Sensitivity and Specificity of Vestibular Evoked Myogenic Potential Elicited By Different Tone Bursts to Diagnose Peripheral Vestibular Disordered

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ABSTRACT

Peripheral vestibular disorder (PVD) is serious and common. Clinically, giving an accurate diagnosis of PVD can be challenging. Vestibular evoked myogenic potential (VEMP) is an objective test to evaluate the integrity of vestibular organs, particularly saccule and/or inferior vestibular nerve. This study was performed to determine the sensitivity and specificity of VEMP using different stimuli. Fourty normal and 65 PVD subjects who fulfilled the inclusion criteria were recruited. While sitting comfortably, VEMP waveforms were recorded with active electrode on sternocleidomastoid muscle and negative electrode on upper forehead. Tone bursts (500, 750 and 1000 Hz) were delivered via headphones at 90 dBnHL and 5/s presentation rate. VEMP parameters for each stimulus (amplitude and latency of P1 and N1 peak) were analyzed accordingly. Receiver operating characteristic (ROC) was performed to determine the sensitivity and specificity of VEMP at different test frequencies. N1 amplitude of 750 Hz stimulus produced the most ideal sensitivity (65% on right and 63% on left) and specificity (83% on right and 78% on left). The importance of using a few tone bursts in VEMP test in order to minimize the false negative in cases might be encountered in clinics as the certain tone burst had inadequate sensitivity in detecting PVD cases. The 750 Hz stimulus produced the most ideal sensitivity and specificity of sensitivity and specificity of sensitivity and specificity of sensitivity in detecting PVD cases. The 750 Hz stimulus produced the most ideal velues of sensitivity and specificity, at least in this study.

Key Words : Sensitivity, specificity, Vestibular evoked myogenic potentials, Peripheral vestibular disorders, saccule

INTRODUCTION

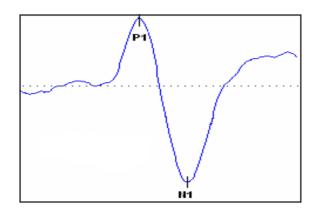
Vestibular disordered is one of the common diseases that will affect patients balance. Vestibular evoked myogenic potential (VEMP) is one of the objective test that able to evaluate function of certain part of vestibular organ. There are a great number of earliest known studies related to VEMP since four decades ago. 'These studies investigated neck muscles and their relation to vestibular potential'.^{1,29} Following these studies, efforts concentrated on vestibular evoked myogenic potentials.^{5,6,10,19,28} 'More current studies found that, if an electrode is placed on Sternocleidomastoid muscles (SCM) or other locations (e.g. forehead or sternum) and a loud sound is introduced via the headphone to the ear, the saccule is stimulated'.^{13,21} The sound is then transmitted to the inferior vestibular nerves, lateral vestibular nucleus, medial vestibulo-spinal tract, and terminates at the motor neurons of the SCM muscles. The objective of this study is to identify the sensitivity and specificity of the VEMPs test value in different tone burst used.

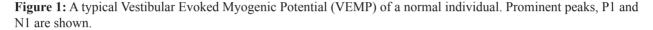
VEMP that is recorded from the SCM muscles is also known as cervical VEMP. In fact, VEMP has several types including 'ocular VEMP',²⁰ 'galvanic VEMP'¹⁷ and 'skull tap VEMP'.² 'Among these variants, the cervical VEMP has been acknowledged as the most convenient test due to its simplicity and reliability'.²⁴ That is, it can be performed using the existing auditory evoked potential machine (that is commonly used to record the auditory brainstem response) without the need of extra equipment. In fact, it is a non-invasive procedure and the electrodes are placed on "comfortable" locations of the subjects. 'The VEMP waveform is also robust and stable over time'.²⁴ In the current study, the word "VEMP" actually refers to the cervical VEMP.

