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Visual Evoked Potential In Normal Individuals And In Diabetic Patients Without Retinopathy - A Comparative Study

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Abstract:

Background: *Diabetic Retinopathy can lead to irreparable loss of vision if not treated early. Visual evoked potential (VEP) is a non-invasive neurophysiological examination that can be used to detect very early retinopathic changes by detecting the retinal ganglion cell damage measured by the latency. In our study we are comparing the VEP in normal individuals and diabetic patients without retinopathy .*

Aim: *To detect changes in Visual Evoked Potential in diabetic patients without retinopathy and to compare the amplitude and latency in normal individuals.*

Methodology:

A cross sectional study.

Inclusion criteria:

Both sexes.

Patients with diabetes and no retinopathy

Patients without Retinopathy.

Exclusion criteria:

Other Metabolic disorders.

Corneal or lenticular opacity.

Disorders of Peripheral nervous system.

Any blood disorders.

Study group: *The patients were divided into 2 groups. 50 patients in each group*

Examination and Testing: *After Detailed history and general examination, all the patients were subjected to ophthalmic examination to rule out retinopathy and subjected to VEP*

Results: *The mean P100 latencies in diabetic patients were significantly prolonged ($p < 0.05$) compared to controls The mean P100-N145 amplitude in diabetic patients were significantly reduced ($P < 0.05$) compared to controls The mean P100 – N145 amplitude was significantly reduced with the increasing duration of diabetes. (p.value <0.05)*

Conclusion: *This study shows that the VEP changes may be related to the poor control and long duration of the disease and hence can be used as a marker for assessing early diabetic retinopathy changes.*

Keywords*: Diabetic retinopathy, VEP latency,Visual evoked potential*

INTRODUCTION:

Diabetes is the most common endocrine disorder characterized by defect in the secretion of insulin and /or resistance to insulin action resulting in hyperglycaemia. In India it has been estimated that nearly

19.4 million individuals are affected by this disease and by the year 2025 it is likely to reach nearly 57 million people and by the year 2030, diabestes affected individuals will reach 62 million[1].

Diabetes leads to both microvascular and macrovascular complications[2]. Most common primary microvascular complications of diabetes can be noted in the eyes as diabetic retinopathy which is caused by damage to the retinal vessels[3]. It occurs in patients with uncontrolled high blood sugar levels over a period of time and can lead to blindness subsequently.

Visual evoked potential (VEP) is a non-invasive neurophysiological examination. It is used to detect very early retinopathic changes by detecting the retinal ganglion cell damage measured by the latency[4]. This can be used as a marker to detect the same.

Visual evoked potential (VEP) can measure the conduction system of the visual pathway which extends from the retina, optic nerve, optic chiasma, optic tract and optic radiation to the occipital lobe of the visual cortex thereby assessing its function[5]. The integrity that was assessed by this recording represents response of cortical and subcortical visual areas to visual stimuli.

The evoked potential can be measured in peak amplitudes (μv) as well as latencies (msec) which can provide quantitative analysis of the neurological examination.

Diabetes being a metabolic disease affects nearly every organ system in the body. Hence early monitoring and proper glycemic control is crucial to avoid complications.

In our study, pattern stimulated VEP (P100 and N75 latencies) in the people with diabetes mellitus shows distinct prolongation of latency period which is explained with findings of **Karlica et al[6]**., who suggested that in Diabetes there is a tendency of ischemia in the neuronal and other retinal structures which could cause microangiopathic changes hence resulting in VEP latency prolongation.

According to **Dobrila Karlica et al.,** the amplitude value decreased progressively and the latency values increased progressively in children with diagnosed diabetes mellitus. In our study, the mean P100 latency was significantly longer in poorly controlled DM group than those with good control; and the mean P100 latency of VEP showed significant difference with the glycemic control of DM.

Verrotti et al., found that P100 latency was significantly delayed in diabetic patients compared to the control group which is in correlation with our study[7].

