

P2 Latency in Infants with Perinatal Asphyxia

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Abstract: Infants with perinatal asphyxia are at an increased risk of developing neuro-developmental delay. Visualevoked potential (VEP) provides a non-invasive and objective method to assess the functional integrity of visual path way. The aim of the study is to show whether there is any P2 latency change in infants with perinatal asphyxia compared to age matched controls and whether there is any difference between the two eyes of cases and between different age groups. An observational, cross-sectional study was under taken where 106 Infants with perinatal asphyxia and 30 controls were subjected to mono-ocular Flash VEP testing with LED goggles following routine protoco laccording to ISCEV standards(2009).Both cases and controls were in the age group 0-12 months and were obtained from Pediatrics OPD.There was statistically significant prolongation of P2 latency in both eyes compared to age matched controls in dicatingvisual path way abnormality. There was no significantdifferencebetween Right and Lefteye and in differentage groups. Thus we can see that VEP canbeused for earlyassessment of functionalintegrity and maturity of visualpathway and CNS function.

Key Words : BirthAsphyxia;Perinatal Asphyxia;Visual Evoked potential; P2 Latency

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I. Introduction

WHO¹ has defined perinatal asphyxia as a “failure to initiate and sustain breathing at birth” The National Neonatal Perinatal Database (NNPD), 2002-03 defined moderate asphyxia as slow gasping breathing or an Apgar score of 4-6 at 1 minute of age. Severe asphyxia was defined as no breathing or an Apgar score of 0-3 at 1 minute of age².

The prevalence of perinatal asphyxia is 2 in 1000 live births in India.²The consequences of perinatal asphyxia range from death to various degree of neuro-developmental sensory or motor deficits³.Perinatal asphyxia leads to multi-organ dysfunction. In term infants with asphyxia, CNS dysfunction occurs in 28% cases⁴.

Visual Evoked Potential (VEP) is the electrical activity of Occipital Cortex in response to visual stimuli recorded from overlying scalp surface with electrodes. It provides a non-invasive and objective method to assess the functional integrity of visual pathway. VEPs are particularly appropriate for infants and young children who cannot communicate visual symptoms or cooperate for standard vision assessment⁵. In infants the type of VEP that can be used to assess visual function is Flash VEP⁶.

The clinical neurological examination of these infants is difficult. VEPcan be an important adjunct to the clinical examination and imaging studies.It provides a means for follow up of visual pathway maturation and evaluation of neurological sequelae in infants with perinatal asphyxia.

We intend to undertake a study to evaluate VEP parameters in infants with perinatal asphyxia. Previous studies provide some data about abnormalities in VEP parameters in the infant^{7,8,9,10}. However, the existing data have not shown any correlation between VEP parameters and age. They also did not mention anything about inter-ocular difference in infants with perinatal asphyxia. There is also very little data about VEP parameters among infants with perinatal asphyxia from Eastern part of India. Present study intends to fill the gap in the knowledge.

In future, a follow up study in a large homogenous population can be undertaken.So, the specific objectives are:

- i. To assess the nature of VEP changes in infants with perinatal asphyxia in our study population.
- ii. To detect whether there is difference between VEP parameter between Right and Left Eyes in infants with perinatal asphyxia.
- iii) Whether there is any correlation of VEP parameters with age in our study population.

II. Material And Method

Study was done after getting clearance from Institutional Ethics Committee, R.G.Kar Medical College and Hospital, Kolkata.

1. Study Area

Department of Physiology and Department of Pediatrics at R.G.Kar Medical College and Hospital.

2. Study Population

The study population was infants who have suffered from Perinatal asphyxia.

The neonates who suffered from Perinatal asphyxia and attended Pediatrics OPD at R.G.Kar Medical College and Hospital were evaluated. Those who have:

1. Five minute APGAR score < 6
2. The neonates with clinical signs of asphyxia sequelae ,
were referred for VEP test in Department Of Physiology at R.G.Kar Medical College and Hospital.

