VISUAL EVOKED POTENTIAL & ELECTRORETINOGRAM RESULTS IN PREVIOUSLY VENTILATED PRETERM INFANTS

By

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ABSTRACT

Background: *Previously ventilated preterms are at a high risk of abnormal visual and neurological development when compared to full term babies and non-ventilated preterms. Preterm birth is associated with retinopathy of prematurity and can also affect the development of brain structures associated with post-retinal processing of visual information. These impairments can continue into adolescence and adulthood and may contribute to the difficulties in learning, attention, behavior and cognition that some children born preterm experience. Electrophysiologic testing of the visual system requires primarily the ERG &VEP which useful in the diagnosis of visual loss in nonverbal patients especially in children.*

Aim of the work: *we aim to assess the VEP and ERG in previously ventilated preterm infants.*

Subject and Method: *this study is prospective case control study. The study was conducted on 100 preterm babies, male and female, less than 37week gestational age. The average age from 1 to 6 months with normal fundus examination. Half of them (50 babies) previously ventilated preterms as case group and 50 babies as control. this work was done for Preterms at Bostan Diagnostic Eye Center "Cairo-Egypt" from October 2021 to March 2022.VEP and ERG was done for each eye separately according to the International Society for Clinical Electrophysiology of Vision (ISCEV) standards protocols.*

Results: *There was a statistically significant association between groups and flash VEP, p value (<0.001). VEP absent in 90% of case group (preterms previously ventilated). A strong positive correlation between oculus dextrus (OD=RT Eye) flash ERG photopic b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated patients. A strong positive correlation between oculus sinister (OS=LT Eye) flash ERG photopic a wave latency in ms and age by months among ventilated patients. A moderate negative correlation between OD eye flash ERG* *photopic b wave amplitude in microvolt and gestational age by weeks among ventilated patients. A moderate positive correlation between OS eye flash erg scotopic 3.0 b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated patients. A weak positive correlation between OS eye flash ERG photopic b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated patients.*

Conclusion: *the result obtained by our study provide that VEP test in previously ventilated preterms was absent in 90% of cases. A strong positive correlation between OD eye flash ERG photopic b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated patients p-value (0.0019) and correlation coefficient (0.429). A strong positive correlation between OS eye flash ERG photopic a wave latency in ms and age by months among ventilated patients p-value (0.0018) and correlation coefficient (0.43).*

Key Words: *VEP, ERG, ISCEV, ventilated preterms.*

INTRODUCTION

Visual electrophysiology provides an objective assessment of the retina, optic nerve, and cortical responses. It is useful in determining the cause of visual impairment or in the monitoring of visual or neurological conditions **(Camuglia et al., 2011)**. The electroretinogram (ERG) represents the biopotential that is produced by the retina in response to a light stimulus **(Gauvin et al., 2018)**. The functional changes that occur in the retina with maturation can be evaluated with the full-field ERG, which represents the summed activity of distal retina in response to light **(Constable et al., 2020)**. The ERG is a useful tool for the study of neonatal ophthalmological disorders including retinopathy of prematurity as well as to study the maturation of the retinal function in preterm infants **(Bi, 2018)**. The VEP is a cortical response measured over the occipital lobes to flashing light or patterned visual stimuli. This is a test to determine the integrity of the nerve transmission from the eye to the brain **(Sandrini & Rossi, 2010)**. Premature infants are at high risk of neurological dysfunction **(T.C.Chen et al., 2010)**. Ophthalmic complications of prematurity include ROP, visual loss due to reduced development of visual cortex, **(Leung et al., 2018)**. Mechanical ventilation is a risk factor for cerebral inflammation and brain injury in preterm neonates. Any ventilation has the potential to have an impact on the immature brain. This is particularly important given that preterm infants are already at a high risk for brain injury simply due to immaturity **(Barton SK.et al.,**

2016). Various resuscitation methods and lifesaving interventions are associated with adverse effects. One such intervention is mechanical ventilation and if prolonged, it is known to cause various morbidities like retinopathy of prematurity (ROP). ROP was the most common complication associated with increasing duration of mechanical ventilation **(Madhu G. N. and Anil H. 2021)**.

