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Original Article

Paediatrics Section

Postnatal Maturation of Amplitude Integrated Electroencephalogram in Preterm SGA and Preterm AGA Neonates: A Prospective Observational Study

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ABSTRACT

Introduction: Maturation of the brain is affected by various biological and environmental factors encountered by the infant during the intensive care period in Neonatal Intensive Care Unit (NICU) due to the medical treatments, procedures, and the noisy environment that disrupts the normal brain development process. Severe neurological sequelae of preterm infants are common because of the immature central nervous system. Cerebral Function Monitor (CFM) or Amplitude integrated Electroencephalogram (a-EEG) is a device for monitoring the background neurological activity.

Aim: To assess postnatal maturation of a-EEG in clinically stable and neurologically normal preterm Small for Gestational Age (SGA) and preterm Appropriate for Gestational Age (AGA) neonates from 30 weeks 0/7 days to 34 weeks 6/7 days of gestation admitted in a tertiary care NICU at J. K. Lon Mother and Child Hospital, attached to Government Medical College, Kota.

Materials and Methods: This prospective observational study was conducted over a one year duration, from January 2020 to December 2020 on 60 preterm neonates that were admitted in NICU of a tertiary care hospital. The serial a-EEG recording was done on haemodynamically stable, included preterm neonates after taking consent, on 3rd, 7th, and 14th postnatal day of life during the course of admission. The postnatal maturation of amplitude integrated EEG of Preterm Small for Gestational Age (PSGA) neonates was compared with their Preterm Appropriate for Gestational Age (PAGA) neonates based on a validated a-EEG scoring. The analysis was done by using Statistical Package for Social Sciences (SPSS) version 21.0. Student t-test was applied.

Results: The total a-EEG scores for 3rd, 7th, and 14th day of SGA group neonates were 7.55±1.45, 7.25±1.02 and 10.22±1.05 and were delayed from the AGA group of neonates with 7.86±1.55, 8.68±1.00 and 10.62±1.01, with mean difference (95% CI), 0.30 (-0.49 to 1.13), 1.43 (0.88 to 1.97) and 0.39 (-0.15 to 0.95) respectively. Only the total a-EEG scores for day 7 were significantly delayed in SGA group.

Conclusion: All the maturation a-EEG scores of clinically stable and neurologically normal PSGA neonates was found to be significantly delayed at any point of life on postnatal day 7th of life.

Keywords: Burdjalov score, Delayed maturation, Preterm appropriate for gestational age, Preterm small for gestational age

INTRODUCTION

During the last few decades, advances in neonatal intensive care have resulted in a decrease in neonatal mortality and a dramatic increase in the survival rate of extremely low birth weight infants [1]. However, severe neurological sequelae of preterm infants are common because of the immature central nervous system [2]. Although various techniques such as cranial ultrasonography are used for neurological evaluation, EEG is one of the most useful tools for predicting neurological outcome in preterm and term infants [3].

The a-EEG is used as a bedside device for continuously assessing the cerebral electrical activity and its practical and prognostic use has been demonstrated in many studies in term and preterm infants [4-10]. CFM or a-EEG is a device for monitoring the background neurological activity.

Born at a critical period of brain development, preterm infants are a high risk for mortality and morbidity, especially neurodevelopmental impairment. Brain maturation is affected by biologic and environmental factors [10], as well as the quality and timing of experience [11], medical treatments and

the NICU environment during the intensive care period, which serves to disrupt normal brain development processes by the inappropriate experiences the infant encounters [12]. Enhancing the skills and tools of neonatal health care providers with regard to neurophysiologic monitoring will optimise the care delivered during the critical period and may contribute to improvements in long term outcomes [13].

There is a large body of literature on the use of a-EEG for prediction of prognosis of neonates with encephalopathy [14,15], and asphyxia [16,17]. A strong association between the early abnormal a-EEG and impaired neurologic outcome has been established [18-24].

There are very few studies [25-27] available on a-EEG maturation pattern in stable preterm neonates as it is difficult to decipher and also there is alteration of a-EEG patterns due to the different morbidities and preterm intracranial insults.