The typical VEMP of a normal indivi²⁴dual is shown in Figure 1. 'In general, there are three prominent peaks of waveforms: inhibitory (P1@p13), excitatory (N1@n23), and a third peak that is assumed to originate from the cochlea'.²⁶ The first two peaks are considered to originate from the vestibular or balance organs. The information from these peaks is useful for the evaluation of the saccule and inferior vestibular nerves. 'VEMP recorded from the neck is believed to be almost completely unilateral'²⁷ and can be obtained from patients with severe to profound hearing loss. 'This suggests the non-auditory origin of the evoked response'.¹⁶

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⁶VEMP test is one of the objective tests valuable to evaluate the function of saccule, inferior vestibular nerve and central vestibular organs¹¹, ¹¹ ^{Abnormal} VEMPs have been found in cases of Meniere's disease^{7,8}, ^{vestibular neuritis¹⁴, ¹⁴ ^{superior} canal dehiscence^{2,24}, ^{Wallenberg syndrome^{2,24} and ^{vestibular schwannoma^{2,24}, ^{Central} pathologies such as brainstem infarcts³ and ^{multiple sclerosis²² produce VEMPs with prolonged latencies. These findings illustrate the importance of VEMP in making clinical diagnoses. Therefore, this study was conducted to determine the sensitivity and specificity of the VEMPs test value in different tone burst used.}}}}

MATERIALS AND METHODS

Subjects

According to sample size calculation we need to recruit at least 40 subjects in each group. 40 normal participants and 65 PVD subjects fulfill the inclusion from the Otorhinolaryngology –Head & Neck Surgery (ORL-HNS) clinic of Hospital Universiti Sains Malaysia (HUSM) who fulfilled the inclusion criteria were recruited.

There are inclusion and exclusion criteria for normal (Phase I) and PVD (Phase II) subjects. The normal subject's inclusion criteria are normal and healthy subjects without any balance and hearing disorders or other chronic diseases (tumor of brain) and the subjects aged 18 years and above. Exclusion criteria are subjects with hearing, balance disorder and chronic diseases and the aged 18 years and above.

For the peripheral vestibular disordered subject, the inclusion criteria are PVD patients (i.e. Benign Paroxysmal Positional Vertigo (BPPV), Meniere's diseases, Poorly Compensated Peripheral Vestibular Disorder (PCPVD) & benign recurrent vertigo) and the patients aged 18 years and above. Meanwhile the exclusion criteria are patients with central lesion and/or central vestibular disorders and the aged 18 years and above.

Sample size calculation

Recall that in the main study, 40 normal subjects and 65 peripheral vestibular disordered patients were recruited. The number of subjects tested was actually adequate and before the study began, we calculated the minimum sample size that was required based on a study by Akkuzu et al. (2006). Using the Power and Sample Size Calculations (PS) software version 3.0 by Duppont & Plummer (2009), the option of independent t-test analysis was chosen. Based on the power of study (1 - B) of 0.8, the alpha (α) value of 0.05, the difference in population means (δ) of 18.1 μ V, the within group standard deviations (SD) of 22.6 and 33.8 μ V and the ratio of control to experimental patients (m) of 1, the minimum sample size required was 40 subjects in each group.

Methods

All normal and PVD subjects were informed and asked to participate in the study by qualified medical personnel. PVD patients are any balance disorder patient due to lesion in peripheral vestibular disorder. Voluntary participation was stressed, confidentiality guaranteed and instructions given about all the procedures. Written consent was obtained from all subjects. Sensitivity and Specificity of Vestibular Evoked Myogenic Potential Elicited By Different Tone Bursts to Diagnose Peripheral Vestibular Disordered

All the subjects were underwent basic clinical test as a gold standard for the test and VEMPs test follow the similar protocol as explained below. While sitting comfortably, VEMP waveforms were recorded with active electrode on sternocleidomastoid muscle and negative electrode on upper forehead. Tone bursts (500, 750 and 1000 Hz) were delivered via headphones at 90 dBnHL and 5/s presentation rate. VEMP parameters for each stimulus (amplitude and latency of P1 and N1 peak) were analyzed accordingly.

a) Vestibular Evoked Myogenic Potential (VEMP) test protocol

i) Equipment used

This test was conducted in a sound treated room with an acceptable ambient noise level (less than 40 dBA). Equipment used included electrodes, scrub gel, a ruler for measurement, marker to mark the location for the electrodes placement, headphones, a chair and the VEMP device (Bio-Logic Navigator Pro. by Natus Medical Inc., USA) (Figure 2).