AIM OF THE WORK

The aim of this work is to study the result of visual evoked potential & electroretinogram in previously ventilated preterms. We also aim at setting normative data for normal (non-ventilated) infants. Also set normative data for this age group who are difficult to examine.

SUBJECTS AND METHODS

Site of the study: this prospective case control study was done for preterms that were previously ventilated. These preterms underwent visual evoked potential and electroretinogram at Bostan Diagnostic Eye Center "Cairo-Egypt"

Inclusion criteria:

1. All babies are less than 37week gestational age.
2. All were previously ventilated at least 48hour. 3-All are in alert state without sedation.

Exclusion criteria:

- Congenital ocular disease.
- Fundus examination abnormalities.

Operational design: The principal investigator introduced him to all included participants' parents. After explaining the study's objectives and potential benefits, he invited them to participate in this study with all ethical considerations.

Ethical consideration:

1. A written informed consent was obtained from parents.
2. An approval by the local ethical committee was obtained before the study.
3. The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of the article.
4. All the data of the patients and results of the study are confidential and the patients have the right to keep it.

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Sample size:

$$\text{Sample size} = \frac{\frac{z^2 \times p\,(1-p)}{e^2}}{1 + \left(\frac{z^2 \times p\,(1-p)}{e^2 N}\right)} = 90$$

Where:

z is the z score

ε is the margin of error

N is the population size

p̂ is the population proportion

Methods:

The study was conducted on 100 preterm babies, male and female, less than 37 week gestational age. Half of them (50 babies) previously ventilated due to respiratory distress syndrome or any other causes related to prematurity. The duration of ventilation was different according to each case. The average age from 1 to 6 months. All babies were brought to the center with their parents, fasting at least 2 hours before examination. They were clinically free (e.g. no fever no cough).

All infants enrolled in the study were subjected to the following:

A. Full history taking:

1. Prenatal history: history of maternal infection, diseases and drug administrated to mother (free medical history).
2. Natal history: gestational age, sex, age, endotracheal intubation and duration on mechanical ventilation.

B. Complete clinical examination:

1. General; Active, conscious, tolerated oral feeding, no pallor or cyanosis, no fever.
2. Systemic;

- Head and neck; open anterior fontanelle not bulging or depressed, normal circumference.
- Chest; bilateral equal air entry, no sign of respiratory distress.

-Heart; s1 and s2 normal, no murmur, normal heart rate.

- Abdomen; lax, soft, no hepatosplenomegaly.
- Extremities; free.
- Neurological; no neurological abnormalities, no history of anticonvulsant medication.
- Eye; normal fundus examination, no congenital disease.

C. Specific investigation:

- Pediatric ERG recording **(ISCEV Standard 2022)**.

The ISCEV Standard protocol includes a minimum period of 20 min dark adaptation to enable assessment of DA (roddominated) retinal function. If recorded after the DA ERGs, a minimum period of 10 min light adaptation minimizes rod contributions and optimizes the selective contributions of the LA cone system. **(Anthony G et al., 2022)**. Infants can be swaddled if necessary. Contact lens electrodes with eyelid specula are suitable for infants, and pediatric sizes will be required. ERGs for this group should ideally be compared to those from typical subjects of the same age, although there may be little reference data available **(Daphne L et al., 2015)**. Infants were tested in an alert state without sedation, One or both parents stayed with the infant during the entire ERG session. Both pupils were dilated with one drop each of 1% tropicamide and 2.5% phenylephrine hydrochloride and then dark adapted for 30 min. The infant was placed supine in a crib and swaddled to prevent arm movements **(Adriana Berezovsky et al., 2003)**. All stimuli were presented in a Ganzfeld dome (a Roland consult German Machin). The Ganzfeld dome was attached to a 'custom-made' frame that allowed it to be lowered over the infant's head. Except for the supine position of the infant, the position of the head with respect to the Ganzfeld dome was the same as that used in standard clinical settings with adults **(Nusinowitz S et al., 1998)**. Signals were amplified (gain, ×10 000; 0.3–500 Hz), digitized, averaged, saved and displayed by a digital plotter (a Roland consult German Machin). ERGs were recorded using the standard ISCEV protocol. Since it was not an easy task to keep the infant alert and cooperative during the entire ERG session, any responses showing artifacts due to muscle activity and/or eye-movement were repeated.