The changes in the latency of VEP correlates with the levels of blood glucose levels and this analysis of VEP can provide early diagnosis of diabetic changes and prognosis during treatment. This can prevent the deadly outcome of diabetes. Thus VEP can be a useful technique to detect any disturbance in the anterior visual conduction.

MATERIALS AND METHODS:

Experimental design:

A cross sectional study.

Subject recruitment:

After explaining the details regarding the study, an informed consent was taken from each of the patient and controls involved in the study.

All the subjects were subjected to a thorough and detailed General examination. The subjects underwent VEP and the results interpreted.

Criteria for selection:

Inclusion criteria:

Both sexes.

Patients with diabetes.

Patients without Retinopathy.

Exclusion criteria:

Other Metabolic disorders.

Corneal or lenticular opacity.

Disorders of Peripheral nervous system.

Any blood disorders.

General examination:

General examination of the selected patients was done in the Department of Medicine and a detailed history was taken followed by thorough physical examination. All the patients were subjected to ophthalmic examination to rule out retinopathy. Patients with diabetic retinopathy were excluded from

the study. The patients were divided into two groups and the study was conducted in accordance with the ethical standards.

Study group:

The study groups were divided into Group I and Group II.

Group I:

50 subjects without diabetes mellitus were included in this group. 25 Males and 25 females and their mean age were 55.96 ± 8.69 years.

Group II:

50 subjects with diabetes and without retinopathy were included in this group. 25 Males and 25 Females with Type II DM (mean age was 57.82 ± 8.65 years), with duration of diabetes varying from 1 year to 15 years (mean age was 6.1 ± 3.59 years).

Electrophysiological Study:

Visual Evoked Potential:

Instrument name:

RMS EMG EP Mk2 was used for the evaluation of visual Evoked potential.

Preparation of the subjects:

Subjects were advised to come without applying oil to the scalp (dry hair) as it can interfere with testing. Use of any pharmacologically dilating eye drops is restricted. Pattern stimuli for VEPs were presented to the subjects on the day of examination. Visual acuity of the subjects was first recorded and then the subjects were optimally refracted for viewing distance of the screen. Distance between the TV screen and each subject was maintained at a constant distance of 100 cms.

The subjects were seated and then advised to view the center of pattern field from a calibrated viewing distance after attaching the standard electrodes. Monocular stimulation is considered as standard.

Placement of Electrodes:

Skin electrode i.e. standard silver-silver chloride was used for recording VEPS. The skin was prepared prior to the placement of the electrodes and gel was used to ensure good stable electrical connection.

The electrode impedances were kept below 5 K ohms, measuring between l0 and 100 Hz. To reduce electrical interference the difference was maintained at less than 20% between the two electrode sites.

The scalp electrodes were placed relative to the bony landmarks, in proportion to the size of the head, according to the International 10/20 system. The active electrode was placed on the scalp over the visual cortex at the level of Oz with reference electrode at Fz. A separate electrode was attached to a relatively indifferent point and connected to the ground; commonly used ground electrode positions include the forehead, vertex (Cz), mastoid, earlobe (Al or A2), or linked earlobes.

Pattern stimuli:

A high contrast black and white checkerboard was used for stimulation (Pattern stimuli). The viewing distance of 100 cm was adjusted to obtain a suitable field size and the required check sizes for any physical size of display screen.

Field and check size:

Patterned stimuli are defined by visual angle subtended by the side of` a single check in degrees (°) or minutes of` arc (min) subtended at the eye. One degree equals to 60 min of` arc. For standard pattern VEPs, two check element sizes were used: 1°±20 and 0.25° ± 20% per side. All checks were square with equal number of light and dark checks. A fixation point is positioned at a corner of four checks which are located at the center of the field.

Luminance and contrast:

The mean luminance of the checkerboard was 50 cd/s/m^2 (40-60 cd/s /m^2) and contrast between black and white squares was high. The luminance and contrast of` the stimulus were maintained uniform between the center and the periphery of the field.

Pattern-reversal stimuli:

For the pattern-reversal stimuli, the black and white checks were abruptly phased (i.e., white to black and black to white) and repeated at a specified number of reversals per second.

