STUDY OF VISUAL EVOKED POTENTIAL IN TERM, APPROPRIATE FOR GESTATIONAL AGE NEWBORNS IN A TERTIARY HEALTH CARE FACILITY OF KOLKATA

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ABSTRACT

INTRODUCTION

Evoked potentials are small magnitude electrical potentials that originate within neural tissues in response to a variety of stimuli which are depicted as a wave or a series of waves. Changes in the wave latencies and amplitudes have been shown to reflect disturbances in neuronal growth rates & myelination of the developing nervous system. Among the different evoked potentials, the Visual Evoked Potentials (VEP), have been shown to be a significantly accurate tool for assessing the degree of neurological handicap among survivors of perinatal asphyxia, especially in the full-term neonates. Thus, the development of a normative database of VEP parameters like wave latencies and amplitudes for term, appropriate-for-gestational age neonates in an Indian NICU set-up was the primary objective of our study as such data can be of great use for future clinical use. The study was a prospective observational study carried out jointly by the Departments of Neonatology and Physiology, of IPGME & R and SSKM Hospital, Kolkata from June' 2012 to September' 2013. Normative statistics like 'mean±2SD' values for N1, P1 & N2 wave latencies of both right & left eyes & also for inter-peak amplitudes (i.e. N1-P1 & P1-N2) of both the eyes was obtained by studying 40 healthy, term newborns. It was also observed that the 'latencies' of VEP waves do not vary significantly between normal male & female newborn babies and the latencies of both the eyes are comparable. The 'inter-peak amplitudes' on the other hand showed much more variability. Hence establishing a normative database of VEP parameters can be of much use and further studies with much larger sample size is highly recommended.

KEYWORDS

Visual evoked potential, Term newborns, Wave latency, Inter-peak amplitude.

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INTRODUCTION: Evoked potentials, first recorded in the early 1950s by George Dawson,[1] are small magnitude electrical potentials that originate within neural tissues in response to a variety of stimuli and are depicted following proper recording as a wave or a series of waves.[2,3] The study of evoked potential waveforms that arise out of stimulation of different sensory modalities like visual, auditory & somatosensory pathways has equipped us with an effective, non-invasive technique that provides in-depth, objective & quantifiable information regarding neurological functional status in a wide range of clinical situations.[3,4] The changes in evoked potential wave latency periods, their amplitudes as well as their overall pattern or 'shape' have been shown to reflect disturbances in neuronal growth rates & myelination of the developing nervous system.[5] Among the different evoked potential techniques, the Visual Evoked Potentials (VEP), which are electrical potentials generated by brief visual stimulation & recorded from the scalp overlying the occipital cortex,[6] have been shown to be a significantly accurate tool for predicting the neurodevelopmental outcome among survivors of all degrees of Hypoxic Ischaemic Encephalopathy (HIE), especially in the full-term neonates.[7,8,9,10] The importance of early identification of the neonates who are at a greater risk of being neurodevelopmentally retarded from among the survivors of HIE lies in the fact that timely institution of intensive follow-up care to prevent the later development of significant neurologic handicap can be provided to them, as well as facilitate timely & proper counselling of their parents. Hence it is imperative that normative data for the different VEP wave latencies and amplitudes for neonatal age group be readily available to clinicians for comparison with values obtained from asphyxiated neonates in order to give a fairly accurate prediction of their future neurodevelopmental outcome.

Thus the primary objective of the study was to develop a normative database of VEP parameters like wave latencies and amplitudes for term, appropriate-for-gestational age neonates in an Indian neonatal intensive care set-up, as such data are scarcely available and can be of great use for early & accurate prognostication of neurodevelopmental

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outcome among survivors of HIE, which still remains as a difficult challenge for all clinicians even after the great advancements made in the field of neonatology in recent times.

METHODOLOGY: The study was an institution based prospective observational study & carried out jointly by the Departments of Neonatology and Physiology, of IPGME & R and SSKM Hospital, Kolkata. Due clearance was obtained from the Institutional Ethics Committee prior to commencement of the study. The total duration of the study was approximately 15 months starting from June' 2012 and concluding in September' 2013. The neonates inducted into the study were all recruited from among those delivered at SSKM Hospital and fulfilled the following selection criteria, viz. they were all:

i. Full-term (i.e. gestational age ≥37 weeks but <42 completed weeks),
ii. Without any evidence of perinatal asphyxia,
iii. Appropriate-for-gestational age (i.e. birth weight ≥2500 gm but <4000 gm), and
iv. Without any obvious illness or congenital malformation.