VEP:

Flash VEP examination was done for each eye separately according to the ISCEV standards. Steady-state stimulation is a useful paradigm in physiologic and clinical situations for VEP. One of the advantages is the easy evaluation of the response via Fourier analysis **(Thomas & Michael, 2000)**. Recordings of flash VEPs were made from an occipital electrode (Oz). A ground electrode was placed on the mastoid, with a frontal electrode (Fz) used as a reference (Hardin get al. 1996). When necessary, the reference electrode was positioned anterior to the Fz to avoid placing it directly over the anterior fontanelle. Standard silver–silver chloride electrodes were fixed to the scalp with conducting paste.

Electrode impedances were usually below 5 ohm but always below 10 ohm. The amplifier bandwidth was 0.8 to 100 Hz and the gain was 5000. The stimulus was a Grass PS 33 plus photo stimulator (Astro-Med Inc., West Warwick, RI, USA). We did this work on Roland Consult machine Germany.

Analysis of the flash VEP:

Two trials were then averaged and all measurements were made from this average. Individual components were defined as ‘present’ if the Signal is more than double the noise and at least 1 μV from baseline on the average flash VEP.

Statistical analysis:

Data were analyzed using R version 4.0.5. Numerical variables; were described using mean, standard deviation, median, interquartile range, minimum and maximum. For categorical variables; frequency and percentage were applied. The Pearson's Chi-squared test was performed to compare the change in categorical variables. For comparing normally distributed numerical variables Welch Two Sample t-test was performed. For comparing non-parametric numerical variables Wilcoxon rank sum test was performed. All tests were two-tailed. A p-value of less than 0.05 was considered statistically significant with a 95% confidence interval (CI).

RESULTS

This study was carried out as prospective case control study; this work was done for 100 preterm babies. Half of them were previously ventilated. They did the electrophysiological assessment at Bostan Diagnostic Eye Center "Cairo-Egypt". The results of this study are presented in the following tables and figures.

Table (1): Descriptive data of preterm babies (N=100)

Preterms Characteristics	Not ventilated, N = 50[1]	ventilated, N = 50[1]
post-natal AGE BY MONTHS	Median (5.00) Range (3.25, 6.00)	3.00 (2.00, 4.00)
GESTATIONAL AGE BY WEEKS	Median 35.00 Range (34.00, 36.00)	33.00 (32.00, 34.00)
GENDER		
Female	24 (48%)	29 (58%)
Male	26 (52%)	21 (42%)
DURATION ON MECHANICAL VENTILATION BY DAY		
2:5_days	0 (0%)	33 (66%)
6:10_days	0 (0%)	11 (22%)
>10_days	0 (0%)	6 (12%)
[1]Median (IQR); n (%)		

This table shows the demographic data of both studied groups.

Table (2): Comparison between ventilated and non-ventilated preterm babies regarding flash ERG in both eyes

Characteristic	Not ventilated, N = 50[1]	ventilated, N = 50[1]	p-value[2]
OD eye flash ERG photopic b wave latency in ms	34.80 (31.47, 36.42)	37.00 (34.23, 39.60)	**0.001**
OD eye flash ERG scotopic 3.0 a wave latency in ms	18.61±2.55	19.89±2.85	**0.0199**
OD Eye flash ERG scotopic 3.0 b wave amplitude in microvolt	63.75 (41.42, 104.67)	42.60 (31.70, 55.02)	**<0.001**
OS eye flash ERG photopic a wave amplitude in microvolt	7.65 (4.58, 13.20)	14.85 (9.03, 21.15)	**0.001**
OS eye flash ERG photopic b wave latency in ms	34.85 (32.50, 37.30)	39.80 (34.10, 42.60)	**0.004**
OS eye flash ERG scotopic 3.0 a wave latency in ms	17.30 (16.40, 18.80)	21.00 (18.65, 21.90)	**<0.001**
OD eye flash ERG scotopic 10.0 a wave latency in ms	16.60 (15.95, 19.40)	18.75 (18.20, 19.30)	**0.001**
OS eye flash ERG scotopic 10.0 a wave latency in ms	17.35 (16.42, 18.90)	27.00 (19.88, 29.78)	**<0.001**
OS eye flash ERG scotopic 10.0 b wave latency in ms	40.50 (35.57, 48.40)	47.90 (46.60, 48.95)	**<0.001**

