Research Article

Comparison of Visual Evoked Potential Latency and Amplitude Values According to Visual Acuity among Normal Adult Eyes in dr. Cipto Mangunkusumo Hospital

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Abstract

Visual Evoked Potential (VEP) is a diagnostic procedure to evaluate pathological conditions affecting the visual pathway with several protocols, including pattern onset/offset VEP, flash VEP, and pattern-reversal VEP (PRVEP), standardized by International Society For Clinical Electrophysiology In Vision (ISCEV). PRVEP, the most common protocol used in clinical practice, is not always directly proportional to visual acuity (VA). Clarity of the refractory media and gender are presumed to affect it; thus, using PRVEP reference value based on refractory status is not casually applicable when the VA does not resemble refractory status. This study aims to determine the changes in VEP latency and amplitude value according to various subjective VA, and to examine and analyze these latency and amplitude values within male and female subject groups. The research was conducted at the Department of Ophthalmology, dr. Cipto Mangunkusumo Hospital from August to October 2017. Latency and amplitude values were measured with PRVEP. Measurement was performed on normal VA and defocus-induced VA to 6/18, 6/30, and 6/60 values, using small and large-sized checkerboard stimuli. Prolonged latency and decreased amplitude were found in male and female subject groups, corresponding with decreasing VA levels. Using 18 min arc and 48 min arc-sized checkerboards gave the closest result to the reference value. The difference in VEP value according to subjects' gender was found in amplitude but not in latency.

Keywords: *pattern reversal visual evoked potential, visual evoked potential, electrophysiology, reference value, visual acuity.*

Perbandingan Nilai Latensi dan Amplitudo Visual Evoked Potential Antar Tingkat Tajam Penglihatan Mata Normal pada Populasi Dewasa di Rumah Sakit Umum Pusat Nasional Cipto Mangunkusumo

Abstrak

Pemeriksaan Visual Evoked Potential (VEP) adalah prosedur diagnostik untuk mengevaluasi kondisi patologis yang memengaruhi jalur visual dengan beberapa protokol, termasuk pattern onset/offset VEP, flash VEP, dan pattern-reversal VEP (PRVEP) yang disusun oleh International Society For Clinical Electrophysiology In Vision (ISCEV). PRVEP, protokol yang paling umum digunakan dalam praktik klinis, tidak selalu berbanding lurus dengan ketajaman visual (VA). Kejernihan media refraktif dan perbedaan jenis kelamin diyakini memengaruhi hasil PRVEP. Oleh karena itu, penggunaan nilai referensi PRVEP berdasarkan status refraktif tidak selalu dapat diterapkan dalam kondisi VA tidak mencerminkan status refraktif. Tujuan dari penelitian ini adalah untuk menentukan perubahan nilai latensi VEP dan amplitudo sesuai dengan berbagai tingkat VA subjektif dan menganalisis nilai latensi serta amplitudo dalam kelompok pria dan wanita. Penelitian ini dilakukan di Departemen Ilmu Mata, Rumah Sakit dr. Cipto Mangunkusumo dari Agustus hingga Oktober 2017. Nilai latensi dan amplitudo diukur dengan PRVEP. Pengukuran dilakukan pada VA normal dan VA yang diinduksi defokus hingga mencapai nilai 6/18, 6/30, dan 6/60, menggunakan stimuli checkerboard kecil dan besar. Ditemukan peningkatan latensi dan penurunan amplitudo pada kelompok subjek laki-laki dan perempuan, sesuai dengan penurunan tingkat VA. Penggunaan checkerboard berukuran 18 min arc dan 48 min arc memberikan hasil yang mendekati nilai referensi. Perbedaan nilai VEP berdasarkan jenis kelamin subjek ditemukan pada amplitudo, tetapi tidak pada latensi.