Inclusion criteria:

1. Age: 0 – 12 months
2. Either gender
3. Parents who have given consent

Exclusion criteria:

1. Infants who have cataract, vitreous opacities, abnormal pupils
 2. Infants with gestational Age < 34 weeks
 3. Infants with Birth Weight < 1500 gms
 4. Infants with h/o other high risk conditions – neonatal hyperbilirubinemia, neonatal meningitis, neonatal sepsis.
 4. Infants with disorders of optic nerve, chiasma, tract
 5. Infants with cerebral white matter disease
 6. Infants on Antiepileptic medications
 7. Infants with phenylketonuria and other metabolic disorders
 8. Infants with congenital anomalies
 8. Infants whose mothers have h/o perinatal substance abuse or antenatal infections
 9. Age > 12 months
 10. Parents who are unwilling to give consent
 11. Infant too ill to participate
- Appropriate Controls were taken.

3. Study Period

The study will be conducted for 6 months.

4. Sample Size

To calculate sample size, we use the statistical formula¹¹

$$N = z \times PQ/L^2$$

Where, N= sample size

Z= 1.96 for 95% confidence level

P= proportion

Q= (100-P)

L=confidence interval (L<P and L<10)

P = 2 in 1000 live births²i.e, 0.002, Q = 1-P

So, n ≥ 106

In this study, 106 infants with perinatal asphyxia were included.

5. Sampling Design

Purposive sampling

6. Study Design

Cross sectional

Analytical Type

7. Parameters to be Studied

1. Age
2. Body Weight
3. APGAR Score¹²

4. Hypoxic Ischemic Encephalopathy scale (HIE Scale) - Sarnat Staging¹³
4. The wave morphology – whether wave P2 was absent or present
5. Wave Latencies (P2) in milisec

8. Study Tool

VEP test was done with Neuro-MEP 4 machine manufactured by Neurosoft Medical Diagnostic Equipment, Ivanovo, Russia.

9. Study Technique

Data collection was done by following method- Infants of perinatal asphyxia were taken as study population as per inclusion and exclusion criteria from the Pediatrics OPD in R. G. Kar Medical College. They had no known history of congenital or metabolic anomalies or no history of maternal or fetal infection (as per records). These infants fulfilling the inclusion and exclusion criteria were referred to the Department of Physiology for VEP test.

Before the test was performed, parents of the infant were informed properly about the procedure and informed consent was taken.

The VEP test was done by maintaining proper prerequisite and procedure following the International Society of Clinical Electrophysiology of Vision (ISCEV) 2009 Standard¹⁴

1. The testing room had minimal electrical noise with background light similar to the luminance of the computer screen.
2. The child was preferably asleep or quiet.
3. Areas for electrode placement were cleaned with cotton and spirit.
4. Silver coated electrodes were applied using electrical paste on -
 - a) Active electrode – Oz
 - b) Reference electrode –Fz
 - c) Ground Electrode –CzISCEV standard montage is Oz–Fz with ground at Cz
5. Impedance was checked. It was below 5 KOhm.
6. Flash light stimulus was delivered by LED goggles.
7. The stimulus parameters are as follows:
 - i) Brief Flash (< 5ms) - to each eye separately.
 - ii) The Flash should subtend a visual angle of 20°
 - iii) Stimulus luminance – 3 candela/m²
 - iv) Red colored Flash with LED Goggles
 - v) Frequency – 1 Hz
8. The waveform obtained is analyzed and wave P2 latencies were evaluated.

According to International Society of Clinical Electrophysiology of Vision (ISCEV), 2009 standards, there are six recognizable wave peaks in a Flash VEP. Among them P2 peak is the most constant and reproducible wave. An abnormal VEP is

- 1) The absence of the component waves,
- 2) Delayed latencies (P2 and N2) and ¹⁴

The results were stored as per recommended methods. The final analysis was done by standard statistical method.

10. Statistical analysis plan

The VEP parameter changes of 106 infants were compared with 30 control infants. To compare data of main group and subgroups with control population, Student's t-test was applied and for qualitative parameter (i.e. sex), Chi Square test was done. Then statistical analysis was done with Graph Pad Quick Calc software, California, USA.

The data was compared between the different age groups using one-way ANOVA test. Statistical analysis was done with statpages.info software, USA.