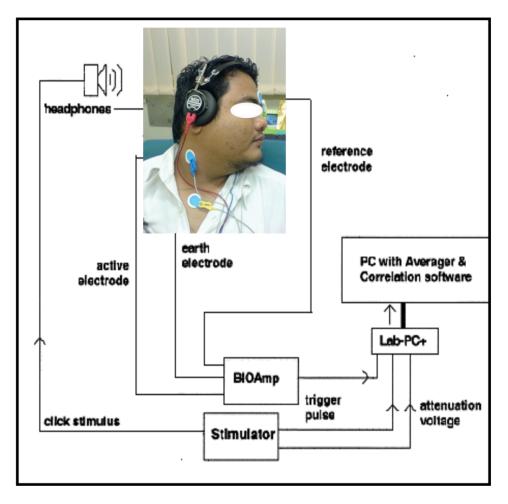


Figure 2: Basic equipment to record VEMP

ii) VEMP Recording

Prior to the recording, subjects were given explanations and instructions regarding the test procedures. Figure 3 shows the summary of the VEMP testing employed in this study.

Once the desired value of electrode impedance had been achieved, the subject wear the headphones and was asked to turn his/her head about 90 degrees to the right to increase the tension of left SCM muscle. To ensure the stability of the recording, the subject was specifically instructed to face a target (i.e. red dot) that was marked symmetrically on the left and right wall (in reference to the subject's position) in the tested room. The stimuli were then presented to the left ear repetitively until the stable waveform was obtained (i.e. at 200 averages). To measure the VEMP on the right side, the same procedures were carried out.

Stimuli used were tone bursts at three different frequencies (i.e. 500, 750 and 1000 Hz) presented at 90 dBnHL with 5/s stimulus rate. The tone bursts were ramped using the Blackman filter with 3-cycle rise/fall time and 0-cycle plateau time (3-0-3 envelope). The time window was set to 53.3 ms with 256 points. The VEMP waveforms were amplified 5000 times and band-passed at 10-1500 Hz. The artifact rejection was set at 2375 μ V to eliminate unwanted responses during the recording.

Patient sat on the chair & electrodes were placed on the allocated areas

[Upper forehead, upper sternum, right and left middle of stenocleidomastoid muscle



Impedance of the electrodes was checked and kept below 5 k Ω

Head was turned 90 degrees to the right with neck positioned on the chair



Auditory stimulus (tone burst, 90dBnHL) was given repetitively via the left headphone at

three different frequencies (500,750 & 1000 kHz)

Head was turned 90 degree to the left with neck positioned on the chair



Auditory stimulus (tone burst, 90dBnHL) was given repetitively via the right headphone at

three different frequencies (500,750 & 1000 kHz)

Test completed

Figure 3: Summary of VEMP recording steps

For each stimulus, at least two replicate waveforms were obtained and averaged for analysis. The prominent peaks of VEMP (P1 and N1) were marked offline to obtain their latency and amplitude values.

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Sensitivity and Specificity of Vestibular Evoked Myogenic Potential Elicited By Different Tone Bursts to Diagnose 13 Peripheral Vestibular Disordered

RESULTS

VEMP contained numerical data, their sensitivity and specificity were determined using the ROC method. Table 2 shows the sensitivity, specificity, cut-off value and Youden index of VEMP parameters at each test frequency. Since VEMP has not been widely used clinically, its cut-off value is yet to be established. In this situation, having the Youden index is helpful in choosing the optimum cut-off point that produces the ideal value of sensitivity and specificity.

As indicated, for the right side, P1 amplitude of 500 Hz test frequency produces the most outstanding results: the sensitivity and specificity of 75.4% and 75%, respectively (Youden index of 0.504). For the left side, N1 amplitude of 500 Hz, N1 amplitude of 750 Hz and P1N1 amplitude of 750 Hz produce the highest Youden index (i.e. 0.406) that yields the sensitivity of 63.1% and specificity of 77.5%. By also considering the Youden index, the least promising test parameter for the right side is P1 latency of 1000 Hz test frequency: the sensitivity and specificity of 16.9% and 90%, respectively (Youden index of 0.669). For the left side, the least sensitive test is N1 amplitude of 500 Hz stimulus (Youden index of 0.156) that produces the sensitivity of 23.1% and specificity of 92.5%.

At this stage, it was of interest to find which VEMP parameter was the "best' in terms of its sensitivity and specificity. So far, initial data showed that the amplitude values of VEMP were more useful than its latency values. To determine which VEMP amplitude was optimum, the ROC method was carried out. By using the area under curve (AUC) analysis, the ROC method was useful to determine the performance of VEMP amplitudes in terms of their sensitivity and specificity. Figure 4 and 5 reveal the ROC curve for P1 amplitude of 500 Hz, N1 amplitude of 750 Hz and P1N1 amplitude of 750 Hz. There is no gross significant difference observed among the test parameters in both sides. As indicated, no significant difference was found between the VEMP amplitudes (p>0.05), suggesting that they have an "equal" capability.