Kata kunci: *pattern reversal visual evoked potential, visual evoked potential, electrophysiology, reference value, visual acuity.*

Introduction

Visual evoked potential (VEP) is a diagnostic procedure performed by acquiring signals from electro-encephalography activities in the occipital cortex, areas 17, 18, and 19, responsive to visual stimuli.[1] VEP examination evaluates pathological conditions that affect the visual pathway and is sensitive to lesions in the optic nerve and anterior to the optic chiasm.[2]

International Society sets standard protocols for VEP examination for Clinical Electrophysiology in Vision (ISCEV). Three VEP protocols exist, which are pattern-reversal VEP, pattern onset/offset VEP, and flash VEP. Pattern reversal VEP (PRVEP) is the most commonly employed protocol in clinical settings due to minimal variability in its waveform and timing.[3]

PRVEP waveforms are obtained by using large checkerboard stimuli, 1° or equal to 60 min arc (range 0.8° - 1.2° or 48 – 72 min arc) and small checkerboard stimuli, 0.25° or equal to 15 min arc (range 0.2°- 0.3° or 12 – 15 min arc). Three waveforms, N75, P100, and N135, are then obtained. The P100 waveform is most commonly used in interpreting the results because it shows the least variability within the subject, interocular, and between examinations.[2,4] Parameters studied in the P100 waveform are its latency time and amplitude.[5]

Normal latency value for PRVEP P100 in ages 21-40 years old is 95.2-117.8 ms in 15 min arc and 91.8-115.2 ms in 60 min arc, and the normal amplitude value is 7.6-24.0 μV in 15 min arc and 6.6-21.4 μV in 60 min arc, when examined using Roland Consult visual electrophysiological system.[6] Those normal values may be affected by race, clarity of refractive media, degree of refractive error, and gender. Refraction error causes defocus of visual input, which ultimately affects VEP results. Small changes in refraction error tend to decrease mean amplitude, approximately 25% amplitude decrement per diopter of defocus, starting from 0.25 D. However, VEP amplitude decrement as measured using refraction error is not sensitive to assess visual acuity potential. Therefore, a reference value according to subjective visual acuity level is required.[7,8]

ISCEV recommends that each center set its normal standard values according to the devices and patients studied by employing appropriate inclusion criteria.[9] Devices used also have several standards because results may also be affected by visual field size, type of electrodes, luminance, contrast, and checkerboard size (12, 15, 18, 48, 60 and 72 min arc). However, in their guideline, ISCEV recommends using 15- and 60-min arc checkerboards.[1,5,9-12] In the Department of Ophthalmology, dr. Cipto Mangunkusumo Hospital, the reference value for normal VEP latency and amplitude values still uses reference values from European and American studies.

This study aims to acquire VEP value according to visual acuity levels and to examine and analyze these latency and amplitude values within male and female subject groups. Therefore, an approximation could be inferred between P100 latency and amplitude values and subjective visual acuity levels in male and female adults.

Methods

This study is an analytic descriptive study with a cross-sectional design, conducted in the Department of Ophthalmology, dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, from August to October 2017. We compare the results of the PRVEP examination performed using one device in Indonesian adult subjects. Ethical approval for this study (reference letter number: 587/UN2. F1/ETIK/2017) was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia, with regards to the protection of human rights and welfare in medical research (Protocol Number: 17-05-0535).

Inclusion criteria consist of Indonesian adults in dr. Cipto Mangunkusumo Hospital, aged 19-49, had clarity of refractive media, agreed to participate in this study and signed the informed consent. Subjects with a history of intraocular surgery, ocular laser, ocular trauma, long-term medications usage, and having moderate to severe lens opacities (lens color and opacity, cortical and posterior capsule opacity of LOCS III > 3) are excluded from this study.

Subjects are chosen using convenient sampling from doctors and employees in the Faculty of Medicine Universitas Indonesia and dr. Cipto Mangunkusumo Hospital. This study is an analytical research, therefore the sample size estimation was calculated using the formula for the comparison of two independent means. We estimated a sample size of 50 eyes from 25 subjects.

Baseline examinations were conducted, consisting of visual acuity and slit lamp examination, intraocular pressure measurement, defocus induction using positive sphere lenses to obtain visual acuity levels of 6/18, 6/30, and

6/60, contrast sensitivity (Pelli-Robson contrast sensitivity chart), color perception (Ishihara plates), visual field examination (Humphrey Field Analyzer model 750i Carl Zeiss), and fundus photography. Afterwards, reverse pattern stimulus VEP was performed in various visual acuity levels (6/6 and consequent defocus-induced visual acuity levels of 6/18, 6/30, and 6/60) using various-sized checkerboards. The examinations were carried out by a single trained nurse examiner and the results were reviewed and interpreted by two neuro-ophthalmologists.