11. There was no conflict of interest

III. Results

1) General Information of cases and controls

1. Sex

Graph 1 - Pie Chart showing No. of Males and Females in cases

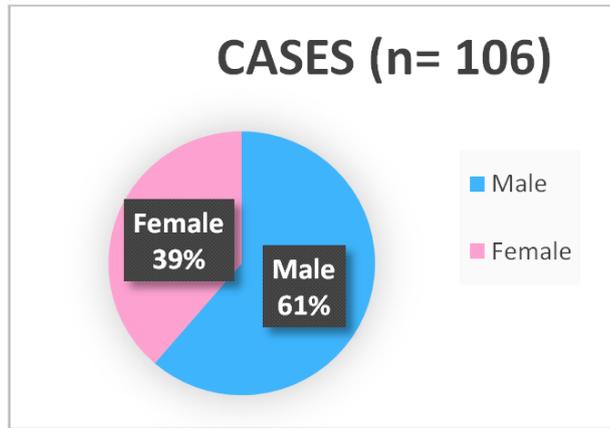


Table 1- Chi Square test was performed to calculate P value

	No. of Cases(n=106)	No. of Controls (n=30)	p- value
Males	65	19	.841277*
Females	41	11	

*Statistically Insignificant

2. Age –

Graph 2 -Bar diagram showing Age group in Cases

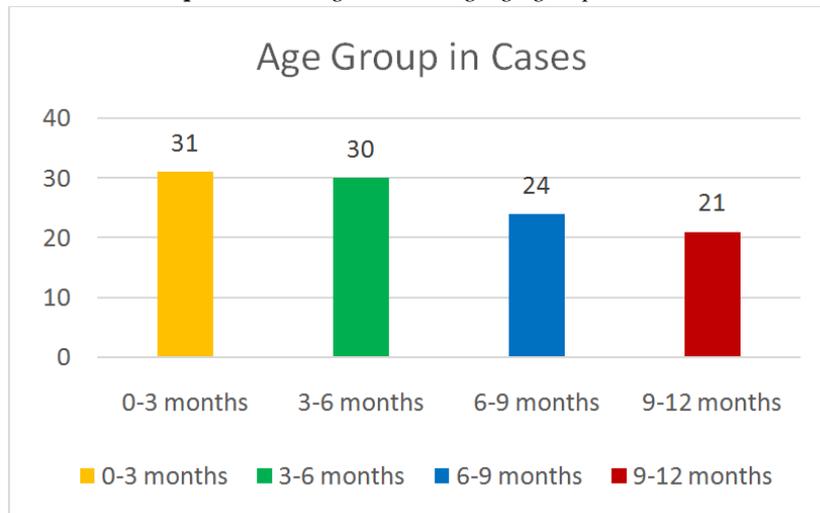


Table 2 b - Chi Square test was performed to calculate P value

Months**	No. of Cases (n=106)	No. of Controls (n=30)	p- value
0-3	31	9	0.9893*
3-6	30	8	
6-9	24	6	
9-12	21	5	

*Statistically Insignificant

** Group interval includes the upper and lower limit

1) Right Eye

A) All Cases

Graph 3 - Pie Chart showing Wave P2 presence

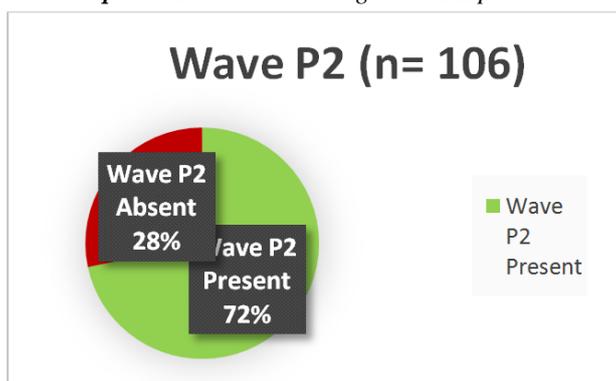


Table 3a - Chi square Test was performed to calculate P value

	No. of Cases (n=106)	No. of Controls (n=30)	p- value
P2 Wave Present	76	30	0.003 *
P2 Wave Absent	30	0	

*Statistically Significant

b) Mean P2 Latencies of Cases and Controls

Table 3b – Mean P2 wave latencies of Cases and Controls of right eye with p-value

VEP Parameter Latency(mS)	CASE Mean(SD) (mS) (n=76)**	CONTROL Mean (SD) (mS) (n=30)	P Value
Wave P2	125.74 (18.50)	98.51 (7.99)	0.0001*

