e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2023; 13(1); 320-329

Original Research Article

Comparing Visual Evoked Potentials in Patients with Chronic Kidney Disease, Hemodialysis, and Renal Transplantation Patients: A Comprehensive Study

Suganya Gunasekaran[1*], Dhivya Krishnamoorthy[1], Ramya Selvaraj[2]

[1]Assistant Professor, Department of Physiology, Government Medical College Namakkal Tamilnadu, India

[2]Assistant Professor, Department of Ophthalmology, Government Medical College Dindigul, Tamilnadu, India.

Received: 18-07-2022 / Revised 26-09-2022 / Accepted 20-11-2022

Corresponding author: Dr Suganya Gunasekaran

Conflict of interest: Nil

Abstract:

Chronic kidney disease (CKD), hemodialysis, and renal transplantation patients are at risk for functional changes in the central nervous system (CNS), even if they show no clinical symptoms in the early stages. These changes can be detected by measuring the electrical activity of the brain (electrocortical activity). Visual evoked potentials (VEPs) are a type of electroencephalography (EEG) test that is more sensitive than traditional EEG for detecting early CNS involvement in CKD, hemodialysis, and renal transplantation patients. In this study, a total of 80 eligible participants were selected in four groups of which 20 were sex and gender matched controls, 20 were CKD patients, 20 were CKD patients on hemodialysis, 20 were CKD patients who underwent renal transplantation. Height, weight, BMI, Serum urea, Serum creatinine, and Blood pressure and VEP parameters were measured. Serum urea and creatinine levels were significantly higher in hemodialysis patients than in CKD patients and CKD patients on renal transplantation. Hemodialysis patients have higher levels of serum urea and creatinine than CKD patients and CKD patients on renal transplantation. In the present study, significant association between serum urea, serum creatinine and N 75, P100, N 145 latency, which was not corroborated by other studies, an association was found between VEP results and biochemical parameters. In summary, our study findings reveal significant differences between the control group and the CKD study groups across various VEP parameters. Notably, in CKD patients, there is a trend of prolonged latencies, particularly in P100, when compared to controls. Additionally, a decrease in VEP amplitude is observed in the study groups, particularly in CKD HD patients, indicating the impact of uremic toxicity. These results emphasize the potential diagnostic value of VEP in assessing CNS involvement in CKD patients.

Keywords: Visual Evoked Potentials, Chronic Kidney Disease, Hemodialysis, and Renal Transplantation Patients, serum urea, serum creatinine

Introduction

Chronic kidney disease (CKD) encompasses various pathophysiological processes associated with abnormal kidney function and a gradual decline in glomerular filtration rate (GFR) over time[1]. CKD is typically defined as kidney damage or an

estimated GFR (eGFR) persisting below 60 ml/min/1.73 m² for at least three months[2]. CKD is categorized into stages based on the degree of kidney damage and GFR reduction. One hallmark of kidney damage in many kidney diseases is albuminuria, defined as an albumin-creatinine ratio exceeding 30 mg/g in two of three spot urine collections[3]. The term "uremia" refers to the symptomatic stage of patients with CKD and is caused by the accumulation of organic waste products usually excreted by the kidneys. Increased plasma urea concentration can have detrimental effects by promoting carbomylation[4-6].

Accumulation of uremic toxins can harm various bodily systems, with the central nervous system (CNS) being particularly susceptible[4]. Although synaptic dysfunction and neuronal axonal degeneration contribute to neural symptoms, the precise basis for CNS abnormalities remains unclear. It is suggested that the buildup of organic and inorganic substances such as urea, creatinine, uric acid, carnitine, polyamines, indolic acid, myoinositol, guanidine compounds, sulfate, phosphate, hippurate, and acetone may affect the CNS[7-9].

Chronic dialysis can mitigate the severity of these disturbances, reducing the overt manifestations of uremia. However, optimal dialysis therapy may not entirely address all issues resulting from impaired kidney function.

Serious complications of progressive CKD involving the CNS, such as uremic encephalopathy, may be detected earlier through alterations in Visual Evoked Potential (VEP) parameters. Given the progressive and irreversible nature of CKD, early evaluation of complications using VEP parameters is advisable[10-12].

VEP is a straightforward, non-invasive test that can provide insights into CNS involvement. This research study aimed to assess the changes in VEP in CKD stage 4-5, CKD patients on Hemodialysis, and those who underwent Renal Transplantation to detect complications as early as possible. Early intervention may help prevent visual loss morbidity in these patients.