Reverse pattern VEP was conducted per ISCEV guideline, using Vision Monitor Monpack One System (Metrovision), as described in the literature.[5] In this study, the right eye was examined first. Latency and amplitude were evaluated in 6/6 visual acuity using 12, 15, 18, 48, 60, and 72 min arc checkerboards. Afterwards, defocus induction was performed using positive sphere lenses until the desired visual acuity level was acquired (6/18, 6/30, and 6/60), and latency and amplitude values were recorded using 15 and 60 min arc checkerboards. The same steps were performed in the fellow left eye afterwards.

Results from the examination were recorded in the study database, and analyses were performed using SPSS version 22.0. Using appropriate statistical tests such as ANOVA test, the Friedman test, and One Sample T-test, hypothesis testing was performed through comparative assessments between two paired and unpaired groups. A p-value of <0.05 was considered statistically significant.

Results

There were 110 eyes from 55 subjects in this study. This study involves an equal proportion of male and female subjects (50.9% male and 49.1% female) with three age groups ranging from 19-29 years old (45.5%), followed by 30-39 years old (40%) and 40-49 years old (14.5%). We compared the mean of P100 latency and median of amplitude values (Table 1). An increase in latency value using 15 min arc checkerboard in accordanece with the decreased visual acuity were found significantly. On the contrary, a decrease in amplitude value was seen significantly in accordance with decreasing visual acuity. A similar result was observed in the 60 min arc checkerboard result, although a significant difference was only seen in the amplitude value (p <0.001).

Table 1. Comparison of VEP P100 Latency and Amplitude Values According to Visual Acuity Levels

Visual acuity	Latency	p †	Amplitude	p ‡
15 min arc		<0.001		<0.001
6/6	107.73±5.67		15.60 (0.50 – 36.50)	
6/18	107.25±4.63		13.30 (0.40 – 33.90)	
6/30	108.61±4.97		11.70 (2.30 – 34.70)	
6/60	111.71±6.62		10.00 (2.10 – 31.30)	
60 min arc				
6/6	102.61±5.23	0.504	11.35 (1.60 – 26.40)	<0.001
6/18	102.77±4.93		10.70 (0.40 – 24.40)	
6/30	102.88±5.54		10.20 (0.30 – 23.70)	
6/60	103.37±5.67		10.20 (1.20 – 24.20)	

†ANOVA test ‡Friedman test

Comparison of P100 VEP latency and amplitude value among different gender groups brought significant results (Table 2). Using a 15 min arc checkerboard, the latency value between male and female subjects within various visual acuity levels marked a significant difference. A significant difference was found in amplitude values between male and female subjects within 6/6, 6/18, and 6/30 visual acuity levels. Conversely, results from 60 min arc checkerboard for latency value between male and female subjects did not show a significant difference. In amplitude value, a significant difference was observed between male and female subjects both in 15 and 60 min arc checkerboard.

Table 2. Comparison of VEP P100 Latency and Amplitude Values According to Gender

Visual acuity	Latency			Amplitude		
	Male	Female	p†	Male	Female	p‡
15 min arc						
6/6	108.0±5.9	107.4±5.4	0.570	14(0.5 -28.9)	18.7(5.4-36.5)	0.001
6/18	107.6±4.8	106.8±4.4	0.361	12.3(2.2 - 26)	15.8(0.4-33.9)	0.001
6/30	108.6±5.0	108.6±4.9	0.963	10.3(2.3 - 25)	14.3(2.8-34.7)	0.003
6/60	110.5±7.0	112.9±6.0	0.062	9.5(2.1-23.9)	11.5(2.4-31.3)	0.178
p	0.032§	0.001§		0.001¶	0.001¶	
60 min arc						
6/6	103.1±5.7	102.1±4.7	0.361	10.6(1.6 – 19.9)	12(4.1-26.4)	0.017
6/18	103.6±4.9	101.9±4.8	0.078	9.2(0.9 - 19)	12.2(0.4-24.4)	0.003
6/30	103.7±5.3	102.0±5.7	0.109	8.8(0.3 - 20.8)	11.6(1.4-23.7)	0.003
6/60	104.6±5.6	102.0±5.4	0.015	8.9(1.8 - 20.7)	11.8(1.2-24.2)	0.010
p	0.282§	0.970§		0.022¶	0.030¶	