Using the aforementioned criteria, a total of 40 healthy, term new-borns, whose parents gave verbal consent after informed counselling, were studied within the specified time period. Conscious attempt was made to maintain a balance between the number of boys and girls that were inducted into the study. Birth weight was recorded using electronic weighing machine with digital display of body weight up to 3 decimal places. Apgar scores of >7 at 1 and 5 minutes of life were designated to be evidence for the absence of perinatal asphyxia. Gestational age was assessed using New Ballard Gestational Age Assessment Scoring Chart.[11]

The recording of neonatal VEPs was done in the Dept. of Neonatology where ideal temperature & illumination for electrophysiological studies was maintained. Proper earthing of all electrical wirings & outlets was ensured prior to commencement of the study. The neonates were examined either in Stage 1 or Stage 2 of the Prechtl & Beintema neonatal wakefulness stage[12] i.e. in deep sleep or in light sleep with eyes closed. This was done to reduce the chance of appearance of artefacts due to limb movements during VEP recording. For the recording of VEP the preferred position of the baby was in their mother's arm. Prior to placement of scalp electrodes for the purpose of VEP recording the areas of their placement was thoroughly cleansed to keep the skin-electrode impedance below 5kΩ during VEP recording. Standard Ag-AgCl scalp electrodes were used & placed over the scalp as per the 10-20 International system of electrode placement[13] with the 'active' electrode placed at Oz (1-2 cm above the Inion at the midline), the reference electrode at Fz (mid-frontal pole) & ground electrode at Cz (vertex). The electrodes were secured to their specified positions with conducting gel & micropore tape. The VEPs were recorded by the 'Neuropack M1-MEB 9200' evoked potential recorder by Nihon-Kohden.

The procedure proper involved stimulating each eye individually with a red-flash of light delivered by the 'LS-102J LED-goggle' provided by Nihon-Kohden, with the goggle being held in front of the neonate's eyes in such a way that little or no extraneous light entered the eyes during testing. Though the stimulus was monocular, the non-tested eye was also kept covered. The stimulus rate was 1 Hz, amplifier gain was set at 10K, bandpass was 1-100 Hz & time epoch was 0-300 ms. A minimum of 100 responses was averaged for each eye automatically by the Neuropack machine & displayed in real-time on the averaging computer (Dell Inspiron laptop PC) attached to it. The reproducibility of the responses was ensured by repeating the test for each eye at least twice. The approximate time taken for each recording session was 20-30 minutes.

The obtained flash-VEP waveforms in term neonates consisted of three separate phases, an initial negative deflection designated N1, a prominent positive deflection designated P1 & a later negative deflection named N2.[14] The peak latencies & inter-peak amplitudes of each waveform were marked and the data was stored in the averaging computer for future analysis.

All the parameters like gender, birth weight, peak-latencies & inter-peak amplitudes for individual flash-VEP waveforms of both eyes were tabulated in Microsoft Office Excel sheet. Normative statistics like mean±2 SD values for N1, P1 & N2 latencies of both right & left eyes & also for inter-peak amplitudes (i.e. N1-P1 & P1-N2) of both the eyes was obtained using Graph-Pad Prism version5 licensed software. Data from both the eyes were compared by using unpaired student-t test. A p value of less than 0.05 was taken to be statistically significant.

RESULTS: A total of 40 healthy term new-borns was studied with 21 (52.5%) of them being males and the rest 19 (47.5%) being females. (Vide Table 1)

Gender	Number (n)	Percentage
Male	21	52.5%
Female	19	47.5%

Table 1: Gender distribution of study group

Comparability of gender distribution was deliberately attempted so as to circumvent any hitherto unknown gender-related significant difference of VEP parameters which might have affected the normative data that were planned to be extrapolated by studying the VEPs.

The bulk of the analytical part of the study involved the computing of the 'Mean±SD' values for the time latencies of individual VEP waves of each eye separately as well as that of the inter-peak amplitudes of the waveforms. Comparative analysis of the values by two-tailed unpaired student t-test for each pair of wave latencies & inter-peak amplitudes showed p values of >0.05 in all cases, indicating that there were no significant difference between the mean latencies of individual waves & the mean inter-peak amplitudes between both the eyes. (Vide Table 2 and Figures 1a and 1b).