OS (Oculus sinister), OD (Oculus dextrus), ERG(Electroretinogram).

This table shows highly significant difference between ventilated & non ventilated preterms regarding all the parameters of flash ERG.

In this result we compare between ventilated and non-ventilated preterms regarding flash ERG photopic b wave latency in both eyes, the p value was statistically highly significant (0.001 in OD and OS 0.004). Flash ERG photopic wave's amplitude in OS, the p value was statistically significant (0.001). The flash ERG scotopic 3.0 a wave latency was a statistically significant in OD and statistically highly significant in OS, P value (0.0199 and <0.001) respectively. The flash ERG scotopic 3.0 wave amplitude in OS, the p value (0.084) was statistically significant. The flash ERG scotopic 3.0 b wave amplitude in OD, the p value (<0.001) was statistically significant. The flash ERG scotopic 10.0 a and b waves latency in OS the p value was statically significant (<0.001) **(Table 2)**.

Table (3): correlation between Flash ERG test and clinical data in previously ventilated preterms

Flash ERG test in patients	Clinical data	p.value
OD eye flash ERG photopic b wave amplitude in microvolt	Post-natal age by months	0.3917288
	Gestational age by weeks	0.0336083 *
	Duration on mechanical ventilation by day	0.0018856 *
OS eye flash ERG photopic a wave latency in ms	Post-natal age by months	0.0018323 *
	Gestational age by weeks	0.9835521
	Duration on mechanical ventilation by day	0.8985154
OS eye flash ERG photopic b wave amplitude in microvolt	Post-natal age by months	0.5531825
	Gestational age by weeks	0.2841565
	Duration on mechanical ventilation by day	0.0379547 *
OS eye flash ERG scotopic 3.0 b wave amplitude in microvolt	Post-natal age by months	0.2233135
	Gestational age by weeks	0.0779167
	Duration on mechanical ventilation by day	0.0147433 *

ERG (Electroretinogram), OS (Oculus sinister), OD (Oculus dextrus),

In our study we also found correlation between ERG test and clinical data as the following: - A strong positive correlation between OD eye flash ERG photopic b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated patients p-value (0.0019) and correlation coefficient (0.429). A strong positive correlation between OS eye flash ERG photopic a wave latency in ms and age by months among ventilated patients p-value (0.0018) and correlation coefficient (0.43). A moderate negative correlation between OD eye flash ERG photopic b wave amplitude in microvolt and gestational age by weeks among ventilated patients p-value (0.0336) and correlation coefficient (-0.301). A moderate positive correlation between OS eye flash ERG scotopic 3.0 b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated patients p-value (0.015) and correlation coefficient (0.34). A weak positive correlation between OS eye flash ERG photopic b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated patients p-value (0.038) and correlation coefficient (0.29) **(Table3)**.

Table (4): Comparison between ventilated and non-ventilated preterm babies regarding OD flash VEP

	Groups		
Characteristic	Not ventilated, N = 50[1]	ventilated, N = 50[1]	p-value[2]
OD flash VEP	50 (100%) **present**	45 (90%) **absent**	**<0.001**

OD (Oculus dextrus), VEP (Visual evoked potential)

This table shows highly significant difference between both groups regarding OD flash VEP.