† Unpaired t test, ‡ Mann Whitney test, §ANOVA test, ¶ Friedman test

A comparison of latency value to the reference value we obtained from Chen et al[13] showed insignificantly different value in both male and female subjects (Table 3) for the small checkerboard. Amplitude in small checkerboard size showed a significant difference with a reference value. Comparison between latency and amplitude value within the large checkerboard size was also done with the reference value, which showed a significant difference in male and female subjects (Table 3).

We also compared latency and amplitude values to the reference value according to the ISCEV guideline (Table 4). In a small checkerboard (15 min arc), a significant difference was found in both male and female subjects' latency values. In contrast, for amplitude, a significant difference for male and female subjects was found only in the 18 min arc checkerboard size.

Comparison of latency and amplitude value to the reference value in large checkerboard size (60 min arc) according to ISCEV guideline (Table 4). In male subjects, a significant difference was observed only for latency value using 72 min arc checkerboard compared to the reference value. Conversely, in female subjects, it was not significantly different. In amplitude value using a large checkerboard, a significant difference was seen in male and female subjects using a 48 min-arc-sized checkerboard.

Discussion

This study found a significantly prolonged latency and decreased amplitude, corresponding to decreasing visual acuity, using 15 and 60 min arc checkerboards. This finding aligns with previous studies.[14,15] However, in this study, the measurement of latency and amplitude is based on visual acuity levels, not on refraction error degree. Therefore, both spherical and astigmatic refractive errors are covered by using this approach.

Latency prolongation and amplitude decrement using a 15 min arc checkerboard appears greater than the 60 min arc checkerboard. Usage of a 10-30 min arc checkerboard is considered ideal for VEP examination because the projected stimulus location in the fovea depends on the checkerboard size.[7]

In comparison between male and female subjects, male subjects showed a trend of prolonged latency in each visual acuity level compared to the female subjects. Sex difference affects VEP result due to difference in head circumference parameter,[16] hormonal difference,[17] and axial length difference.[11]

Table 3. Comparison of P100 Latency and Amplitude Value among Small and Large Checkerboards in 6/6 Visual Acuity to the Reference Value

P100	Male					Female				
Small checkerboard	**12 min arc**	**15 min arc**	**18 min arc**	**p**	**Ref value†**	**12 min arc**	**15 min arc**	**18 min arc**	**p**	**Ref value†**
Latency	110.1±5.8	108.0±5.9	105.0+3.9	<0.001‡	106.8±10.7 (NS) §	109.3±5.4	107.4±5.4	104.8+4.5	<0.001‡	103.6±6.4 (NS)§
Amplitude	13.7±5.9	13.7±6.7	12.7±5.2	0.586‡	5.42±2.49 (S) §	18.3 (6-37.8)	18.7 (5.4–36.5)	17.6 (5,5-39.5)	0.425¶	5.99±2.46 (S)§
Large checkerboard	**48 min arc**	**60 min arc**	**72 min arc**	**p**	**Ref value†**	**48 min arc**	**60 min arc**	**72 min arc**	**p**	**Ref value†**
Latency	103.1±4.2	103.1±5.7	104.3±4.7	0.001‡	100.8±7.4 (S)§	102.5±4.4	102.1±4.7	102.9±5.4	0.001‡	96.4±3.8 (S)§
Amplitude	11.0±5.1	10.2±4.4	9.9±4.6	0.001‡	5.6±1.3 (S)§	14.5±6.3	13.2±6.0	13.1±5.49	0.001‡	6.3±2.2 (S)§

†Reference value from Chen et al [13] , ‡ ANOVA test , § One sample t-test , ¶ Friedman test, (S) Significant, (NS) Not significant

Table 4. Comparison of P100 Latency and Amplitude Value among Small and Large Checkerboards in 6/6 Visual Acuity to the Guideline Reference Value