Sl. No.	Parameter	Mean±SD	p value (significance)
1	N1 latency of Rt. Eye	74.9±3.11 ms	0.59 (NS)
	N1 latency of Lt. Eye	75.3±2.99 ms	
2	P1 latency of Rt. Eye	97.1±2.94 ms	0.83 (NS)
	P1 latency of Lt. Eye	97.2±3.72 ms	
3	N2 latency of Rt. Eye	134.4±4.36 ms	0.22 (NS)
	N2 latency of Lt. Eye	135.5±3.91 ms	
4	N1-P1 amplitude of Rt. Eye	2.32±1.62 µv	0.21 (NS)
	N1-P1 amplitude of Lt. Eye	2.77±1.58 µv	
5	P1-N2 amplitude of Rt. Eye	2.45±1.79 µv	0.75 (NS)
	P1-N2 amplitude of Lt. eye	2.59±2.37 µv	

Table 2: Mean±SD values of wave latencies and inter-peak amplitudes along with p value obtained from comparative study of each set of parameters for each eye

NS: Not Significant (Significant if p value <0.05)

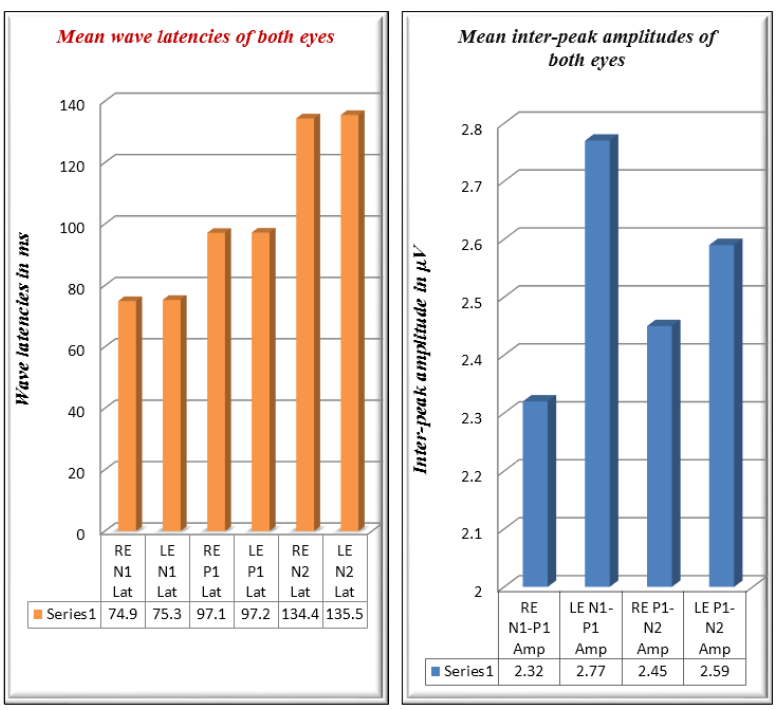

Fig. 1a and 1b: Bar diagrams showing Mean±SD values of wave latencies (1a) and inter-peak amplitudes (1b) for each eye taken separately

The VEP parameters when analysed after gender segregation i.e. Mean±SD values of wave latencies and inter-peak amplitudes of both eyes taken together for boys and girls, also did not show any significant difference on comparative analysis by two-tailed unpaired student t-test. The individual p values for each set of waves and for each set of inter-peak amplitudes were all >0.05 thus indicating that there were no significant difference between the mean latencies of individual waves & the mean inter-peak amplitudes between the sexes. (Vide Table 3).

Sl. No.	Parameter	Mean±SD	p value (Significance)
1	N1 latency of both eyes in boys	75.33±3.52 ms	0.48 (NS)
	N1 latency of both eyes in girls	74.85±2.41 ms	
2	P1 latency of both eyes in boys	96.38±3.47 ms	0.37 (NS)
	P1 latency of both eyes in girls	97.92±3.01 ms	
3	N2 latency of both eyes in boys	134.6±4.55 ms	0.36 (NS)
	N2 latency of both eyes in girls	135.4±3.67 ms	
4	N1-P1 amplitude of both eyes in boys	3.05±1.72 µv	0.41 (NS)
	N1-P1 amplitude of both eyes in girls	2.98±1.25 µv	

5	P1-N2 amplitude of both eyes in boys	2.7±2.29 μv	0.40 (NS)
	P1-N2 amplitude of both eyes in girls	2.31±1.84 μv	

Table 3: Mean±SD values of wave latencies and inter-peak amplitudes along with p value obtained from comparative study of each set of parameters for both eyes in boys and girls

NS: Not Significant (Significant if p value <0.05)

The normative data for VEP parameters for term neonates comprising of latencies of waves N1, P1 and N2 in milliseconds (ms) as well as inter-peak amplitudes of N1-P1 and P1-N2 in microvolts (μv) for each eye taken separately was computed after statistically establishing the fact that these parameters are not affected by the gender of the new-born. The normal range for each parameter was ascribed to be 'Mean± 2SD' so that by definition any value falling outside that range can be designated to be lying beyond 95% confidence limits for that parameter and hence would be considered 'abnormal' during future studies using neonatal VEPs.

The normative values thus obtained are displayed in Table 4 and 5.

