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The Difference of Brainstem Auditory Evoked Potential Latency in Diabetic Patient with Good and Poor Glycemic Control

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Abstract

BACKGROUND: Diabetes mellitus (DM) is a metabolic disorder which may complicate other organs, including the nervous system. Literatures which discuss about DM complications in the peripheral nervous system are easy to find but not so many of the central nervous system. Central diabetic neuropathy is a new concept which could be detected by a simple and non-invasive method, called brainstem auditory evoked potential (BAEP).

AIM: The aim of the study was to find differences in BAEP latencies of a diabetic patient with good and poor glycemic control.

METHODS: This was a cross-sectional study of 80 patients who came for follow-up in diabetic center and neurology polyclinic at Sanglah Hospital, from April to July 2016. The subjects were divided into two groups, depending on their glycemic control, then having BAEP examination.

RESULTS: The unpaired t-test found prolonged BAEP latencies (either peak latency of wave III, V, IPL I-III, III-V, and I-V) in both ears at the poor glycemic control group, but the results were not differed significantly ($p > 0.05$).

CONCLUSION: BAEP wave latencies were found prolonged in DM patient with poor glycemic control but not statistically significant. Further evaluation of BAEP latencies in DM patients is needed with prolonged duration and their relation with other comorbid factors, especially smoking habit.

Introduction

Diabetes mellitus (DM) is a common metabolic disorder. It may cause disability in many other organs, including the nervous system. This disorder rapidly becomes an epidemic in both developed and middle-income countries. Associated with the nervous system itself, much of the literature mentioned DM complication in the peripheral nervous system, whereas the central nervous system (CNS) complication was less frequently studied. Some researchers recently show that diabetes may also cause neuropathy in CNS.

Diabetes prevalence has reached epidemic proportion. In January 2011, the national diabetic factsheet states there are about 246 million diabetics worldwide throughout 2010, with an incidence of 11.3% aged between 20 and 65 years [1]. The latest estimate from the International Diabetic Federation is 382 million people living with diabetes by 2013. In 2035, the amount is estimated to increase to 592 million people [2]. It was estimated that of 382 million people, 175 million of them had not appropriately diagnosed, which may have complication without proper prevention. The proportion of DM in Indonesia based on Riskesdas 2013 was 6.9%. If the estimated population of Indonesian aged 15 or more in 2013 is 176.689.336, then the estimated amount was about 12 million people with DM [3].

Prolonged hyperglycemia due to diabetes may cause complication to various body systems, including neuropathy [3]. Diabetic neuropathy obtained in nearly half of the diabetic population and result in higher morbidity and mortality. Poorly controlled blood sugar level (which reflected through HbA1C level in blood), duration of suffering DM, and other cardiovascular risk factors such as smoking and hypertension, are also become the risk of diabetic neuropathy [2].

Diabetic neuropathy complication can interfere with CNS as well. Some studies mention that diabetes is related with hearing impairment, and seems that good A1C level related with less frequent hearing loss in DM patient [4], [5], [6], [7]. This hearing function in CNS can be detected by a simple and non-invasive method which called brainstem auditory evoked potential (BAEP). This examination can detect abnormalities of the acoustic nerve function up to upper brainstem at an early stage by showing changes in wave latencies [8]. The amplitude of BAEP was often not taken into account because the variability is too high [9].

Standard BAEP results consist of seven waves. The first five waves were used in routine clinical

practice because of its consistency [10]. Wave I comes from the peripheral part of cranial nerve VIII (auditory nerve) near the cochlear nucleus. Wave II comes from the cochlear nucleus, wave III of the superior oliva nucleus, wave IV of the lateral lemniscus, and wave V of the inferior colliculus in mesencephalon [11]. Central diabetic neuropathy of auditory pathways in the brainstem may cause hearing loss. Many sufferers do not realize that they have suffered from hearing loss due to the disease's slow progression. Therefore, clinicians need to monitor hearing function in patients with DM, in addition to other routine evaluation of DM complication so that early intervention can be provided if necessary [11].

Some studies of BAEP abnormalities in patients with DM have been done in various places around the world, but the results vary [12]. Research by Li *et al*. (2005) found that latency wave BAEP, for example, wave III and V and interpeak latency (IPL) I-III and III-V was prolonged in patients with DM compared with healthy individuals [13].