VEP, or Visual Evoked Potential, records electrical responses from the nervous system in response to visual stimuli. It reflects the mass response of cortical and subcortical areas following visual stimulation. The physiological basis of VEP involves the generation of electrical activity at three locations: photoreceptors, bipolar cells, and ganglion cells.

In normal resting cells, there is a constant potential difference between the inside and outside of the cell membrane, known as the Resting Membrane Potential[10]. During depolarization, caused by the movement of Na+ and K+ ions, a potential difference is generated between two electrodes. Impedance is the resistance offered to current flow by intervening tissue.

The P100 waveform of VEPs primarily originates in the occipital cortex through the activation of the primary visual cortex and surrounding areas by thalamocortical fibers. The visualized waveforms include N75, P100, and N145. P100 peak latency, amplitude, and duration are commonly used for VEP analysis[12].

In summary, CKD is associated with various pathophysiological changes, and VEP is a valuable tool for assessing CNS involvement in these patients. Early detection and intervention may help mitigate complications associated with CKD.

Aim and Objective:

To evaluate the visual evoked potential in patients with chronic kidneydisease, patients on hemodialysis and renal transplant patients.

1. To evaluate the subclinical neuropathy in chronic kidney disease patients, patients on hemodialysis and renal transplant patients.
2. To compare the visual evoked potential in patients with chronic

kidney disease, hemodialysis and renal transplant patients and age and sexmatched controls.

Materials & Methods:

This is Comparative cross sectional study carried out in Government Kilpauk Medical College in Chennai.Patients were recruited and laboratory measurements were conducted as part of a routine visit to the outpatient transplant clinic at the Department of Nephrology, Transplantation, and Internal Medicine located at Government Kilpauk Medical College in Chennai. In the study design, we have employed a comparative cross-sectional approach involving a total sample size of 80 participants, divided into four distinct groups:

1. Group 1: This group comprises 20 healthy volunteers, carefully selected to match in terms of age and gender, and they will serve as our control subjects.

2. Group 2: In this group, we have included 20 individuals who are diagnosed with Chronic Kidney Disease (CKD) and possess a Glomerular Filtration Rate (GFR) within the range of 15-30 ml/min. These patients have been dealing with CKD for a period exceeding 3 months.

3. Group 3: Consisting of 20 participants, this group comprises individuals with CKD who have a GFR below 15 ml/min and have been coping with the condition for over 3 months. Notably, these patients are undergoing hemodialysis treatment.

4. Group 4: In this group, we have enlisted 20 individuals who have previously undergone renal transplantation and are currently managing CKD.

Each group plays a distinct role in our study, contributing valuable insights into the impact of CKD on various patient populations.

Height, weight, BMI, Serum urea, Serum creatinine, and Blood pressure and VEP parameters were measured. Statistical analysis was done to compare the findings between the controls and the study groups and also within the study groups. ANOVA and Post Hoctest LSD – Least Significant Difference were used for Multiple Comparisons between controls and study groups and also within the study groups. The mean difference is significant at the 0.05 level. This study was done in accordance with the Declaration of Helsinki and approved by Institutional Ethics Committee, Government Kilpauk Medical College in Chennai (Protocol ID No10/2017 Dated: 08-06-2017).

Inclusion criteria: The inclusion criteria for this study are as follows:

1. Patients must have been diagnosed with chronic kidney disease (CKD) in the Department of Nephrology and have a Glomerular Filtration Rate (GFR) between 15 and 30 ml/min.
2. The duration of CKD should be greater than 3 months.
3. Male and female individuals between the ages of 20 and 35 are eligible.
4. Patients must express a willingness to participate in the study.

Exclusion criteria:

The exclusion criteria for this study are as follows: Presence of cataract, Diagnosis of glaucoma, Presence of optic atrophy, Any underlying neurological disorder, Visual acuity less than 6/18, History of traumatic neuropathy, Use of nephrotoxic drugs. These criteria specify the conditions or factors that would disqualify individuals from participating in the study.

Patients who qualify for the study will be enrolled and undergo the following assessments: Blood pressure, Height, Weight, Visual acuity using Snellen's chart, Fundus examination to rule out retinal pathology, Brief history to rule out drug intake, hypertension, and diabetes mellitus and General clinical examination.