		500 Hz		750 Hz		1000Hz	
		Right	Left	Right	Left	Right	Left
P1 Amplitude	Sensitivity (%)	75.4	47.7	63.1	73.8	70.8	49.2
	Specificity (%)	75	90	80	65	67.5	70
	Cut-off point (µV)	22.73	10.69	24.5	32.58	10.91	9.28
	Youden index	0.504	0.377	0.431	0.388	0.383	0.192
N1 Amplitude	Sensitivity (%)	60	63.1	64.6	63.1	73.8	56.9
	Specificity (%)	87.5	77.5	85	77.5	65	67.5
	Cut-off point (µV)	17.71	18.85	30.64	35.21	13.13	12.63
	Youden index	0.475	0.406	0.496	0.406	0.388	0.244
P1N1 Amplitude	Sensitivity (%)	70.8	52.3	63.1	63.1	78.5	38.5
	Specificity (%)	77.5	85	85	77.5	57.5	85
	Cut-off point (µV)	41.96	26.24	54.48	63.5	28.99	15.56
	Youden index	0.483	0.373	0.481	0.406	0.36	0.235
P1 Latency	Sensitivity (%)	46.2	69.2	56.9	53.8	16.9	66.2
	Specificity (%)	75	62.5	65	72.5	90	52.5
	Cut-off point (ms)	15.8	14.4	14.2	14.6	11.7	13.13
	Youden index	0.212	0.317	0.219	0.263	0.069	0.187
N1 Latency	Sensitivity (%)	41.5	23.1	53.8	80	27.7	56.9
	Specificity (%)	70	92.5	60	45	85	62.5
	Cut-off point (ms)	25	25.4	23.3	22.1	20.4	22.3
	Youden index	0.115	0.156	0.138	0.25	0.127	0.194

Table 2: Sensitivity and specificity of VEMP parameters at each test frequency using ROC method

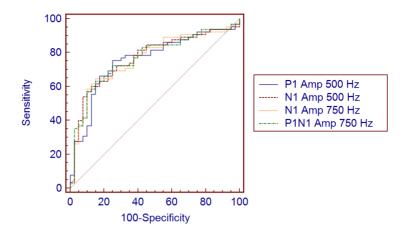


Figure 4: Comparison of ROC curve for P1 amplitude of 500 Hz, N1 amplitude of 500 Hz), N1 amplitude of 750 Hz and P1N1 amplitude of 750 Hz in the right side

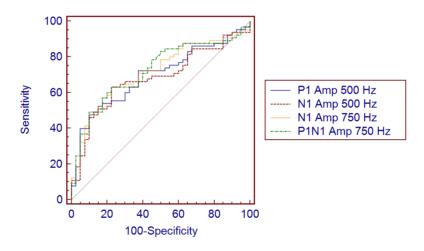


Figure 5: Comparison of ROC curve for P1 amplitude of 500 Hz, N1 amplitude of 500 Hz), N1 amplitude of 750 Hz and P1N1 amplitude of 750 Hz in the left side

Among the amplitude values, the P1 amplitude produced the highest Youden index (i.e. 0.504 for the right side). However, for the left side, the P1 amplitude of 500 Hz produced a low Youden index (i.e. 0.377). Furthermore, as shown in Table 3.13, this Youden index yields a low sensitivity value (i.e. 47.7%) and both sides have an obviously different cut-off value (22.73 μ V and 10.69 μ V for the right and left side, respectively). Based on these outcomes, the P1 amplitude of 500 Hz was not considered to be the optimum VEMP test parameter.

On the other hand, the N1 amplitude of 750 Hz seemed to be the better option for several reasons. Firstly, its Youden index for the right side was the second highest (i.e. 0.496) that produced the sensitivity of 64.6% and specificity of 85%. Secondly, its Youden index for the left side was the highest (i.e. 0.406) that yielded the sensitivity of 63.1% and specificity of 77.5%. Thirdly, its cut-off value was not so different for both sides (i.e. 30.64 μ V and 35.21 μ V for the right and left side, respectively). Finally, as indicated in Table 2, the performance of N1 amplitude of 750 Hz was not statistically different from the P1 amplitude of 500 Hz (that had the highest Youden index in the right side). In fact, the present study attempted to combine several VEMP parameters as an effort to increase the sensitivity of VEMP. Unfortunately, it was then found that the combinations of the test parameters only produced slight increments in the sensitivity but the specificity was greatly reduced. In conclusion, the present study decided to use only one parameter of VEMP (i.e. N1 amplitude of 750 Hz) for subsequent analyses.