According to Abo-Elfetoh *et al*. (2015), patients with poor glycemic control had prolonged absolute BAEP latency which is significant from wave I with the extension followed by wave latency III and V; also IPL III-V compared to the control group (healthy individuals) [14]. This may indicate the involvement of both peripheral and central auditory pathways. The study by Bayazit *et al*., 2000, was also consistent with other studies using BAEP [15], [16], which found the elongation of wave latency III and V. However, there were some researches, [17], [18] León-Morales *et al*. and Talebi *et al*. reported that there was no correlation between HbA1C levels and BAEP results.

Data related to the effect of HbA1c levels on hearing function in patients with DM are still a controversy. Some research does not even show that poor blood sugar control harms hearing function [19] other than that, not much data have been obtained regarding BAEP abnormalities in DM patients at Indonesia.

The American Diabetes Association and other organizations, which define the target concentration of HbA1C as the target of optimal blood sugar control [20]. The 2015 Indonesian Endocrine Associates Consensus recommends the main objective of DM therapy is the value of HbA1c <7% [21].

Until now, various studies that perform BAEP examination in patients with DM used a healthy individual as control [9], [14], [16], [18], [22], [23], [24], while in this study we compare BAEP results in patients with DM only.

As far as, our knowledge, in Bali, there is no research yet using BAEP to assess the possibility of central diabetic neuropathy in the auditory system of DM patients. The purpose of the study is to find differences in BAEP latencies of a diabetic patient with good and poor glycemic control.

Materials and Methods

Based on the statistical calculation, minimal sample required was 40 subjects of each group. Subjects of this study were collected with consecutive random sampling. All subjects who meet eligibility were taken as a sample until the required amount was complete. This is a cross-sectional study of patients who came for follow-up in Diabetic Center and Neurology polyclinic at Sanglah Hospital, from April to July 2016. The subjects were divided into two groups, depending on their glycemic control by assessing HbA1C level within the past 3 months, before both ears BAEP.

Inclusion criteria

The following criteria were included in the study:

- DM patient with good glycemic control (HbA1C <7%) or poor glycemic control (HbA1C≥7%)
- Age between 40 and 65 years old
- Patients were fully alert, evaluated with the Glasgow Coma scale, and willing to join this study by sign in the consent form.

Exclusion criteria

The following criteria were excluded from the study:

- Having diabetics for more than 10 years
- The patient who is on acute ENT inflammation
- Patient with a chronic media ear infection or other ear illness which cause permanent hearing loss
- Malignancy of ENT area
- History of ototoxic medicines consumption continuously more than 3 months
- Noise working environment or living area
- History of having high explosion sound near both ears
- History of HIV infection, chronic kidney disease, and multiple sclerosis.

Subject characteristics were taken from the interview and medical records. Physical examination of outer ear by otoscope and hearing function was evaluated by tuning fork 256 Hz. The BAEP latencies were done by EMG/EP Keypoint Dantec machine, made in Denmark 2015. The BAEP wave recorded with headphone, click sound stimulus, with duration 0.1 ms, stimulus frequency 10 Hz, averaging 2000, and stimulus intensity 90 dB. The active electrode was placed at both mastoid bones; the ground electrode was in the middle of the frontal bone (Fpz). Normal value was as mentioned by the machine standard in milliseconds (ms). Normal

peak latency of wave I: 2 ms; wave III: 4.28 ms; and wave V: 6.2 ms. The normal value for IPL I-III: 2.4 ms; IPL III-V: 2.26 ms; and IPL I-V: 4.46 ms. Glycemic control measurement using HbA1c level, which evaluated within the last 3 months. The HbA1c level was checked with turbidimetry method by an automatic autoanalyzer (Cobas Integra 400 Plus analyzer from Roche). Diabetic patient with good and poor glycemic control was the independent variable, while BAEP latencies were the dependent variable. Duration of diabetic, dyslipidemia, hypertension, and smoking history were acted as bias. All collected data were then statistically analyzed with SPSS 17.0 for windows.

Results

The unpaired t-test found prolonged persistent BAEP latencies (either peak latency of wave III, V, IPL I-III, III-V, and I-V) in both ears at the poor glycemic control group, but the results were not differed significantly ($p > 0.05$). However, there was significant difference of BAEP latency base on duration of DM group and cigarettes consumption group, as shown in Table 1.