A written informed consent was obtained from patients after explaining the

procedure and its significance in their vernacular language. Institutional Ethical committee approval was obtained from Kilpauk Medical College.

Visual evoked potentials will be carried out on a computerized Nerve conduction testing equipment: Medicaid, computerize dphysiolab, Neuroperfect plus.

Procedure of VEP:

The patient is put at ease and made to sit comfortably in a relaxed state. Thorough cleaning of the electrode recording sites on the scalp. Electrode paste is applied on the recording surface of disk electrodes. Then electrodes are affixed at predetermined positions on the scalp according to 10/20 international system of electrode placement. The patient is asked to fix the gaze at the centre of the checkerboard screen. Each eye is checked separately. Prerequisites: i. Hairspray or oil after hair wash is advised not to use. ii. Spectacles should be put on during the test. iii. Visual acuity is done before the test. iv. Miotic or Mydriatic drugs 12 hours before the test is avoided. Equipment set up for VEP: Suggested Montage: i. Recording electrode is placed at Oz. ii. Reference electrode is placed at Fpz or 12cm above the nasion. iii. Ground electrode is placed at the wrist. Recording conditions: i Filter: low filter cut at 1-3 Hz, high filter cut at 100-300 Hz. ii. Amplification between 20, 00 and 1, 00,000. iii. Sweep duration between 250 and 500 msec. iv. Number of epochs: At least 100 are averaged. v. Electrode impedence kept below 5 kilo-ohms. Stimulation options: i. Black and white checkerboard or vertical grating. ii. Distance between subject and screen 70-100cm. iii. Contrast between 50-80%. iv. Fixation point for full field size > 8º. v. Size of pattern element 14 X 16 minute. vi. Stimulation rate for transient VEP 1 Hz and for steady state VEP 4-8 Hz. vii. Central luminance 50cd/m2 and background luminance 20-40 cd/m2.

The signals picked up by the electrodes are filtered, amplified, averaged and displayed on the screen of MEDICAID, Computerised Physiolab, Neuro perfect plus, and recorded. The normal VEP recording consists of N75, P100, N145 waves. Normal Value

Any deviations from these normal values, Latency 100 ± 3.2msec, Amplitude 10± 4.2µV and Duration 60 ± 7.7sec are considered abnormal. Any deviations from these normal values are considered abnormal.The visual Evoked Potentials of patients with chronic kidney disease will be analysed and compared with age and gender matched controls.

Data analysis:

The VEP measurements were assessed based on the reference values provided by ISCEV and presented as percentages relative to the study participants. Data from both the right and left eyes were combined and then individually examined. The main focus of this study was to determine the relative alterations in VEP parameters compared to the baseline values. Furthermore, supplementary analyses were conducted to explore the factors contributing to the variability in VEP measurements**,** encompassing age, eGFR, tacrolimus level, and various laboratory parameters.

The statistical analysis for the required sample size per group was carried out using Statistica version 9 (StatSoft, Inc, 1984-2009, USA). All other statistical analyses were performed using the Statistical Package for Social Sciences for Windows 8.0 software. The results are presented as means with their respective standard deviations. To make comparisons, analysis of variance (ANOVA) was employed, followed by Tukey's post hoc test for multiple comparisons and the independent samples Student's t-test. Pearson correlation analysis was used to calculate correlations between variables. The results were evaluated within a 95% confidence interval, and significance was determined with a probability level of less than 0.05.

Results

The mean ± SD of the Height and Weight

of the study groups were compared with the P value of 0.902 and 0.142 respectively which is insignificant. The mean ± SD of the BMI of the study groups were compared with theP value of 0.076 which is insignificant (Table-1)In the control group, 9 were females, 11 were males. The mean ± SD of height and weight of the control group is 160.65±7.22 and 60.10±7.31 (table 1) respectively.The mean ± SD of BMI 23.29 ± 2.20 (table 1), S.urea 27.00 ± 0.77(table 2) and S.creatinine 0.77± 0.13 (table 2) respectively. In the study groups, which consisted of CKD patients, the distribution of genders was as follows:

- Group 1 (CKD patients): 6 females and 14 males.

- Group 2 (CKD patients on Hemodialysis): 6 females and 14 males.

- Group 3 (CKD patients who underwent Renal Transplantation): 7 females and 13 males.

The S.urea and S.creatinine of the study groups were compared with control group withsignificant P value <0.01 as shown in table-2.