Sl. No.	Parameter	Mean (in ms)	Std. Dev (SD)	Normal Range (in ms) (Mean±2SD)
1	Rt. Eye N1 latency	74.9	3.11	68.7-81.1
2	Lt. Eye N1 latency	75.3	2.99	69.3-81.3
3	Rt. Eye P1 latency	97.1	2.94	91.2-103
4	Lt. Eye P1 latency	97.2	3.72	89.7-104.6
5	Rt. Eye N2 latency	134.4	4.36	125.7-143.1
6	Lt. Eye N2 latency	135.5	3.91	127.7-143.3

Table 4: Normative data of VEP wave latencies

Sl. No.	Parameter	Mean (in μV)	Std. Dev (SD)	Normal Range (in μV) (Mean±2SD)
1	Rt. Eye N1-P1 amplitude	2.32	1.62	-0.92 to 5.56
2	Lt. Eye N1-P1 amplitude	2.77	1.58	-0.39 to 5.93
3	Rt. Eye P1-N2 amplitude	2.45	1.79	-1.13 to 6.03
4	Lt. Eye P1-N2 amplitude	2.59	2.37	-2.15 to 7.33

Table 5: Normative data of VEP inter-peak amplitudes

DISCUSSION: Visual evoked potentials has been widely used in neonates and young infants for tracking developmental changes in neuronal maturation and assessing cortical function at birth.[15,16] Among the different clinical scenarios, neonatal VEPs has been most commonly used as a modality for assessing the aftermath of asphyxial injury on the developing neonatal brain as well as for prediction of neurodevelopmental outcome of the survivors of HIE.

Earlier studies by Gambi et al,[10] Hrbek et al[17] and Hakamada et al[18] using VEPs for assessing neuronal damage & outcome in asphyxiated new-borns were limited by inclusion of both term & preterm neonates as study population, presence of a variety of perinatal disorders affecting the new-borns and lack of normal control groups. Later studies by Petersen et al,[19] Stanley et al[20] and Thordstein et al[21] revealed that VEP parameters are known to get altered in both growth-retarded as well as large-for-date neonates and presence of other co-morbidities like prematurity, intrauterine growth restriction, maternal diabetes & consequent macrosomia, neonatal septicaemia with/without meningitis, congenital disorders affecting the central nervous system etc. further adversely affected VEP waveforms. Thus a strict birth weight criterion was followed and only term, appropriate-for-gestational age neonates without significant co-morbidities were selected as study subjects.

The VEP parameters that were analysed for the development of the normative data were:

a) Latency of individual 'peaks' i.e. the time interval from the application of flash stimulus by LED goggle to the appearance of the individual peaks (in ms) in the VEP waveform for each eye separately. The peaks consisted of an initial 'negative' deflection (N1) followed by a prominent 'positive' deflection (P1) & a later 'negative' deflection (N2) in each waveform. Monga et al[22] in their study concerning the correlation of VEP parameters with prevalence of iron deficiency anaemia in very young infants also used latencies of N1, P1 & N2 waves to develop the normative data for their study.
b) Inter-peak amplitudes of individual waveforms of each eye separately. The different inter-peak amplitudes were N1-P1 amplitude between N1 wave peak & P1 wave-peak & P1-N2 amplitude between P1 wave peak & N2 wave peak (in μV).

For computation of the normative values pertaining to 'wave latency' and 'inter-peak amplitudes', the values obtained from individual waveforms of each eye from all 40 neonates were noted & their 'mean' & 'standard deviation' values were calculated. The 'normal range' of individual parameters for each eye was taken as 'Mean±2SD' value, so that by definition any value that falls outside that range can be designated to be lying beyond 95% confidence limits for that particular parameter and hence could be considered 'abnormal' (Table 4 and 5). Muttitt et al[7] in their study involving the use of serial VEP recordings in term

asphyxiated neonates for predicting their neurodevelopmental outcome advocated the development of normative data for any subsequent similar study which was later corroborated by Whyte.[9] As VEP parameters were not standardized for neonates, showed appreciable maturational changes with advancing gestational age and could even be altered by difference in prevailing environmental conditions, it was recommended to develop normative values of VEP parameters for each NICU set-up separately for it to be a useful tool in studies involving neonatal neuroelectrophysiology.

CONCLUSION: The objective of our study was to create a normative database of VEP parameters in term, appropriate-for-gestational age neonates in an Indian NICU set-up for it to be useful in future studies using VEP in different clinical situations, especially in outcome prediction of post-asphyxiated term neonates. In due course we also observed that the 'latencies' of VEP waves do not vary significantly between normal male & female newborn babies and the latencies of both the eyes are comparable. The 'inter-peak amplitudes' on the other hand showed much more variability. As several studies in first world nations have established the efficacy of VEPs as a neurodevelopmental outcome predictor in term neonates afflicted by perinatal asphyxia hence establishing a normative database of VEP parameters can be of much use and further studies with much larger sample size is highly recommended.

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