Table 1: Basic characteristics of research subject

Variable	Good glycemic control (n=40) n (%)	Poor glycemic control (n=40) n (%)	p
Age mean (years)	54±5.292	53±7.491	0.219
HbA1c	6.155±0.665	8.992±1.504	0.001*
Gender			
Male	26 (65)	26 (65)	1.000
Female	14 (35)	14 (35)	
Education level			
No school	5 (12.5)	2 (5)	0.127
Elementary school	6 (15)	5 (12.5)	
Junior high school	3 (7.5)	2 (5)	
Senior high school	12 (30)	11 (27.5)	
University	14 (35)	20 (50)	
Job			
Farmer/laborers	4 (10)	2 (5)	0.102
Entrepreneur	10 (25)	9 (22.5)	
Private employee	6 (15)	8 (20)	
Government employee	9 (22.5)	14 (35)	
Others	11 (27.5)	7 (17.5)	
Duration of DM (years)			
<5	30 (75)	17 (42.5)	0.003*
5–10	10 (25)	23 (57.5)	
Hypertension			
Yes	14 (35)	9 (22.5)	0.220
No	26 (65)	31 (77.5)	
Dyslipidemia			
Yes	16 (40)	22 (55)	0.182
No	24 (60)	18 (45)	
Hearing loss			
Yes	6 (15)	7 (17.5)	0.763
No	34 (85)	33 (82.5)	
Tuning fork test			
SNHL	3 (7.5)	7 (17.5)	0.179
Normal	37 (92.5)	33 (82.5)	
Smoking			
Yes	6 (15)	11 (27.5)	0.174
No	34 (85)	29 (72.5)	
DM medication			
Insulin	18 (45)	31 (77.5)	0.021*
Oral antidiabetic	22 (55)	4 (10)	
Insulin+oral medicine	0	5 (12.5)	

*Statistically significant.

Bivariate analysis of BAEP latency with glycemic control in DM patients

The latency of wave III, V, IPL I-III, III-V, and I-V (measured at 90 dB intensity) from both ears is tested for normality with Kolmogorov–Smirnov, showing normal scattered data except in the right and left IPL III-V. Hypothesis test used is unpaired t-test (in normally distributed data), and Mann–Whitney test (on non-distributed data), significance level measured with $p < 0.05$. BAEP latency analysis results in each ear are presented in Table 2.

Table 2: The unpaired t-test bivariate analyzes of BAEP mean latency in the good and poor glycemic control group

Ear stimulation site	Wave	Good glycemic control (n=40)	Poor glycemic control (n=40)	p
Left Ear	Latency III	4.080 ± 0.260	4.098 ± 0.284	0.775
	Latency V	6.023 ± 0.429	6.333 ± 0.402	0.166
	IPL I-III	2.520 ± 0.318	2.530 ± 0.355	0.895
	IPL III-V	2.098 ± 0.468	2.288 ± 0.662	0.145
	IPL I-V	4.643 ± 0.459	4.688 ± 0.532	0.686
Right Ear	Latency III	4.013 ± 0.351	4.075 ± 0.298	0.393
	Latency V	6.025 ± 0.439	6.338 ± 0.384	0.155
	IPL I-III	2.495 ± 0.410	2.544 ± 0.342	0.561
	IPL III-V	2.192 ± 0.471	2.303 ± 0.618	0.646
	IPL I-V	4.688 ± 0.546	4.755 ± 0.496	0.564

The results of statistical analysis from the data above indicate persistent prolonged BAEP wave latency either in wave latency III, V, IPL I-III, III-V, and IPL I-V, in both ears ($p>0.05$).

Statistical analysis of other factors possibly influences the difference between BAEP prolonged latency in diabetic patients

Other factors that may also affect the difference in BAEP latency in patients with DM are duration suffering from DM, hypertension, dyslipidemia, and cigarette consumption. The relationship between the four variables was analyzed by unpaired t-test. Mean value is set at probability value $p < 0.05$.

In this study, statistical analysis of BAEP latency shows no significant difference related to hypertension and dyslipidemia. Our subjects were then divided into two groups based on the duration of DM, i.e., less than 5 years and groups of 5–10 years. The result of the different analysis of BAEP latency average is shown in Table 3.

