European Archives of Oto-Rhino-Laryngology (2019) 276:3257–3265
https://doi.org/10.1007/s00405-019-05674-4

REVIEW ARTICLE

Clinical significance of cervical and ocular vestibular evoked myogenic potentials in benign paroxysmal positional vertigo: a meta-analysis

Ryohei Oya[1] · Takao Imai[1] · Yukinori Takenaka[2] · Takashi Sato[1] · Kazuo Oshima[1] · Yumi Ohta[1] · Hidenori Inohara[1]

Received: 19 August 2019 / Accepted: 27 September 2019 / Published online: 11 October 2019

Abstract

Purpose As the pathological cause of benign paroxysmal positional vertigo (BPPV), the dislocation or degeneration of otoconia in the utricle and saccule is suggested. Vestibular evoked myogenic potential (VEMP) could reflect otolithic dysfunction due to these etiologies of BPPV. The aim of this study was to validate the clinical significance of cervical (c) and ocular (o) VEMP in BPPV by a meta-analysis of previous articles.

Methods Articles related to BPPV with data on cVEMP and oVEMP were collected. The following keywords were used to search PubMed and Scopus for English language articles: benign paroxysmal positional vertigo or BPPV and vestibular evoked myogenic potential or VEMP.

Results The p13 latency in cVEMP and n1 latency in oVEMP were slightly but significantly prolonged in BPPV patients compared to control patients. AR in oVEMP of BPPV patients also showed higher value than that of control patients. However, the n23 latency and AR in cVEMP and p1 latency in oVEMP showed no significant difference between BPPV and control patients. Furthermore, latencies in VEMPs also showed no significant difference between an affected and a non-affected ear in BPPV patients.

Conclusions Our results indicated that otolith dysfunction of BPPVs was detected by latencies in VEMPs, and AR in oVEMP more sensitively reflects the difference between affected and non-affected ears in BPPV patients. The otolith dysfunction of BPPV might be induced by the systemic condition. However, the differences of latencies between BPPV patients and control patients were too small to use VEMPs as a prognostic predictor.

Keywords Benign paroxysmal positional vertigo · Vestibular evoked myogenic potential · Meta-analysis

Introduction

Benign paroxysmal positional vertigo (BPPV) is the most common cause of peripheral vertigo [1]. BPPV is characterized by brief attacks of vertigo provoked by head movement. This phenomenon is suggested to originate from the otolithic organs, in which otoconia are dislocated from the utricle and move into the lumen of the semicircular canals [2]. In addition, several previous reports suggested that the saccular macula and the ganglion cells of the saccular nerve also degenerate in BPPV [3, 4]. Thus, both utricular and saccular dysfunctions may be observed in BPPV.

Vestibular evoked myogenic potential (VEMP) is an electromyographic response to loud auditory stimulation. There are two methods of measuring VEMP, cervical VEMP (cVEMP) and ocular VEMP (oVEMP). The difference between these two methods is the muscles used to record the myogenic potential. The sternocleidomastoid muscle (SCM) is used in cVEMP, and the extraocular muscles including inferior rectus and inferior oblique are used in oVEMP. It has been suggested that cVEMP is generated from a sacculocollic reflex that starts in the saccule and proceeds through the inferior branch of the vestibular nerve [5, 6] and oVEMP is generated from utricle and carried along the otolith-ocular crossed pathway [7, 8]. Thus, VEMPs reflect the otolith function of patients.

✉ Ryohei Oya
ryoheioya0706.tennesseerose@gmail.com

[1] Department of Otorhinolaryngology Head and Neck Surgery, Osaka University Graduate School of Medicine, 2-15 Yamadaoka, Suita, Osaka, Japan

[2] Department of Otorhinolaryngology Head and Neck Surgery, Kansai Medical Hospital, 1-7-2 Shinsenrinishimachi, Toyonaka, Osaka, Japan

The method of recording and analyzing cVEMP was previously described [9–11]. The preferred click or tone-burst intensity and frequency was above 90 or 100 dB (normal hearing level, nHL) [9] and 500 Hz [12], respectively. The electromyographic activity was bandpass-filtered, and the resultant response consisted of a biphasic wave with an initial positive peak at 12–13-ms latency (p13) and a subsequent negative peak at 22–23-ms latency (n23) [13]. In several articles, asymmetry ratio (AR) was used to compare the peak-to-peak amplitude of p13 and n23 among bilateral ears. Murofushi et al. standardized a formula to calculate AR as follows: $100[(An-Ad)/(An+Ad)]$, where An is the peak-to-peak amplitude in a non-affected ear, and Ad is the peak-to-peak amplitude in an affected ear [14].