Table (5): Comparison between ventilated and non-ventilated preterm babies regarding OS flash VEP

	Groups		
Characteristic	Not ventilated, N = 50[1]	ventilated, N = 50[1]	p-value[2]
OS flash VEP	50 (100%) **present**	45 (90%) **absent**	<0.001

OS (Oculus sinister), VEP (Visual evoked potential)

In This table there is high significant difference between both studied groups regarding OS flash VEP.

A chi-square test was conducted between groups and flash VEP in both eyes. There was a statistically significant association between groups and flash VEP, p (<0.001). Also we found All control group (preterms non-ventilated) had present flash VEP bilaterally but absent in 90% of case group (preterms previously ventilated) **(Tables 4 and 5)**.

DISCUSSION

Due to advances in perinatal intensive care, there has been a distinct decrease in the mortality of newborns with low birth weight and neurological morbidity. While the number of live newborns in the lowest weight categories has only slightly increased, the number of these newborns that survive the neonatal period has significantly increased **(Henry and Fouladkhah, 2019)**. The immature visual pathway is very sensitive to various perinatal insults **(Vaes et al., 2019)**. The parieto-occipital cortex is one of the area's most sensitive to hypoxia, and impairment of this area may be associated with visual defects of varying severity **(Choi et al., 2022)**. CNS immaturity is quite frequently complicated by periventricular and/or intraventricular hemorrhage, and strabismus develops in 50% of these patients. Intraventricular hemorrhage can cause post-hemorrhagic hydrocephalus and appears in 30 - 40% of newborns with a gestational age of 32 weeks or less **(Pehere et al., 2018)**. **Daphne L et al., (2015)** premature infants require special recording protocols and norms outside of this International Society for Clinical Electrophysiology of Vision (ISCEV) Standard. Later in infancy, ERGs approach adult waveforms and amplitudes. ERGs can be recorded from infants and children. The infant, the more chance that adult norms will not apply. ERGs mature during infancy, and signals from young infants must be interpreted with caution. **Jing et al., (2013)** reported that preterm and term infants underwent FVEP recordings and neurodevelopmental examinations at 1, 3, 6, 9, 12, and 18 months of corrected and chronological ages. **Erhan A. (2019)** found that visual maturation was better in females; the most prominent maturation began in the period of 3-6 months of (corrected) age, it continued gradually in the following months, and visual maturation generally approached the final adult values by drawing a plateau between 12-18 months of (corrected) age. In our work also A chi-square test was conducted between groups and flash VEP in both eyes. There was a statistically significant association between groups and flash VEP, p (<0.001). Also we found All control group (preterms non-ventilated) had present flash VEP bilaterally but absent in 90% of case group (preterms previously ventilated).