Table 1: Comparison of anthropometry of subjects betweencontrols and cases –CKD, CKD on hemodialysis, CKD underwent renal transplantation

PARAMETERS	CONTROLS	CKD	HD	RT	P VALUE
N		N = 20	N = 20	N = 20	
HEIGHT (CMS)	160.65 ± 7.22	162±7.49	161.35±7.08	160.55±5.75	0.902
WEIGHT (KG)	60.1±7.31	62.45±7.03	61.3±7.16	57.6±5.52	0.142
BMI	23.29±2.20	23.77±1.63	23.48±1.35	22.36±1.77	0.076.

CKD – chronic kidney disease, HD – hemodialysis, RT- renal transplant

Table 2: Comparison of s. Urea, and s. Creatinine between controls and cases –CKD, CKD on hemodialysis, CKD underwent renal transplantation

	CONTROLS N = 20	CKD N = 20	HD N = 20	RT N = 20	P VALUE
S.UREA	27 ± 0.776	66.1± 5.22	91.50 ± 11.16	42.65 ± 1.715	< 0.01
S.CREATININE	0.776 ± 0.13	5.22 ± 1.64	11.16 ± 1.70	1.71 ± 0.65	< 0.01.

CKD – chronic kidney disease, HD – hemodialysis, RT- renal transplant.

Figure-1 shows The study groups are compared with control groups with a F value 195.849 (systolic BP) and 80.981(Diastolic BP) and highly significant P value 0.000.

The Serum urea and Serum creatinine of the study groups were compared with control group with significant P value <0.01 (table 2,). Group 3 patients on Hemodialysis having high mean ± SD (S.urea 91.50±11.160, S.creatinine 11.160±1.7065) compared to CKD group 2 (S.urea 66.10± 5.225, S.creatinine 5.2251.6428) and CKD on RT group 4 (S.urea 42.65±1.715, S.creatinine 1.715± 0.6556).

In the study group the mean ± SD of Systolic and Diastolic BP of group3 (153.50 ±4.80, 100.60 ± 3.61) is comparatively higher than group 2 CKD (144.90±7.2, 95.80±3.88) and group 4 (129.80±4.80, 82.70±5.77) (Figure-1) In the control group the mean ± SD of Systolic and Diastolic BP is 109.80±7.13 , 79.70±6.23. Study groups compared with control groups with a F value 195.849 (systolic BP) and 80.981(Diastolic BP) and highly significant P value 0.000.

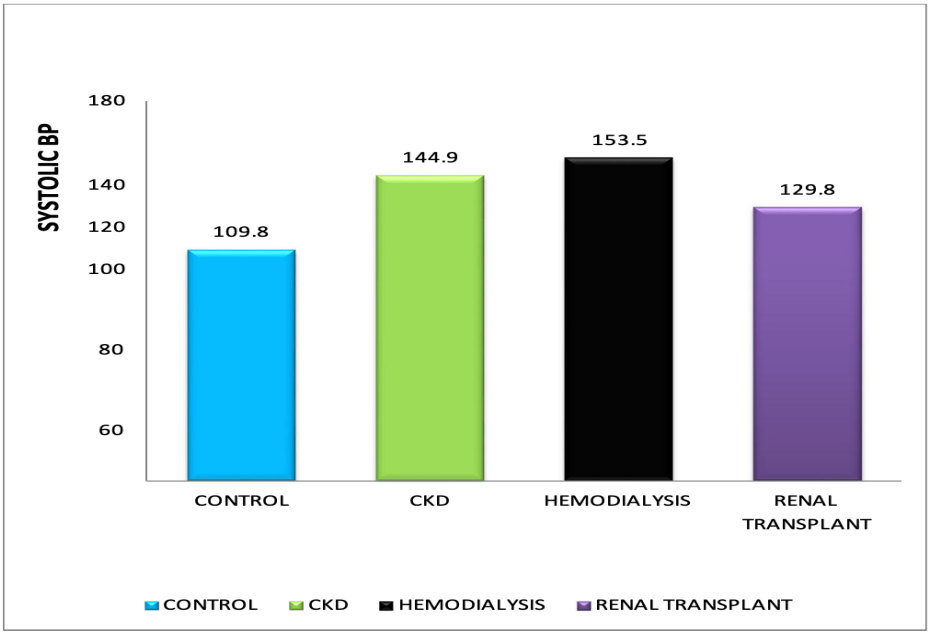

Figure 1: Comparison of systolic BP between controls and cases – CKD, CKD on hemodialysis, CKD underwent renal transplantation