The large check of 1° and small check of 0.25° stimuli are specified by the check width (visual angle), the stimulus rate (in reversals per second), and the number of reversals, the mean luminance, the pattern contrast, and the field size. Reversal rate of two reversal per second (±10%) were used to elicit the standard pattern-reversal VEP.

Amplification and filtering

Amplification of the input signal by 20,000-50,000 times was used for recording the VEP. Input impedance of the preamplifiers were kept at least 100dB and the common mode rejection ratio not exceeding 120 dB.

The amplifiers were electrically isolated from the subject and (noted to meet the current standards for safety for clinical biologic recording equipment. The analogue signal was digitized at minimum sample rate of 500 samples/s/ channel with a minimum resolution of 12 bits. The Automatic artifact rejection which is based on signal amplitude was used to exclude the signals exceeding ±50-100 μV in amplitude.

Amplifiers were returned to baseline following rapid artifactual signals. The Analogue high pass and low pass filters [-3 dB points] were set at Bl Hz and at C100 Hz, respectively.

The Analogue filter roll-off slopes were not exceeded l2 dB/octave for lower frequencies and 24 dB/octave for the higher frequencies.

Analysis time:

The analysis time (sweep duration) 0f 300 msec was kept for all the subjects with pattern reversal VEPs.

VEP report:

Two recordings of each VEP condition was acquired, measured, and displayed to confirm the reproducibility of the data. The peak Pl00 latency, N75 latency and P100-N145 amplitude were studied.

VEP interpretation:

VEP is interpreted based on latency of P100 and N75 wavelength and amplitude of P100 - N145 waveform for both controls and diabetics. Results were analysed.

RESULTS:

Study Group:

Group I:

50 subjects, 25 Males and 25 Females were selected as control group. Their mean age was 55.96 ± 8.69 years

Group II:

50 subjects, 25 Males and 25 Females with DM (mean age was 57.82 ± 8.65 years), with duration of diabetes varying from 1 year to 15 years (mean duration was 6.1 ± 3.59 years).

Statistical Analysis

Data were collected, tabulated, and analysed using SPSS computer program for windows version 16.0. Qualitative data were presented as numbers and percentages. Quantitative data were expressed as mean and standard deviation (SD). Student‘t’ test/ Independent sample t test was used for the comparison of VEP between non diabetic and diabetes group. In order to investigate the statistical significance between groups, we used "Independent sample t test ($p < 0.05$).

One way analysis of variance (ANOVA) was used for comparing the VEP latencies and amplitude with duration of DM and different level of glycemic control.

VEP P100 latency between control and diabetes:

The mean P100 latencies in diabetic patients were significantly prolonged ($p < 0.05$) compared to controls i.e. 102.32 ± 4.05msec Vs 94.12 ± 2.63 msec.

VEP amplitude between control and diabetes:

The mean P100-N145 amplitude in diabetic patients were significantly reduced ($P < 0.05$) compared to controls i.e. 3.23 ± 0.94 μv Vs 7.41 ± 1.11 μv

	No. of Subjects	Amplitude (μv) (mean ± SD)	p value
Controls	50	7.41 ± 1.11	0.02
Diabetes	50	3.23 ± 0.94	

Table 1: A comparison of Amplitude of Visual Evoked Potential between Controls and DM.

Relationship between duration of diabetes and VEP latency and amplitude:

Among the subjects, the duration of type II diabetes mellitus was found to be between 1 year and 15 years with a mean of 6.1 ± 3.59 years. The subjects were distributed into 3 groups based on the duration of diabetes - Subjects <5 years, 5 – 10 years and > 10 years duration of diabetes mellitus.

Latency of VEP and duration of diabetes:

Distribution < 5 years: 20 subjects, 5 to 10 years: 22 subjects, >10 years: 08subjects. The mean P100 latency in test groups with the duration of diabetes <5 yrs was 100.913±5.02, 5 to 10 yrs was 102.86±2.83 and > 10 years was 103.62 ± 3.44 msec. The difference between the mean P100 latencies among the 3 groups was found to be highly significant with $p < 0.05$.