For instance, using a higher cut-off value will result in lower sensitivity but high specificity. In contrast, using a lower cut-off value will produce a test with high sensitivity but low specificity. To correct this situation, Youden (1969) suggested the use of Youden Index (sensitivity + specificity - 1) in determining the optimum cut-off point. The cut-off point that produces the highest Youden Index is considered to be the 'best' value. The Youden index is indeed useful to help researchers finding an optimum cut-off value.

Sensitivity and Specificity of Vestibular Evoked Myogenic Potential Elicited By Different Tone Bursts to Diagnose 15 Peripheral Vestibular Disordered

DISCUSSION

VEMP findings in normal and PVD subjects.

In normal subjects, mean latency and amplitude of P1 and N1 of VEMP obtained in this study was consistent with previous studies. At all test frequencies (500Hz, 750Hz and 1000Hz), no significant difference was found when the VEMP findings from left and right side were compared. These outcomes were actually expected since any normal subject should have a symmetrical VEMP. This also suggests that the recording techniques to measure VEMP were optimum, whereby no obvious variability was observed between left and right side. Further analyses found that the 1000 Hz test frequency produced the lowest peaks of VEMP and this is in line with the past studies (Ferdinand et al., 2009). One of the reasons why 1000 Hz is not a "choice" to record VEMP might be related to these "small" peaks. This study, on the other hand, wanted to compare the VEMP outcomes produced by different test frequencies as an effort to increase the sensitivity of VEMP. Nevertheless, in this study, all normal subjects produced an identifiable VEMP on both sides at 1000 Hz test frequency, whereby subsequent analyses could be conducted to answer the research objectives.

The mean latency and amplitude of P1 and N1 of VEMP test in PVD subjects are consistent with some studies. At all test frequencies, no significant difference was found when the VEMP findings were compared between the left and right side. This suggests that PVD subjects have VEMP that was equally "affected" on both sides. This finding is actually in line with other studies. In contrast, some studies have found that VEMP on one side was more affected than the other side (Ferdinand et al., 2009). For instance, a study by Ferdinand et al. (2009) revealed that most subjects with vestibular disorders had asymmetrical VEMP. The reason for this discrepancy is possibly due to the different "pathological" subjects tested.

Generally, when the three frequencies were compared, all of them were able to differentiate between normal and PVD subjects (p values of less than 0.05 in most of VEMP peaks). This clearly demonstrates that PVD patients had significantly abnormal VEMP peaks at all test frequencies if compared to normal group. In this regard, the PVD subjects tend to produce more abnormal peak amplitudes rather than peak latencies of VEMP. This is consistent with the previous studies (Ferdinand et al., 2009). Prolongation of latency was more common in multiple sclerotic patients (Patkó et al., 2006).

Sensitivity and specificity of VEMP

In this study, the sensitivity and specificity value of each VEMP peak was calculated with the ROC method. By considering the Youden Index, the N1 amplitude of 750 Hz was found to be most ideal parameter of VEMP. Its sensitivity was reasonably high, i.e., 64.6% on the right side and 63.1% on the left side. Its specificity was also high, i.e., 85% on the right side and 77.5% on the left side. These results are consistent with previous studies, which showed the low frequencies (500 - 1000 Hz) are the most sensitive and specific stimuli (Murofushi et al., 1999 and Welgampola et al., 2001). The possible reason for this discrepancy is that the study by Ushio et al. employed clicks to record the VEMP, while our study used tone bursts at different frequencies for similar purposes.

CONCLUSION

In conclusion, the combinations of the test parameters only produced slight increments in the sensitivity but the specificity was greatly reduced. In conclusion, the present study decided to use only one parameter of VEMP (i.e. N1 amplitude of 750 Hz) for subsequent analyses. Future study with greater sample size will give a better results and outcomes.

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Malaysian Journal of Medicine and Health Sciences Vol. 10 (2) June 2014

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