It was contemplated that there would be delaying of brain maturation in PSGA in comparison to PAGA neonates, and this study was designed to evaluate the a-EEG maturation pattern in PSGA neonates and compare their maturation with PAGA neonates, by using a validated a-EEG maturation scoring.

MATERIALS AND METHODS

This prospective observational study was conducted over a one year duration starting from January 2020 to December 2020, on preterm neonates that admitted in a tertiary care NICU at J. K. Lon Mother and Child Hospital, attached to Government Medical College, Kota. Ethical clearance was obtained by letter number 1804 dated on 16/12/2019, from Institutional Ethics Committee on human subject research before the commencement of the study.

Sample size calculation: The sample size was 56 and it was calculated by using the formula (Daniel WW, 1999 [28])

$$n=\frac{z^2p(1-p)}{d^2}$$

(n=desired sample size,

z=z statistic for a level of confidence (1.96),

p=prevalence, prevalence was taken 18% in this study [29],

d=precision)

Inclusion and Exclusion criteria: All Clinically stable preterm neonates (30 weeks 0/7 days to 34 weeks 6/7 days) admitted before 3rd day of life and parents/guardians who gave consent to the study were included. Neonates experiencing perinatal insult at birth (i.e., APGAR <2 at 5 min), any grades of Intraventicular Haemorrhage (IVH), periventricular leukomalacia, Necrotising enterocolotis, Central Nervous System (CNS) infections, clinically identified seizures, suspected metabolic disorders, clinically unstable neonates, major congenital anomalies, preterm neonates (30 weeks 0/7 days to 34 weeks 6/7 days) admitted after 3rd day of life and parents/guardians who did not give consent were excluded before or during the study time.

Study Procedure

All clinically stable preterm neonates admitted to the NICU of the hospital satisfying the inclusion criteria were enrolled in the study. At the time of enrolment, an informed written consent was taken from the parents. The included neonates were plotted against standard All India Institute of Medical Sciences (AIIMS) intrauterine growth curves [30] and then allotted into SGA and AGA based on their weight and their respective gestational ages. The gestational age was determined by the last menstrual period date as mentioned in the mother's antenatal card or antenatal documents like antenatal obstetric Ultrasonography (USG) or was calculated by New Ballard's' score [31].

Serial cranial sonography was performed on these neonates on day 3rd, 7th and 14th in collaboration with the Department of Radiology, a-EEG recording was also done on haemodynamically stable included neonates on postnatal day 3rd, 7th and 14th during admission. All these data were noted in preformed study proforma. The a-EEG tracings were recorded using the amplitude integrated EEG machine "NIHON KOHDEN EEG-1250" model as per standard methodology. Each recording was done for at least four hour duration to ensure good sleep-wake cycling recording. Continuous impedance tracing was done throughout the recording and tracing with impedance >20 kOhm were not included. All the respective a-EEG recordings were collected and then scored individually as continuity, cycling, amplitude and bandwidth span score from the Scoring system according to the method proposed by Burdjalov VF et al., [6].

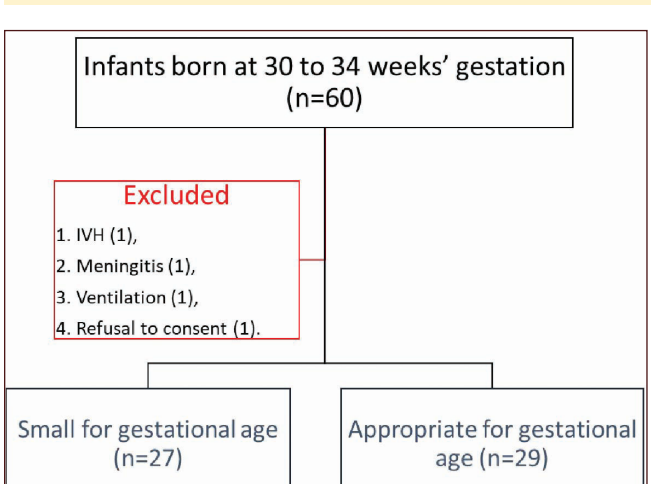
STATISTICAL ANALYSIS

The data was entered in MS Excel spreadsheet and analysis was done using SPSS version 21.0. All baseline variables were tabulated and analysed statistically. Normally distributed, continuous data was analysed by student t-test. The p-value of <0.05 was considered as significant.