Table 3: The unpaired t-test bivariate analyzes of BAEP mean latency based on DM duration group

Ear stimulation site	Wave	Duration <5 years	Duration 5–10 years	p
Left Ear	Latency III	4.043 ± 0.303	4.155 ± 0.205	0.068
	Latency V	6.153 ± 0.401	6.430 ± 0.393	0.003*
	IPL I-III	2.481 ± 0.369	2.588 ± 0.272	0.160
	IPL III-V	2.100 ± 0.387	2.324 ± 0.706	0.087
	IPL I-V	4.581 ± 0.445	4.785 ± 0.541	0.069
Right Ear	Latency III	3.979 ± 0.329	4.136 ± 0.299	0.032*
	Latency V	6.191 ± 0.456	6.385 ± 0.323	0.040*
	IPL I-III	2.470 ± 0.370	2.591 ± 0.378	0.156
	IPL III-V	2.209 ± 0.503	2.303 ± 0.612	0.452
	IPL I-V	4.677 ± 0.536	4.785 ± 0.541	0.362

*Statistically significant.

Based on the data in the table, there are significant latency differences in latency V left ear ($p = 0.003$), latency III ($p = 0.032$), and latency V ($p = 0.040$) of right ear. Another BAEP latency was also found to be consistently longer in both ears in the group with DM 5–10 years duration, but statistically, there were no significant difference.

Cigarettes are thought to affect the latency of BAEP in DM patients. In this study, the subjects were divided into two groups, namely, smokers and non-smokers. Individuals are said to be smokers when

they meet the criteria of smoking history = 10 cigarettes/days for more than 1 year regularly [25]. In this study, no data obtained detail on how long the subject had been smoking before it stopped. Our data also do not include passive smoking conditions. The statistical analysis result of BAEP latency on diabetic smoker and non-smoker group is listed in Table 4.

Table 4: The unpaired t-test bivariate analyzes of BAEP mean latency based on smoker and non-smoker group

Ear stimulation site	Wave	Smoker	Non-smoker	p
Left	Latency III	3.944 ± 0.334	4.114 ± 0.248	0.105
Ear	Latency V	6.294 ± 0.439	6.260 ± 0.416	0.770
	IPL I-III	2.500 ± 0.302	2.532 ± 0.345	0.731
	IPL III-V	2.453 ± 0.855	2.122 ± 0.462	0.035*
	IPL I-V	4.647 ± 0.612	4.670 ± 0.463	0.867
Right	Latency III	3.994 ± 0.327	4.057 ± 0.326	0.481
Ear	Latency V	6.371 ± 0.348	6.244 ± 0.431	0.269
	IPL I-III	2.447 ± 0.322	2.539 ± 0.389	0.373
	IPL III-V	2.482 ± 0.754	2.184 ± 0.467	0.046*
	IPL I-V	4.718 ± 0.514	4.722 ± 0.524	0.975

*Statistically significant

The data in Table 4 show that IPL III-V left and right ear were longer in the smokers' group ($p < 0.05$).

Discussion

The age of our subjects was limited from 40 to 65 years old. This was done to obtain the uniformity of the sample variant and to reduce the likelihood of bias on BAEP results due to presbycusis that possibly occurs in individuals over 65 years old [26]. The mean age of the two groups did not differ significantly with $p = 0.219$ ($p > 0.05$). The mean age is similar to study from Talebi *et al*. [18].

Based on sex, there were 52 male subjects (65%) and 14 female (35%) spread evenly in each group. Uniformity of the sample by sex in both groups got by chance. Similar previous studies have also gained men more than women [1], [9], [27].

Most of the study subjects suffered from DM with duration of fewer than 5 years (58.75%) while subjects who suffered from DM for 5–10 years as much as 41.25%. The same period was also used in previous studies [9], [14]. Most of the research similar take samples of DM patients with the duration of the disease more than 10 years [8], [11], [16], [18], while Gupta *et al*. (2010) use the duration range suffered DM less than 5 years in the sample research [27]. Research subjects in both groups more non-smoker (78.8%) than smoker (21.3%).

BAEP latency differences in diabetic patients with good and poor glycemic control

BAEP was examined in both groups after being classified depends on their glycemic control (by assessing the HbA1c level). The examination performed with "click" sound stimulus provided through headphones, with 90 dB intensity. Patients lying supine, having paired active electrode placed in both mastoid bones (A1 and A2), and the reference electrode was placed in Cz and ground electrode in Fpz. BAEP wave was recorded twice in each ear to ensure uniformity of the wave generated. This examination method was similar to other earlier studies [9], [14], [18].

Some previous studies which evaluated BAEP latency in DM patients obtained that latency of wave I was no different in a group of DM patient compare with healthy person group [11], [27]. Our research only evaluated BAEP latency of wave III, V, IPL I-III, III-V, and I-V from both ears.