*Statistically Significant

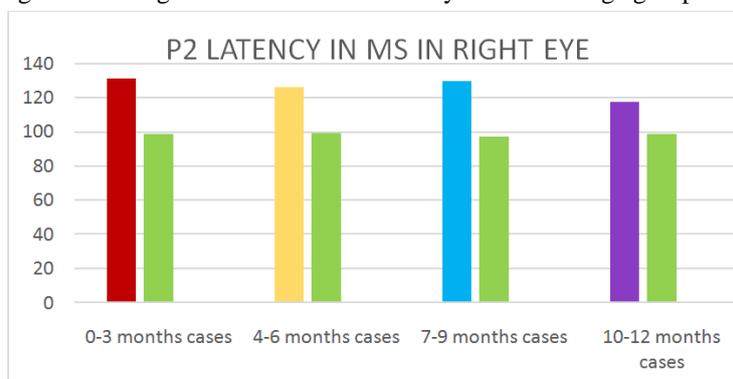
B) For different age groups –

Table 4 – Showing mean latencies of P2 wave in different age groups

VEP Parameter Latency(mS)	CASE Mean(SD) (mS)	CONTROL Mean(SD) (mS)	P Value
0 – 3 months	131.38 (17.25) (n = 15)**	98.9 (8.2) (n = 9)	0.0001 *
4-6 months	125.85 (15.60) (n = 23) **	99.12 (8.18) (n = 8)	0.0001 *
7-9 months	129.38 (20.61) (n = 19) **	97.42 (7.86) (n = 6)	0.0013 *
10 – 12 months	117.32 (17.85) (n = 19) **	98.6 (7.7) (n = 5)	0.0340 *

** No of cases with Wave P2 present *Insignificant

Graph 4 – Bar diagram showing the mean P2 wave latency in different age groups compared to controls



2) Left Eye

A) All Cases

Graph 5 – Pie chart showing no. cases with Present and Absent P2

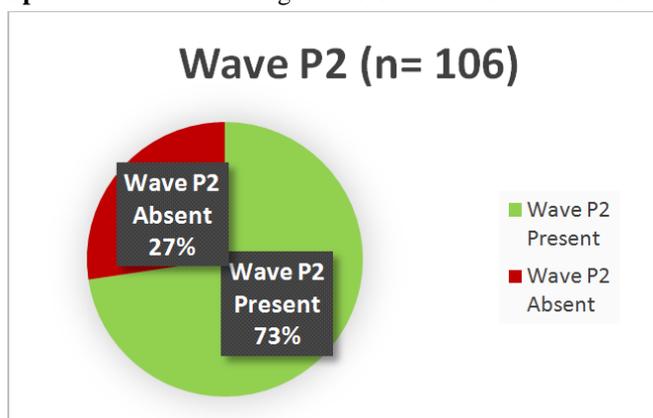


Table 5 a- Chi square Test was performed to calculate P value

	No. of Cases (n=106)	No. of Controls (n=30)	p- value
P2 Wave Present	77	30	.004 *
P2 Wave Absent	29	0	

*statistically significant

Table 5 b – Mean P2 wave latencies of Cases and Controls of left eye with p-value

VEP Parameter Latency(mS)	CASE Mean(SD) (mS) (n=77)**	CONTROL Mean(SD) (mS) (n=30)	P Value
Wave P2	126.49 (18.41)	98.82 (4.74)	0.0001 *

*statistically Significant

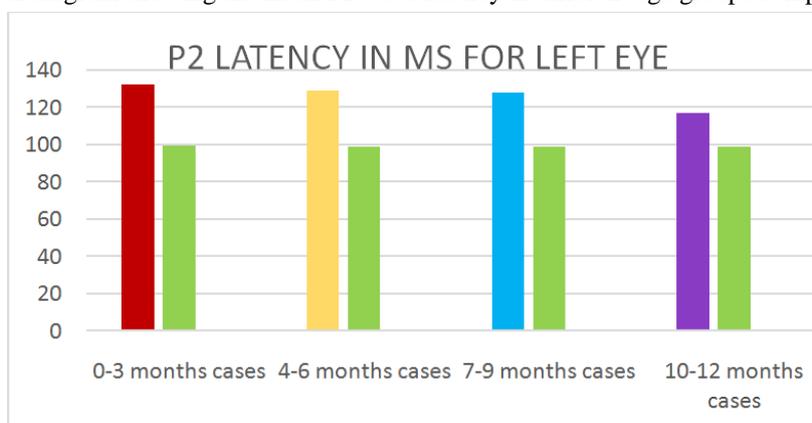
Table 6 - Showing mean latencies of P2 wave in different age groups

