n=57)	ED Group (n=40)	P value
Burst suppression yes / no (%)	28 / 29 (49 / 51)	22 / 18 (55 / 45)	n.s.
Burst suppression duration (sec)	318 ± 531	261 ± 462	n.s.
Isoelectric line duration (sec)	192 ± 407	159 ± 328	n.s.

Table 2 Comparing EEG suppression during anaesthesia for children with Emergence delirium (ED group) and children without Emergence delirium (Non ED group). (Mann-Whitney-U Test). *ED: Emergence delirium.

Table 3 Confounders considered risk factors for Emergence delirium in children

Confounders	Odds ratio	95% CI lower limit	95% CI upper limit	p Value
Age (months)	0.986	0.973	1.000	0.046
Anaesthesia Induction (Sevoflurane / Propofol / mix of both)	0.691	0.275	1.737	0.432
Anaesthesia Maintenance (Sevoflurane / Propofol)	0.699	0.427	2.420	0.971
Concentration of Midazolam (mg/kg body weight)	2.886	0.253	32.867	0.393
Concentration of Remifentanil (µg/kg body weight / min)	0.465	0	798.215	0.840
Anaesthesia duration (min)	1.005	1.001	1.010	0.025
Burst suppression occurrence (yes / no)	1.266	0.563	2.848	0.569
Burst suppression duration (sec)	1	0.999	1.001	0.583

Table 3 Univariate logistic regression accounting for confounders considered risk factors triggering emergence delirium after general anaesthesia in children. Only age (months) and anaesthesia duration (min) showed a significant association.

Figures

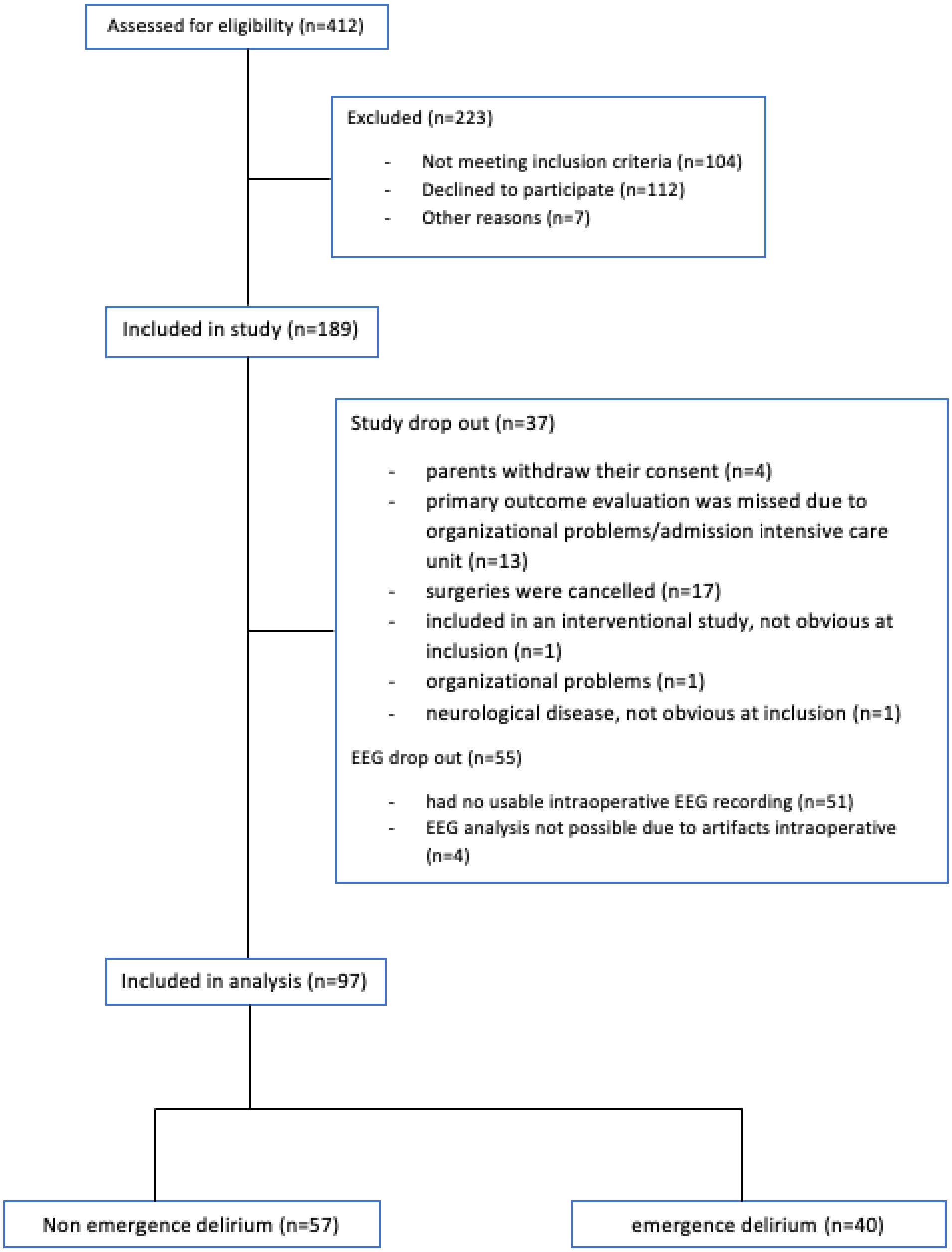

Figure 1

Flow diagram

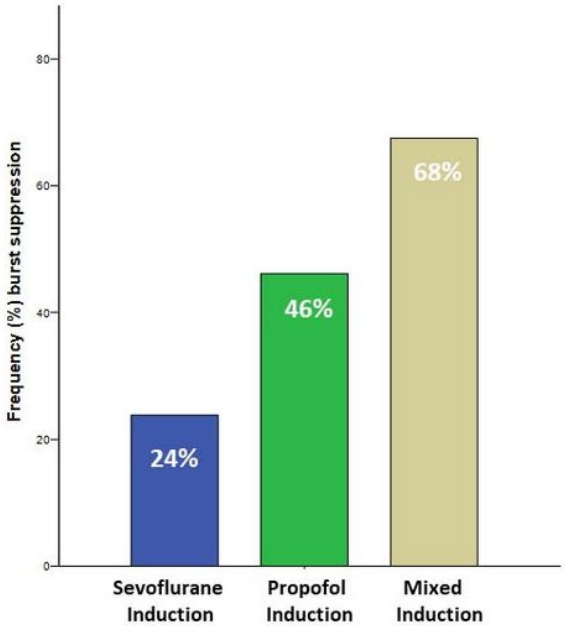

Figure 2

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