Table 3: Comparison of N 75 latency, P 100 latency, N 145 latency and amplitude in right & left eye between controls and cases –CKD, CKD on hemodialysis, ckd underwent renal transplantation

	CONTROLS N = 20		**CKD N = 20**		**HD N = 20**		**RT N = 20**		**P VALUE**
	RIGHT EYE	***LEFT EYE***	***RIGHT EYE***	***LEFT EYE***	***RIGHT EYE***	***LEFT EYE***	***RIGHT EYE***	***LEFT EYE***	
LATENCY N 75	74.97 ± 0.549	75.17 ± 0.74	81.82 ± 0.59	81.82 ± 0.92	76.85 ±0.56	77.02 ± 0.86	76.6 ± 0.83	76.75 ± 0.86	**< 0.01**
LATENCY P 100	100.10 ± 0.44	100.25 ± 0.573	108.17 ± 0.67	108.17 ± 0.94	115.12 ± 0.74	115.20 ±0.817	101.70 ± 0.93	102.05 ± 1.29	**< 0.01**
LATENCY N 145	144.95 ± 0.605	145.05 ± 0.759	148.55 ± 0.605	148.35 ± 0.860	154.75 ±0.679	155.00 ± 0.843	147.78 ± 1.658	147.98 ± 1.943	**< 0.01**
AMPLITUDE	8.03 ± 0.418	8.124 ± 0.523	5.14 ± 0.543	5.092 ± 0.694	2.86 ± 0.443	2.868 ± 0.409	6.96 ±0.422	6.800 ± 0.709	**< 0.01**

CKD – chronic kidney disease, HD – hemodialysis, RT- renal transplant

Table 3 presents In the study, various groups including chronic kidney disease (CKD), hemodialysis (HD), and renal transplant (RT) patients were compared with control groups. The analysis revealed significant differences, with high F values and low P values, indicating notable variations in VEP parameters. Specifically, the P100 latency was significantly different compared to the N75 and N145 latencies in the right eye, with a highly significant F value of 1805.100 and a P value of 0.000. The N145 latency in the right eye was also significantly different when compared to

the control group, with an F value of 346.18 and a P value of less than 0.01.

Similarly, in the left eye, the study groups exhibited significant differences in VEP parameters compared to the control groups, with F values of 791.910 and 1022.711 and highly significant P values of 0.000. The N145 latency in the left eye also showed a significant difference with an F value of 243.781 and a P value of less than 0.01.

The study observed significant differences in VEP parameters between the study groups (CKD, HD, RT) and control groups. In the right eye, the study groups exhibited significant variations in VEP parameters, with F values of 1390.209 and 1805.100 and highly significant P values of 0.000 for N75 and P100 latencies, respectively. The N145 latency in the right eye also showed a significant difference with an F value of 346.187 and a P value of less than 0.01.

Similarly, in the left eye, significant differences were observed in VEP parameters between the study groups and control groups, with F values of 791.910 and 1022.711 and highly significant P values of 0.000 for N75 and P100 latencies, respectively. The N145 latency in the left eye also exhibited a significant difference with an F value of 243.781 and a P value of less than 0.01.

Furthermore, the amplitude (μv) of VEP decreased as latency prolonged, particularly in patients with uremic toxicity (group 2 CKD HD). The mean ± SD of amplitude values for both right and left eyes showed notable differences between the control group and the study groups.

Overall, these findings indicate significant variations in VEP parameters among the study groups, reflecting the impact of kidney-related conditions on visual evoked potentials, including latency and amplitude. (table 3).

The amplitude (μv) is compared with F value right eye 485.066, Left eye 288.956 and highly significant P value 0.000.

In this study N 75, P 100, N 145 latencies and amplitude of the VEP parameters of both right and left eye are graphically displayed as box plot as itsvalues are continuous variables.

In box plot descriptive statistics it is a method of depicting groups of numerical data through their quartiles. The vertical line from the boxes (whiskers) indicates minimum and maximum of all the data. Rectangle drawn represents first and third quartiles with the line inside represents median value. It can be drawn either vertically or horizontally.

Discussion

The nervous system can be affected by uremia in CKD. In several studies Cranial nerve involvement in CKD has been investigated nonetheless, only little attention has been paid to optic nerve involvement that is VEP results in CKD. The present study thereby sought to assess VEP changes in CKD patients, CKD patients who underwent hemodialysis, CKD patients who underwent renal transplantation.