RESULTS

A total of 60 neonates participated in the study that were admitted in NICU between 30-34 weeks of gestation, out of which 4 neonates were excluded [Table/Fig-1]. More than 50% of the mothers in both the cohorts were multigravidas. Females were slightly predominant in SGA neonates [Table/Fig-2].

The total a-EEG score for day 3, 7 and 14 for SGA group neonates were 7.55±1.45, 7.25±1.02 and 10.22±1.05 and were delayed from the AGA group of neonates with 7.86±1.55,



[Table/Fig-1]: Flow chart of patients.

Variables	SGA (n=27)	AGA (n=29)
Maternal characteristics, n (%)		
Multigravida	15 (55.5%)	17 (58.6%)
Gestational HTN	12 (44.4%)	14 (48.3%)
GDM	1 (3.7%)	0
PPROM	5 (18.5%)	7 (24.1%)
Neonatal characteristics at birth		
Gestation (weeks), median (range)	32 (30-34)	31 (30-34)
Weight (kg) (mean±SD)	1.196 ±0.18	1.326±0.21
Male, n (%)	13 (48.1%)	16 (55.2%)
Mode of delivery		
Vaginal delivery, n (%)	13 (48.1%)	15 (51.7%)
Twins, n (%)	0	2 (6.9%)
APGAR at 5 minutes, median (range)	8 (7-9)	8 (7-9)
Postnatal complications, n (%)		
NNS	9 (33.3%)	5 (17.2%)
RDS	2 (7.4%)	1 (3.4%)
TTNB	8 (29.6%)	9 (31.0%)
NNJ	12 (44.4%)	13 (44.8%)

[Table/Fig-2]: Baseline variables of the study population.
GDM: Gestational diabetes mellitus; HTN: Hypertension; RDS: Respiratory distress syndrome; PPROM: Preterm premature rupture of membranes; NNS: Neonatal sepsis; NNJ: Neonatal jaundice; TTNB: Transient tachypnea of new born

8.68±1.00 and 10.62±1.01, with mean difference (95% CI) 0.30 (-0.49 to 1.13), 1.43 (0.88 to 1.97) and 0.39 (-0.15 to 0.95), respectively [Table/Fig-3]. The mean cycling, continuity and amplitude score on day 7 was significantly delayed in SGA group neonates [Table/Fig-4].

a-EEG recording	SGA (n=27)*	AGA (n=29)*	Mean difference (95%CI)#	p-value
Day 3	7.55±1.45	7.86±1.55	0.30 (-0.49 to 1.13)	0.449
Day 7	7.25±1.02	8.68±1.00	1.43 (0.88 to 1.97)	<0.0001
Day 14	10.22±1.05	10.62±1.01	0.39 (-0.15 to 0.95)	0.154

[Table/Fig-3]: Total a-EEG score.
*Values expressed as mean (SD); #Adjusted for correlated values by Generalised Estimating Equation (GEE), unpaired t-test used

a-EEG recording	SGA (n=27)*	AGA (n=29)*	Mean difference (95%CI)#	p-value
Continuity (Out of 2)				
Day 3	1.11±0.50	1.55±0.50	0.440 (0.16 to 0.71)	0.002
Day 7	1.11±0.50	1.72±0.45	0.613 (0.35 to 0.87)	<0.0001
Day 14	2.00±0.00	2.00±0.00	NA	NA
Cycling score (Out of 5)				
Day 3	2.07±0.54	2.10±0.72	0.02 (-0.13 to 0.37)	0.865
Day 7	1.92±0.26	2.51±0.50	0.59 (0.37 to 0.81)	<0.0001
Day 14	3.33±0.69	3.27±0.45	0.053 (-0.25 to 0.36)	0.732
Amplitude (Out of 2)				
Day 3	1.74±0.44	1.65±0.48	-0.08 (-0.33 to 0.16)	0.495
Day 7	1.62±0.56	1.89±0.40	0.26 (0.003 to 0.52)	0.046
Day 14	1.96±0.33	2.00±0.00	NA	NA
Bandwidth span score (Out of 4)				
Day 3	2.62±0.62	2.55±0.57	-0.07 (-0.39 to 0.24)	0.629
Day 7	2.59±0.50	2.55±0.50	-0.04 (-0.31 to 0.22)	0.762
Day 14	3.03±0.70	3.34±0.76	0.30 (-0.08 to 0.70)	0.125

[Table/Fig-4]: Individual Scores as per Burdjalov VF et al., [6].
*Values expressed as mean (SD); #adjusted for correlated values by Generalised Estimating Equation (GEE), unpaired t-test used

DISCUSSION

This study on fifty-six neonates (after excluding four) noted that, the different mean individual scores and mean total a-EEG scores was delayed in SGA group neonates than the AGA group of neonates.