P100	Male					Female				
Small checkerboard	**12 min arc**		**15 min arc**	**18 min arc**		**12 min arc**		**15 min arc**	**18 min arc**	
	Mean	**p**	**Mean**	**Mean**	**p**	**Mean**	**p**	**Mean**	**Mean**	**p**
Latency	110.1±5.8	<0.001†	108.0±5.9	105.0±3.9	<0.001†	109.3±5.4	<0.001†	107.4±5.4	104.8±4.5	<0.001†
Amplitude	13.7±5.9	0.849†	13.7±6.7	12.7±5.2	0.008†	18.3(6-37.8)	0.184‡	18.7(5.4-36.5)	17.6 (5.5–39.5)	0.049‡
Large checkerboard	**48 min arc**		**60 min arc**	**72 min arc**		**48 min arc**		**60 min arc**	**72 min arc**	
	Mean	**p**	**Mean**	**Mean**	**p**	**Mean**	**p**	**Mean**	**Mean**	**p**
Latency	103.1±4.2	0.904†	103.1±5.7	104.3±4.7	0.015†	102.5±4.4	0.366†	102.1±4.7	102.9±5.4	0.108†
Amplitude	11.0±5.1	0.003†	10.2 ±4.4	9.9±4.6	0.392†	14.5±6.3	<0.001†	13.2±6.0	13.1±5.49	0.783*†

* Wilcoxon test, ** Paired t test, † Paired t-test, ‡ ANOVA test

Latency value in the small checkerboard group showed a non-significant difference between male and female subjects compared to the reference value from Chen et al.[13] However, amplitude values in the small checkerboard group showed a significant difference to the reference value. Reference value from Chen et al. is used because only their study classified their subjects according to gender (man and woman) and checkerboard size (15 and 60 min arc).

The usage of a large checkerboard in 6/6 visual acuity showed prolonged latency among male and female subjects. This finding aligns with the study by Kothari[7] and Kurita-Tashima et al.[18] Prolonged latency and decreased amplitude occurred on large checkerboards, especially on sizes larger than 30 min arc. Checkerboard selection, which approximates the reference value for male and female subjects is 60 min arc checkerboard for latency value and 72 min arc checkerboard for amplitude value.

There was a significant difference in latency value between male and female subjects found in the 12 and 18 min checkerboard, compared to the ISCEV reference value from using the 15-min arc checkerboard. Compared to the reference value from Chen et al[13], the latency value from the 18 min arc checkerboard approximates the closest to the reference value. Conversely, in using a large checkerboard, the most considerable difference in latency value to the reference value appears in using the 72 min arc checkerboard. A significant difference was found between the three checkerboard sizes in female subjects. Compared to the reference value, using a 48 min arc checkerboard approximates the closest to the reference value.

On amplitude evaluation, 12 min arc checkerboard usage did not show a significant difference in the reference value in male and female subjects. When compared with the reference value, using an 18 min arc checkerboard gives the closest approximation to the reference value. It should be noted that the 18 min arc checkerboard usage in this study showed a significant difference in amplitude value to the reference value. A similar result is also found in the usage of large checkerboard sizes. Consequently, in determining a normal value for P100 amplitude, the result from this study could be used as the normal value standard in the Department of Ophthalmology, dr. Cipto Mangunkusumo Hospital.

The strength of this study includes acquiring PRVEP examination obtained from various visual acuity levels and grouped to the subjects' gender, which have not been explored in previous studies in Indonesia. Limitation on this study lies in its focus on adult data, preventing its application to children and the elderly. This study's findings cannot be extended to children and the elderly, even though PRVEP is an important test for the pediatric population.

Conclusion

The use of a 15 min arc checkerboard showed a significant difference in latency values between male and female subjects across various visual acuity levels, while the 60 min arc showed no significant difference. Gender difference was not a significant factor that affected the latency value on 15 min arc or 60 min arc checkerboard, while it appears significant to the amplitude value. In the small checkerboard group, latency value was significantly affected for male and female subjects and conversely for amplitude value. The latency value in male subjects showed a significant difference compared to the reference value, but not in female subjects. Amplitude value significantly differed from the reference value in male and female subjects. In the large checkerboard group, both latency and amplitude values appear to be affected significantly in male and female subjects. On comparison of latency and amplitude value to the reference value, a significant difference was found in male and female subject groups.

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