Rizzo PA,Pierelli F et al Pathological latency increase of VEPs in six patients had been observed. These findings are related by the authors to the action of toxic substances uremia, or the presence of minimal demyelinating lesions of CNS. Since these abnormal findings were observed in patients who were normal at the clinical examination, it has been suggested that the evoked potentials recording might be a sensitive index of initial early lesions of the CNS in uremic patients[13].

In several studies, the involvement of central and peripheral nervous system in CKD has been investigated. However, cranial nerve involvement and its association with different CKD therapies (peritoneal dialysis, hemodialysis, and renal transplantation) are less considered.

Kuba et al. assessed VEP in 3 groups with CKD patients on hemodialysis, drug treatment and renal transplantation. The authors mentioned that there was significant

prolonged latency in P 100 &decreased amplitude in hemodialysis group, compared to controls. However, our results also demonstrated the same significant difference in P100 latency and amplitude compared to the control group[14].

Demirbilek et al. assessed VEP parameters in 19 children undergoing hemodialysis and peritoneal dialysis, and compared them with control group. They found that there is no significant difference in VEP results between cases and controls. In the above study, the results were not compared between the 2 case groups[15]. Our findings showed a significant difference in P100 latency between case groups, not withstanding the normal nervous signs. The results were compared between the 3case groups also and it shows a significant decrease in latencies and increase of amplitude after renal transplantation in comparison to CKD and CKD patients on hemodialysis[15].

In comparison with hemodialysis, studies indicated improvement of VEP parameters a positive effect of renal transplantation Talebi M[16]. Similarly our study also shows a significant decrease in latencies and increase of amplitude after renal transplantation in comparison to CKD and CKD patients on hemodialysis.

Cohen SN, Syndulko K et al studied auditory event-related potentials elicited in target detection paradigm (P300) and pattern shift visual evoked potentials (PVEPs) in 22 patients with CRF and no clinical evidence of cognitive or visual impairment. They are grouped into two categories on low protein diet and on dialysis. P300 and PVEP latencies were abnormal in both groups. However, our results also demonstrated the same significant difference in P100 latency and amplitude compared to the control group[17].

J.S.Saini, I.S.Jain et al discussed in their study that remarkable improvement in vision after first hemodialysis. The vision improved and showed rapid improvement after every hemodialysis. Optic neuropathy was related to some metabolic toxic product7[a]. This is in contrast to this study that VEP changes are prolonged in CKD hemodialysis patients compared to CKD patients, but its prolonged in both CKD patients, CKD patients on hemodialysis compared to controls.[18]

The prolongation of VEP parameters like N75,P100,N145 latencies and decreased amplitude was observed in this study which is similar to Derici. U et al where they also found that there is a altered P100 latencies in dialysis patients. It suggests the axonal degeneration of central nervous system.

All the earlier studies have given certain clear findings regarding the CNS changes in CKD and its sub classification during various types of treatment and grades of disease.

Our study has given certain clear understanding of VEP changes in our patients. Although it looks very close to western population there are many subtle changes to be noted from our study. Pathophysiological changes during the CKD and other forms are very significant. The probable physiological cause which involves is uremic toxicity and demyelination.

Very rarely our patients of this nature are investigated for VEP but from this study we feel that it is necessary to do VEP along with other routine investigations.

Conclusion:

This study reveals clear optic nerve impairment in CKD patients, indicated by the prolonged latency and reduced amplitude of VEP parameters (N75, P100, N145). A significant association was found between serum urea, serum creatinine, and N75, P100, N145 latency, indicating a link between VEP results and biochemical parameters. The decline in VEP parameters seen in CKD patients after transplantation, compared to CKD patients on Hemodialysis but elevated when compared to controls, might be due to the delay in renal transplantation. The duration of CRF

significantly impacted most VEP parameters, suggesting that a longer duration of CRF leads to decreased chances of returning to normal VEP changes after transplantation. Therefore, VEP could be considered a routine screening tool to detect early subclinical optic nerve involvement in these patients.

Limitations:

As this was a single center study with a comparatively short sample size, results of this study cannot be generalized. Generalization requires the support of results from similar large studies. Patient compliance: Some patients may have difficulty following the instructions for the VEP test, which can affect the accuracy of the results. Finding suitable participants: It can be difficult to find a large number of patients with CKD, CKD on hemodialysis, and CKD after renal transplantation who are also willing and able to participate in a research study.