VEP Parameter Latency(mS) (LEFT)	CASE Mean(SD) (mS)	CONTROL Mean(SD) (mS)	P Value
0 – 3 months	132.21 (15.72) (n = 14)**	99.1 (4.40) (n = 9)	0.0001 *
4-6 months	128.99 (15.88) (n = 25)**	98.81 (4.45) (n = 8)	0.0001 *
7-9 months	127.89 (21.40) (n = 19)**	98.64 (4.61) (n = 6)	0.0033 *
10 – 12 months	117.09 (16.76) (n = 19)**	98.71 (5.48) (n = 5)	0.0262 *

** No of cases with Wave P2 present

*Insignificant

Graph 6 - – Bar diagram showing the mean P2 wave latency in different age groups compared to controls



3) Mean P2 latency comparison between right and left eye

Table 7– Mean P2 latency in cases where P2 wave is present in cases

VEP Parameter Latency(mS)	Right Mean(SD) (mS) (n=76)**	Left Mean(SD) (mS) (n=77)	P Value
Wave P2	125.74 (18.50)	126.49 (18.41)	0.8019*

* Not statistically insignificant

** Cases where Wave P2 is present

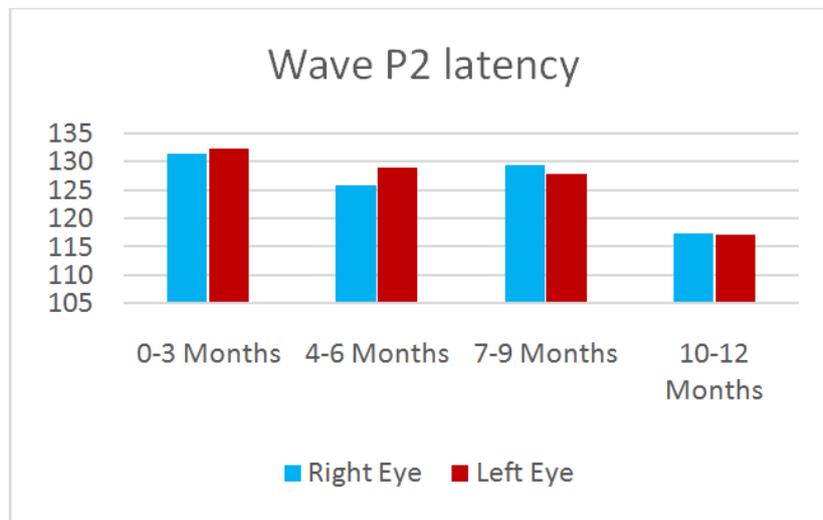
4) Inter Group ANOVA

Table 8 - showing Comparison of mean P2 wave latencies between the different age groups with p values

P2 Latency	GROUPS (AGE IN MONTHS) Mean (SD)				P Value
	0-3	4-6	7-9	10-12	
Right Eye	131.38 (17.25)	125.85 (15.60)	129.38 (20.61)	117.32 (17.85)	0.098*
Left Eye	132.21 (15.72)	128.99 (15.88)	127.89 (21.40)	117.09 (16.76)	0.065*

*Not statistically significant

Comparison between Wave P2 Latency of both eye in different age Groups



Analysis of results

Out of 106 infants with Perinatal asphyxia, 65 (61.32%) were males and 41 (38.68 %) were females (Graph 1). 31 (29.25 %) of the infants belonged to the age group of 0-3 months, 30(28.30%) in the 4-6 months age group, 24(22.64%) in 7-9 months age group and 21(19.81 %) in the 10-12 months age group. (Graph 2). 30 controls were taken. Chi square test was performed and it was found that with respect to age and sex, the cases and controls were not very different. The cases were properly matched with controls with respect to age and sex. Out of the 106 infants, 89 (83.96%) showed some degree of visual dysfunction in one or both eyes(absence of P2 or prolongation of P2 latency)

Wave P2 changes with respect to right eye-

Wave P2 was absent in 30 (28.30 %) cases (Graph 3). The P value is 0.003, so, there is statistically significant association between Wave P2 presence of Case and Controls (Table 3a). Among the cases where

Wave P2 was present (n=76), there was statistically significant prolongation of Wave P2 latency (Table 3b) compared to controls. This indicates a dysfunction of visual pathway.