The measuring method of oVEMP was also described previously [8, 15]. The participant was placed in a supine position and instructed to maintain a visual fixation point of approximately 30° upward during the recording. The positive electrode is placed on the orbital margin below the center of the eye and the reference electrode was placed 15–30 mm below on the cheek, and the ground electrode on the forehead [7, 8]. The electromyographic activity was bandpass-filtered, and the resultant response consisted of a biphasic wave with an initial negative peak n1 and a subsequent positive peak p1 [15].

To date, several articles have reported the VEMP value in patients with BPPV, but it is necessary to determine the consistency of these findings. The aim of this study was to investigate the clinical importance of VEMP in BPPV by conducting a meta-analysis of the literature.

Materials and methods

Patient data collection

A literature search related to BPPV was performed by searching electronic databases for articles published from the inception of each database until April 30, 2019. The search terms included "benign paroxysmal positional vertigo" or "BPPV" and "vestibular evoked myogenic potential" or "VEMP."

The databases used were PubMed (www.ncbi.nlm.nih.gov/pubmed) and Scopus (www.elsevier.com/online-tools/scopus), which had 100% coverage of MEDLINE and EMBASE. Additionally, the references in the retrieved articles were manually searched for associated studies. Nonhuman studies, those in languages other than English, case reports, meta-analyses, and reviews were excluded.

The articles that were enrolled in the study comprised the parameters of cVEMP, including p13 latency, n23 latency, or AR (mean and standard deviation) and the parameters of oVEMP, including n1 latency, n2 latency, or AR (mean and standard deviation) of patients with BPPV. The peak-to-peak amplitude was also an important parameter of VEMP. There were several articles presenting peak-to-peak amplitude; however, the scale of the amplitude varied among the devices that measured the myogenic potential. The amplitude was amplified to make the peak obvious in various arrangements between each institute; therefore, we analyzed AR instead of the peak-to-peak amplitude in the present study. In the articles, healthy individuals who did not have vertigo were enrolled as control patients. Thus, in our manuscript, the control patients mean the healthy individuals.

Study selection and data extraction were performed independently by two of the authors (R.O. and T.I.), and discrepancies were resolved by consensus.

Inter-reviewer agreement was assessed by Cohen's kappa. Finally, 11 articles that included the parameters of cVEMP and five articles that included the parameters of oVEMP were enrolled in the present study.

The Newcastle–Ottawa Scale (NOS) [16] was used to assess the quality of the included studies, and those with a score of 6 or more were considered high quality studies. NOS was used to assess the quality of nonrandomized studies by grading in the three following sections: selection, comparability, and exposure. The total NOS score ranged from 0, indicating low quality, to 9, indicating high quality.

Statistical analysis

For patient data analysis, a random effect model was used and presented as a forest plot because the included articles had different characteristics. Publication bias was assessed using a funnel plot and tested using Egger's regression intercept test. Heterogeneity was assessed using the Cochran Q test and I^2 statistics. Meta-analyses of aggregated data were performed by using Comprehensive Meta-Analysis software (Biostat, Englewood, NJ, USA).

Results

Literature search results

A flow diagram of the article selection is shown in Fig. 1. Electronic database searches retrieved 189 records, and manual searches retrieved two additional articles. Several articles were excluded as follows: 51 duplicated articles, 24 in languages other than English, 39 articles that did not present the parameters of VEMP, 48 articles that focused on other topics, 5 case reports, and 13 review and meta-analysis articles. In total, 14 articles were included in our study [3, 7, 15, 17–27]. Cohen's kappa for inter-reviewer agreement was 0.81, which indicated almost perfect agreement.