Acknowledgments: The authors would like to thank all of the study participants and the administration of Department of Physiology and Department of Nephrology Government Kilpauk Medical College, Chennai, Tamilnadu, India for granting permission to carry out the research work.

Ethical statement: Institutional ethical committee accepted this study. The study was approved by the institutional human ethics committee, Government Kilpauk Medical College in Chennai (Protocol ID No10/2017 Dated: 08-06-2017). Informed written consent was obtained from all the study participants and only those participants willing to sign the informed consent were included in the study. The risks and benefits involved in the study and the voluntary nature of participation were explained to the participants before obtaining consent. The confidentiality of the study participants was maintained.

Data availability: All datasets generated or analyzed during this study are included in the manuscript.

Informed consent: Written informed consent was obtained from the participants before enrolling in the study

References:

1. Harrison's principles of internal medicine -nineteenth Edition Chapter 335 chronic kidney disease: page-1811
2. Comprehensive clinical nephrology Feehaly 5th edition - Management of the Diabetic Patient with Chronic Kidney Disease Ahmad Abou-Saleh, Stephen C. Bain, and David J. A. Goldsmith - chapter 32. Pathophysiology of Chronic Kidney Disease Meguid El Nahas and Arif Khwaja. chapter 79.
3. Harrison's principles of internal medicine -Eighteenth Edition (Volume 3) Chapter 280 Chronic Kidney Disease: Introduction page-2308-2322, Chapter 281 Dialysis in the Treatment of Renal Failure pages-.2322-2326.
4. Per Grinsted. Kidney failure (renal failure with uremia, or azotaemia). 2009-05-26.
5. Khadra MH, Pickard RS, Charlton M, et al.A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol. 2000; 163:524-527.
6. Karl Tryggvason. Jaakko Patrakka: Thin basementmembrane nephropathy. J Am Soc Nephrol. 2006; 17:813-822.
7. Raskin NH, Fishman RA. Neurologic disorders in renal failure. N Engl JMed. 1976; 294:143-148.
8. Arieff AI. Neurological complications of uremia. In: Brenner SM, Rector FC, eds. The kidney. Philadelphia: W.B. Saunders; 1981:2306- 2323.
9. Giannotta SL, Delaney-Harder J. Neurologic complicationsof renal failure, dialysis, and renal transplantation. In: Wilson SE, ed. Vascular access surgery. Chicago: Yearbook Medical Publishers; 1979:321-335.
10. Hamel B, Bourne JB, Ward JW, Teschan PE. Visually evoked corticalpotentials in renal failure: transient potentials. Electro encephalogr Clin

Neurophysiol. 1978; 44:606-616.
11. Donnell J. Creel -Visually Evoked Potentials. Electroencephalogr Clin-Neurophysiol. 1981; 52(5):435-441
12. Lewis EG, Dustman RE, Beck EC. Visual and somatosensory evokedpotential characteristic of patients undergoing hemodialysis and kidney transplanta tion. Electroenceph Clin Neurophysiol. 1978; 44:223- 231.
13. Rizzo PA, Pierelli F et al Pattern visual evoked potentials and brainstem auditory evoked responses in uremic patients. ActaNeurol Belg. 1982 Mar-Apr;82(2):72-9.
14. Kuba M, Peregrin J, Vit F, Hanušová I, Erben J: Pattern-reversal visual evoked potentials in patients with chronic renal insufficiency. Electroencephalogr Clin Neurophysiol1983, 56: 438-42.
15. Demirbilek V, Çalışkan S, Çokar Ö, Angay A, Sever L, Dervent A: A study on visual evoked responses in children with chronic renal failure. Neurophysiol Clin. 2005, 35: 135-41.
16. Talebi M, Sayadnasiri M, AbediAzar S: Effect of Renal Transplantation on Visual Evoked Potential Abnormalities of Chronic Renal Failure. Transplant Proc. 2010; 42:3994-7.
17. Cohen J, Rees AJ, Williams. A Prospective randomised control trialof perioperative antibiotic prophylaxis in renal transplantation. Jhosp infect..1988; 11; 357-363.
18. J.S. Saini, I.S. Jain. Uremic optic Neuropathy, Journal of clinicalneuro ophthalmology. 1989; 9 (2): 131 – 133.