Duration (yrs)	No. of Subjects	P100 latency (msec) (mean ± SD)	p value
<5	20	100.913 ± 5.02	0.0001
5 – 10	22	102.86 ± 2.83	
> 10	08	103.62 ± 3.44	

Table 2: Analysis of P100 Latency in regard with different durations of Diabetes Mellitus:

Amplitude of VEP and duration of diabetes:

The mean and SD of Visual Evoked Potential P100-N145 in test groups with the duration of diabetes <5, 5 to 10, > 10 years was 3.34 ± 1.08mv, 3.29 ± 0.82μv and 2.8 ± 0.9 μv. The mean P100 – N145 amplitude was significantly reduced with the increasing duration of diabetes. (p.value <0.05)

Duration (yrs)	No. of Subjects	Amplitude (ms) (mean ± SD)	p value
<5	20	3.34 ± 1.08	< 0.0001
5 – 10	22	3.29 ± 0.82	
> 10	08	2.8 ± 0.9	

Table 3: Analysis of the mean P100-N145 Amplitude in regard with durations of Diabetes Mellitus:

DISCUSSION:

Diabetes is a common metabolic disease which affects most of the population. The complications of diabetes are preventable if diagnosed early and strict glycemic control is maintained.

Latency delay in visual evoked potentials is found in certain central demyelinating diseases and metabolic disorders. This change in potential gives an outline regarding the progression and severity of diabetes. It can be therefore used as an useful investigational method in establishing neuropathy developing in the central nervous system especially in Diabetes. Poor control of glucose levels leads to changes in the potential. It is therefore the **duty of physician to control the glucose levels adequately to prevent complications.**

In our study, the mean P100 latency was significantly longer in poorly controlled DM group than those with good control; and the mean P100 latency of VEP showed significant difference with the glycemic control of DM.

The mean P100 latency was significantly longer and the mean P100 - N145 amplitude was significantly reduced with the increasing duration of diabetes.

Dobrila Karlica et al., found statistically significant correlation between diabetes duration and P100 wave latency and amplitude, which indicates that ischemic neuronal and other retinal structure damage generated by microangiopathy is the major but not the only cause of neurophysiologic changes. Latency values, in patients with diabetes, tend to increase with time, which is a direct sign of ganglion cell damage. In our study VEP latency and amplitude is correlated with duration of the diabetes and was found that there was a significant changes in VEP.

Thus, VEP can serve as a marker for progression and severity of the disease.

CONCLUSION:

Visual evoked potential is an useful non invasive investigatory method in establishing central nervous system neuropathy developing in diabetes.

This study also shows that the VEP changes may be related to the poor control and long duration of the disease, both of which were associated with significant VEP latency prolongation and decreased amplitude.

To conclude, the biophysiological explanation for the cause of VEP abnormalities and hyperglycemia can be explained on the basis of elevated glucose which can alter cell osmolarity and ion transport and it is more relevant to the time scale of the effects observed in the current study. In tissues that do not require insulin for glucose transport across the cell membrane (e.g., cornea, lens, and retina of the eye), glucose enters the cells at a rate directly proportional to that of ambient glucose levels.

Elevated glucose has been shown to impair the operation of sodium potassium- adenosine triphosphatase, which produces alterations in the Na+-H+ exchange process and in pH, in addition to increase intracellular sorbitol through the action of the polyol pathway. These three processes are highly interconnected and have been shown to alter myoinositol uptake and metabolism, leading to further decrease in sodium-potassium- adenosine triphosphatase and thus changes in essential sodium, calcium, and potassium- dependent cellular processes.

Such processes are essential for the normal function of all cells, and their importance for the normal function of the photoreceptors, retinal pigment epithelium, and neural tissues of the visual system is readily apparent. This might be the cause for the VEP abnormalities in poorly controlled diabetes mellitus group.

This study also clearly shows that changes in VEP may be detected in diabetics before the onset of retinopathy.

Thus VEP measurement may be considered as a method for detecting pre retinopathy changes and has the potential to reduce DM complications.

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