In the age group 0-3 months, 16 (51.61%) infants showed absent Wave P2. Out of the 15 (48.39 %) infants in whom the wave P2 was present, there was statistically significant prolongation of Wave P2 latency. (Table 4) This indicates a dysfunction of visual pathway.

In the 4-6 months, 7 (23.33%) cases had absent wave P2. Out of the 23(76.67 %) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2 latency.(Table 4). This indicates a dysfunction of visual pathway.

In the age group 7-9 months, 5 (28.83 %) cases had absent wave P2. Out of the 19 (79.17%) infants in whom Wave P2 was present, there was statistically significant change in any of the wave latencies (Table 4). This indicates a dysfunction of visual pathway.

In the age group 10-12 months, 2(9.52 %) cases had absent wave P2. Out of the 19 (90.48%) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2 latency(Table 4). This indicates a dysfunction of visual pathway.

Wave P2 changes with respect to left eye-

Wave P2 was absent in 29(27.36 %) cases (Graph 5). There is statistically significant association between Wave P2 presence of Case and Controls (Table 5 a)

Among the cases where Wave P2 was present (n=77), there was statistically significant prolongation of Wave P2 latency(Table 5 b). This indicates a dysfunction of visual pathway

In the age group 0-3 months, 17 (54.84 %) infants showed absent Wave P2. Out of the 14 (45.16 %) infants in whom the wave P2 was present, there was statistically significant prolongation of Wave V latency (Table 6). This indicates a dysfunction of visual pathway.

In the age group 4-6 months, 5(16.67 %) cases had absent wave P2. Out of the 25 (83.33%) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2(Table 6). This indicates a dysfunction of visual pathway.

In the age group 7-9 months, 5(20.83 %) cases had absent wave P2. Out of the 19 (79.17) infants in whom Wave P2 was present, there was no statistically significant change in any of the wave latencies (Table 6).

In the age group 10-12 months, 2 (9.52 %) cases had absent wave P2. Out of the 19 (90.48%) infants in whom Wave P2 was present, there was statistically significant prolongation of Wave P2 latency (Table 6). This indicates a dysfunction of visual pathway.

There is no statistically significant P2 prolongation between the right and left ear (Table 7)

Inter group ANNOVA

Inter group one way ANNOVA for different age groups (Table 8) show that there was no statistically significant relation of Wave P2 latency between the different age groups in both eyes.

IV. Discussion

This cross sectional and observational study was carried out with 106 infants with history of Perinatal asphyxia and 30 age and sex matched control. All the infants belonged to the age group of 0-12 months. They were subjected to VEP testing according to International Society of Clinical Electrophysiology of Vision (ISCEV), 2009 standards¹⁴ and the VEP findings of the cases were analysed with respect to the controls. The parameters studied was the presence of waveform and latency of Wave P2 of each eye. These parameters were used to assess the presence of visual pathway abnormality in the infants with h/o Perinatal asphyxia.

The extent of organ system dysfunction determines the early outcome of an asphyxiated neonate. Hypoxic ischemic encephalopathy (HIE) refers to the CNS dysfunction associated with perinatal asphyxia. HIE is of foremost concern in an asphyxiated neonate because of its potential to cause serious long-term neuromotor sequelae among survivors.

In spite of scientific and technological advances in perinatal care, prenatal or perinatal brain injuries in survivors of neonatal intensive-care units do occur and are of concern to clinicians¹⁵. Early identification of those who have sustained insult to the immature nervous system is essential to instigate effective remedial action without delay¹⁶ and to reduce the severity of neurological injury¹⁷. Visual evoked potentials (VEPs) are potentially valuable prognostic tools in high-risk newborn infants. The test objectively evaluates the functional integrity of specific ascending pathways of the nervous system which are vulnerable to hypoxic-ischemic

Injury^{5, 9, 10}. A number of studies show that VEPs are sensitive to acute alteration of CNS function during and following asphyxia and provide information for long term prognosis^{18, 19, 20}.