Malnutrition during the critical phase of brain development leads to delayed myelination and subsequently to delayed maturation

pattern. The delaying of maturation score at any time point for preterm SGA neonates seems to be related to the underlying reasons of growth retardation and delay in starting the enteral feeds. This seems to be a plausible reason for the delayed maturation scores on day 7.

Olischar M et al., in their study, monitored the neonates over the first two weeks of life and showed that the amount of continuous activity increased with higher Gestational Age (GA), whereas the amount of discontinuous activity decreased with higher GA [32]. This effect is only one example of extrauterine influences on postnatal maturity. Similar to this above study, this study showed increasing total a-EEG scores with increasing gestational age of the neonates.

Klebermass K et al., and Sisman J et al., showed in their study that very preterm infants monitored over several weeks showed that the a-EEG pattern matured not only with higher GA, but with postmenstrual age (PMA) as well, and infants with higher PMA have more mature patterns than those with lower PMA, despite a lower GA [33,34]. The results of this study showed that a-EEG scores matured over time since their birth with postmenstrual age.

Curzi-Dascalova L et al., have shown sleep state differentiation in neurologically normal infants at 27 weeks [35]. The presence of sleep wake cycling in preterm infants is strongly associated with good long term prognosis [36] and is absent in most infants with severe IVH [37]. This study showed maturing cycling scores over their postmenstrual age but did not look for long term prognosis in these neonates and did not quantify cycling scores in cases of IVH, as it was one of the exclusion criteria.

Soubasi V et al., in their study on "The influence of extrauterine life on the a-EEG maturation in normal preterm infants" found a positive effect of GA in the measurements of all the four components of the a-EEG tracing [38]. Specifically, with advanced GA the a-EEG becomes more continuous (p: 0.022), it displays definite sleep-wake cycles (p: 0.011), and its bandwidth acquires the mature pattern (p: 0.012) and a positive significant interaction of PMA and GA was found regarding continuity (p: 0.002), sleep-wake cycling (p: 0.002) and bandwidth (p: 0.02), implying that preterm infant of lower GA, displays an accelerated maturation of the a-EEG as compared with infants of higher GA in the same PMA. This study observed that, a-EEG becomes more continuous, cycling and shows better amplitude scores with advancing gestational ages. This observation was more profound in the AGA group than the SGA group, implying that postnatal maturation neonatal a-EEG increases with advancing gestational and postconceptional ages. By further extending of this a-EEG maturation study and follow-up of neonates for neurodevelopmental aspect, it may be useful in predicting neurodevelopmental outcome.

The strengths of this study included the comparison of clinically stable neurologically sound preterm neonates without requiring sedation or having any major morbidities. The controls included were also from the similar gestational age. The minimal study duration was four hours to ensure increased detection of immature sleep wake cycling. It was also ensured for continuous check on impedance and adequate electrode contact. The serial recordings of maturation pattern of preterm neonates up to the age of first two weeks was also added.

Limitation(s)

The study was limited by it's small sample size, it can also be extended to a larger study group with inclusion of premature neonates of less than 30 weeks of gestation, late preterms and term neonates. The study did not have multiple assessors to assess the a-EEG scores and also their blinding. The study also did not follow up with long term implications of the delayed maturation of a-EEG in preterm SGA neonates.

CONCLUSION(S)

The total a-EEG maturation scores in PSGA neonates as compared to PAGA is delayed on 3rd, 7th, and 14th postnatal days indicating a delayed maturation in these neonates. All the individual maturation a-EEG scores of clinically stable and neurologically normal PSGA neonates were found to be significantly delayed at any point of life on postnatal day 7th of life.

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