Most studies which evaluate BAEP latency in DM patients compare its results with a healthy control group and are found to be significantly differed [12], [18], [22]. In this study, both groups were people with DM.

As a final result, in this study, we find consistently prolonged BAEP latency on poor glycemic control group of both ears at the latency of wave III, V, IPL I-III, III-V, and IPL I-V compare than the good glycemic control group. However, the BAEP wave latency was not statistically significant ($p > 0.05$) in both groups.

The results of this study are similar to the previous studies [10], [17], [18]. Those researches also showed no significant correlation between HbA1c levels with BAEP latency. A study by Abdulkadiroglu *et al*. (1999) also found no correlation between the extension of latency BAEP and glycemic control [9].

Mahalik *et al*. (2014) conducted a study comparing patients with good glycemic control Type 2 DM, compared with healthy people. The analysis result shows that there was an extension of wave III latency on DM patients compared to the control group ($p = 0.001$), but no significant difference in wave latency V ($p = 0.16$). It also obtained significant IPL extension between-group diabetics compared to the healthy control group.

Our study differ from that of Abo-Elfetoh *et al*. (2015) who compared three groups of samples, i.e., DM patient with good and poor glycemic control and healthy individuals. BAEP examination is done with the same intensity as our study. This study found significant latency elongation of the waves V, IPL I-III, and III-V in poor glycemic control group [14], [23]. However, this study includes samples with age range of 32–70 years old. It may play an important role because of presbycusis events increased sharply over the age of 65 years [26].

The difference in BAEP latency based on DM duration

In our study, subjects were divided into two groups based on the length of DM, i.e., <5 years

and between 5 and 10 years. Based on the result of statistical data analysis with unpaired t-test, there is a significant difference of BAEP latency on wave III right ear (p = 0,032), wave V left and right ear (p = 0.003 and 0.040, respectively).

This result is similar to other studies [9], [15]. In both studies, it was concluded that central and peripheral neuropathy in DM was related to the duration of illness and is not associated with blood sugar levels and metabolic control. It was concluded that the duration of diabetes is a definitive risk factor for the occurrence of central diabetic neuropathy [15], [27]. Study by Shatdal *et al*. (2013) also found significant IPL III-V elongation in DM patients whom diagnosed for more than 5 years [10].

Our study has a different result to Takkar *et al*. (2013) which found there was no statistically significant difference related to duration suffers from DM, due to well controlled blood sugar [8].

BAEP latency differences in DM smokers and non-smokers

In this study, we also want to know whether cigarettes consumption has affect BAEP latency in DM patient. Statistical analysis shows a significant difference in BAEP latency ($p < 0.05$) among smoking groups compared with the non-smoking.

Heavy smokers (more than 20 cigarettes per day) are reported to have a higher risk of insulin resistance, up to 61%, while less frequent smokers (<20 cigarettes per day) were associated with a 29% risk. Former smokers have a risk of only 23% higher. Mitochondrial dysfunction, oxidative stress, and inflammation are some mechanism involved in the underlying nicotine-induced nerve toxicity [28]. There are also research data which states that DM patients who are active smoker had a 14-fold risk of developing DM complications compared with patients with DM alone or smokers only [29].

Smoking and nicotine consumption will raise hormone levels in such to circulating catecholamines, glucagon, and growth hormone, which can interfere with work insulin. From the research was concluded that nicotine especially could cause damage to people who have a fragile prior health condition health, for example, patients with DM [30]. This explanation can be a reason why in our study we found significantly elongation of BAEP latency in DM patient who smokes ($p < 0.05$).

Conclusion

Based on the results of this study, it was concluded that BAEP wave latency consistently longer in the group of diabetic patients with poor glycemic control ($p > 0.05$). Our study also found significant prolonged BAEP wave latency related to DM duration and in DM patient group who was smoker ($p < 0.05$).

Suggestion

Some suggestions based from our study results are:

1. BAEP can be used as an early screening in DM patients for the possibility of central neuropathy diabetic. More awareness should be given to DM patient with poor glycemic control, smoker and has been suffering DM for more than 5 years
2. It is best to give proper education about the importance of glycemic control and routine evaluation regarding possible complications of DM
3. Need to do further research with the longer duration of DM (>10 years) to see whether longer DM duration will significantly affect BAEP latency. Further research on DM patients can also be completed by screening for central diabetic neuropathy compared with peripheral nerve conduction examination. Expected to get data whether central diabetic neuropathy occurred after, before, or simultaneously with peripheral neuropathy.

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