Sayeur et al. (2015A) found no significant differences between preterm and full-term groups for either amplitude or latency of N1 and P1 components. At school age, the preterm group manifested significantly higher N1 amplitudes and tended to show higher P1 amplitudes than the full-term group. Statistical significance is usually evaluated by testing individual or group results against the data of a control group, e.g., the ISCEV standards recommend the recording of normal values for each recording condition **(Harding GFA et al., 1996)**, **(Marmor MF et al., 1996)**. **Sayeur et al. (2015B)** reported that VEP abnormality was found more common in premature infants as compared to full-term infants. In the study conducted by **Kim et al., (2018)** it is suggested that prolonged VEP latencies may be an indicator of psychomotor retardation. VEPs test has become important in detecting low visual acuity at subclinical level. VEP values have prognostic significance in asphyxiated newborns **(Kato T and Watanabe K, 2006)**. **Pike AA and Marlow N (2000)** reported that VEP may give a clue about the neurodevelopmental process of cerebral palsy as early as 12 - 24 months. It was indicated that changes in P100 latency in the VEP test were significant in the first 6 months, it usually reaches the adult values around 1 year of age, and premature infants reach these values a little later **(Drislane FW., 2007)**. Our current study findings indicate that correlation between ERG test and gestational age by weeks and, age by months, duration on mechanical ventilation as the following; A statistically significant moderate negative correlation between OD eye flash ERG photopic b wave amplitude in microvolt and gestational age by weeks among ventilated preterm babies p-value (0.0336) and correlation coefficient (-0.301). also The results of our present study found that A statistically significant strong positive correlation between OS eye flash ERG photopic a wave latency in ms and age by months among ventilated preterm babies p-value (0.0018) and correlation coefficient (0.43). **Daphne L et al., (2015)** lower ERG amplitudes and longer peak times generally apply below 6–12 months of age under dark-adapted conditions, and below 2–3 months of age under light-adapted conditions. Below 6 months of age, the dark-adapted 3 ERG may be poorly defined in healthy infants; dark-adapted 10 ERGs are usually well defined in infants without retinal disease at all ages. Note that ERG amplitudes increase rapidly in early infancy and decrease with age in adults, most substantially in elderly populations. **Parvaresh et al. (2009)** showed that no significant difference was found between right and left eye measurements by gender and age. There was also no significant difference between male and female ERG amplitudes and implicit times within different age groups. A statistically significant effect of gender on ERG recordings has been reported by **(Zeidler, 1959) (Birch DC & anderson JL., 1992)**. But, **Parvaresh et al. (2009)** did not observe any difference between male and female subjects in their study. **Daphne L et al., (2015)** Pediatric ERGs should ideally be compared to those from typical subjects of the same age, although there may be little reference data available. Moreover, a statistically significant strong positive correlation between OD eye flash ERG photopic b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated preterm babies p-value (0.0019) and correlation coefficient (0.429). In addition, in this study a statistically significant weak positive correlation between OS eye flash ERG photopic b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated preterm babies p-value (0.038) and correlation coefficient (0.29). In a study done by us a statistically significant moderate positive correlation between OS eye flash erg scotopic 3.0 b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated preterm babies p-value (0.015) and correlation coefficient (0.34). **Madhu GN et al. (2021)** stated that retinopathy of prematurity was seen in 19 cases and was the most common complication associated with increasing duration of mechanical ventilation, which accounted for 48% of total complications.

In our study we compare between ventilated and non-ventilated preterms regarding flash ERG in both eyes we found that; Flash ERG photopic b wave latency in both eyes, the p value was statistically highly significant (0.001 in OD and OS 0.004). Flash ERG photopic a waves amplitude in OS, the p value was statistically significant (0.001). Flash ERG scotopic 3.0 A wave latency was a statistically significant in OD and statistically highly significant in OS, P value (0.0199 and <0.001) respectively. Flash ERG scotopic 3.0 wave amplitude in OS, the p value (0.084) was statistically significant. The flash ERG scotopic 3.0 b wave amplitude in OD, the p value (<0.001) was statistically significant. Flash ERG scotopic 10.0 a and b waves latency in OS the p value was statically significant (<0.001). The purpose of this study was to determine electroretinographic parameters according to ISCEV in previously ventilated preterms with normal fundus. **Adriana B et al., (2003)** found that a small maturational change in ERG parameters from 3 to 8 weeks of age.

CONCLUSION

The result obtained by our study provide that VEP test in previously ventilated preterms was absent in 90% of cases. A strong positive correlation between OD eye flash ERG photopic b wave amplitude in microvolt and duration on mechanical ventilation by day among ventilated patients p-value (0.0019) and correlation coefficient (0.429). A strong positive correlation between OS eye flash ERG photopic a wave latency in ms and age by months among ventilated patients p-value (0.0018) and correlation coefficient (0.43).

RECOMMENDATIONS

We recommended that VEP and ERG screening for all previously ventilated preterms. Flash VEP&ERG test should be done as early as possible after birth. Further studies with larger sample size and follow up the VEP&ERG during the first year of life. The prognosis of preterms should be established by using clinical assessment, neuroimaging. On the basis of this information, parents should be informed about the prognosis for their babies' condition to start the plan of treatment and follow up.

LIMITATION

Need more number of cases (previously ventilated preterms). Not easy to collect this data and in compare with the same age groups. Explanation to the parents to accept the test and start follow up with treatment. Examination of the cases without sedation

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