The hypoxic damage results from various neurotoxic mechanisms secondary to the hypoxic insult including free radical injury, increased intracellular calcium, inflammatory cytokines, increased release of excitatory neurotransmitters. This ultimately leads to apoptosis and neuronal cell death.^{21,22,23}

Scalais et al showed that infants with perinatal asphyxia showed VEP waveform with increased latency of its components. Some cases had missing components while others had absent waveform⁷

de Vries et al showed that the VEP components latencies were delayed or absent in infants with perinatal asphyxia. Some cases had unusual waveform. The study showed that Visual evoked potentials (VEPs) are of predictive value for both neurological and visual outcome in the full-term infant with hypoxic ischemic encephalopathy (HIE)⁸.

Muttitt et al also showed similar VEP findings (delayed latencies, absent components) in infants with perinatal asphyxia. The study also showed good correlation with neurodevelopmental outcome in term infants

with Perinatal asphyxia and provide accurate prognostic information useful in the clinical management of these infants⁹

McCulloch et al showed abnormal latencies of VEP components or absent VEP. The study found strong association between normal, abnormal, or absent visual evoked potentials in the early postnatal period and long-term visual outcome¹⁰.

The aim and objectives of our study was to assess the nature of VEP changes in infants of perinatal asphyxia and to find out whether there is any difference between the findings of right and left eye.

In our study, out of 106 infants with perinatal asphyxia, 89 (83.96%) showed some degree of visual dysfunction in one or both eyes. Scalais et al, de Vries et al, Muttitt et al and McCulloch et al. show that there is similar P2 wave latency prolongation and absent components associated with perinatal asphyxia but in our study the percentage of abnormality is much more.

In our study, in addition, we attempted to analyse the VEP parameters separately in both eyes.

In Right eye, P2 wave was absent in 28.3 % cases and out of the ones where wave P2 was present, there was statistically significant prolongation of P2 wave, indicting visual pathway dysfunction. Similar findings were obtained from left eye. It was also found that there is There is no statistically significant P2 prolongation between the right and left ear.

This corresponds with the findings of study of Daphne L. et al which states that no significant differences exist in latencies to the first major positive peak for the right and left eyes in normal infants.²⁴ So, from our study we see that perinatal asphyxia does not contribute to any change in inter ocular VEP difference and affects both eyes equally.

In our study we divided the infants into 4 age groups and analysed the P2 latencies in two eyes separately. The age groups taken are:- 0-3 months, 4-6 months, 7-9 months and 10-12 months.

There is statistically significant prolongation in all the age groups in both the eyes in infants with perinatal asphyxia compared to control.

We find that the mean P2 latency is maximum in infants in the age group 0-3 months for both the eyes with gradual decrease in latency in the higher age groups. However, we do see that there is a spike of mean P2 latency in the age group 7-9 months in right ear but it is inconclusive.

However intergroup annova shows that there is no statistically significant changes among the different age groups. This is not in accordance with the findings found in a study by Lenassie E. et al, which stated that there is age-dependent exponential decreases in latencies in Flash VEPs in normal infants and pre-school children.²⁵

This can be possibly due to the fact that our study includes different grades of severity of perinatal asphyxia which affects the P2 latencies and masks the age-related changes. This effect of different grades of hypoxic ischemic encephalopathy on P2 latency in different age groups needs to be further explored.

From the above discussion we see that there are significant VEP changes in infants with history of perinatal asphyxia in our population. There is no interocular difference in the VEP findings implying that perinatal asphyxia affects both sides similarly. Our study also shows that there is no statistically significant age related P2 latency prolongation. The age related VEP changes in these infants have to be further explored with analysis of the effect of grades of hypoxic ischemic encephalopathy on VEP parameters at different ages.

Thus, based on the above findings we can say that VEP can serve as an early objective and non-invasive test to asses the neurological status and visual pathway in infants with birth asphyxia. This early diagnosis can help us initiate early rehabilitative and therapeutic measures and limit the socio-developmental adverse outcomes associated with birth asphyxia.

Limitations of my study include the lack of assessment of hypoxic ischaemic encephalopathy grade specific P2 latency changes. No follow up was done so the long term VEP changes could not be assessed.

V. Conclusion

VEP can be used for early assessment of the functional integrity and maturity of visual pathway and CNS function in infants of birth asphyxia. This helps in early initiation of rehabilitation process. Further follow up studies with larger sample sizes can be undertaken to strengthen the knowledge gained from this study.

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