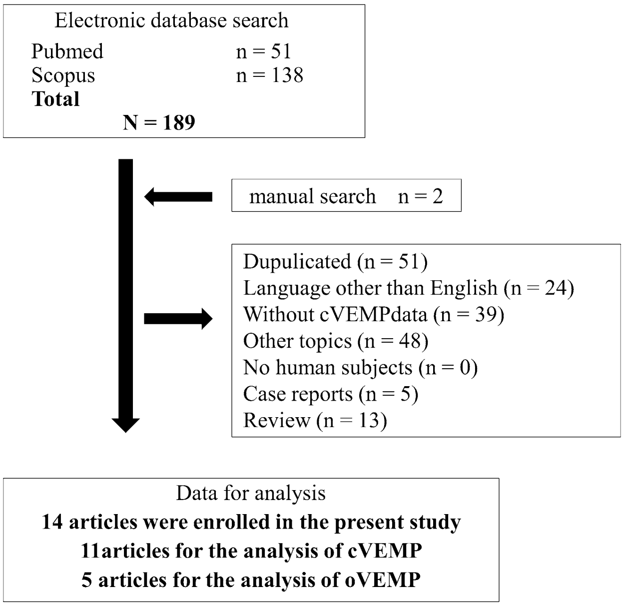

Fig. 1 Flow diagram of the article selection

For analysis of cVEMP parameters, ten articles presented p13 latency [3, 17–21, 23–26] and eight [3, 17, 18, 20, 21, 24–26] presented n23 latency of BPPV and control patients. Out of them, four articles [21, 23, 25, 26] presented AR of BPPV and control patients. These articles were used to analyze the difference in the values of cVEMP parameters between BPPV and control patients. Singh et al. used Jonkee's formula [28] to calculate AR, and it was substantially the same as Murofushi's formula [14]. Additionally, nine articles [17–22, 24–26] presented p13 latency, and eight articles [17, 18, 20–22, 24–26] presented n23 latency of the affected and the non-affected ears of patients with BPPV. These articles were used to analyze the difference in the values of cVEMP parameters between the affected and the non-affected ears of patients with BPPV.

For analysis of oVEMP parameters, four articles presented n1 latency [7, 23, 26, 27] and three [7, 26, 27] presented p1 latency of BPPV and control patients. Out of them, four articles [7, 23, 26, 27] presented AR of BPPV and control patients. These articles were used to analyze the difference in the values of oVEMP parameters between BPPV and control patients. Additionally, four articles [7, 15, 26, 27] presented n1 latency and p1 latency of the affected and the non-affected ears of patients with BPPV. These articles were used to analyze the difference in the values of oVEMP parameters between the affected and the non-affected ears of patients with BPPV.

The individual profiles of the articles related to cVEMP and oVEMP are presented in Tables 1 and 2, respectively. The threshold of auditory stimulation was different among studies, and the semicircular canals involved in BPPV were also different. Especially, the posterior canal is most commonly involved in BPPV [29]. To reduce these biases, we used a random effects model for statistical analysis.

cVEMP parameters between patients with BPPV and control patients

A forest plot showing a comparison of p13 latency between BPPV and control patients is shown in Fig. 2a. The standardized mean difference (SMD) ± standard error (SE) for p13 latency of patients with BPPV compared with control patients was 0.62 ± 0.07. The p13 latency of patients with BPPV was significantly more prolonged than that of the

Table 1 Individual profiles and the Newcastle–Ottawa Scale scores of articles presenting cVEMP parameters

First author	Year	*N*	Age (mean, year)	Sex (male/female)	Type of BPPV	cVEMP threshold	NOS
Akkuzu [3]	2006	25	52.9	19/6	N/A	100 dB nHL, 500 Hz tone-burst	7
Yang [17]	2008	41	59	N/A	Posterior and horizontal	95 dB nHL, click	7
Korres [18}	2011	27	47[a]	14/13	Posterior	95 dB nHL, 500 Hz tone-burst	6
Eryaman [19]	2012	31	51.9	12/19	Posterior	100 dB nHL, 500 Hz tone-burst	7
Longo [20]	2012	23	59	8/15	Posterior	127 dB SPL, 500 Hz	6
Singh [21]	2014	30	42.3	16/14	N/A	95 dB nHL, 500 Hz tone-burst	7
Yetister [22]	2014	102	42.3	36/66	Posterior and horizontal	95 dB nHL, 500 Hz tone-burst	7
Kim [23]	2015	112	62.8	48/64	Posterior and horizontal	100 dB nHL, 1000 Hz tone-burst	7
Sreenivasan [24]	2015	15	41.3	5/10	Posterior	105 dB nHL, 500 Hz tone-burst	5
Karataş [25]	2016	36	47.2	26/10	Posterior and horizontal	100 dB nHL, 500 Hz tone-burst	7
Singh [26]	2016	31	42	N/A	Posterior	125 dB SPL, 500 Hz tone-burst	7

BPPV benign paroxysmal positional vertigo, *cVEMP* cervical vestibular evoked myogenic potential, *NOS* Newcastle–Ottawa Scale, *nHL* normal hearing level, *SPL* sound pressure level

[a]Korres et al. presented median of patients' age

Table 2 Individual profiles and the Newcastle–Ottawa Scale scores of articles presenting oVEMP parameters

First author	Year	*N*	Age (mean, years)	Sex (male/female)	Type of BPPV	oVEMP threshold	NOS
Seo [15]	2013	16	45.2	6/10	Posterior	135 dB SPL, 700 Hz tone-burst	7
Kim [23]	2015	112	62.8	48/64	Posterior and horizontal	100 dB nHL, 1000 Hz tone-burst	7
Singh [7]	2015	30	44.7	16/14	N/A	125 dB SPL, 500 Hz tone-burst	7
Singh [26]	2016	31	42	N/A	Posterior	125 dB SPL, 500 Hz tone-burst	7
Dabbous [27]	2019	30	41.1	6/24	Posterior	100 dB SPL, 500 Hz tone-burst	7

BPPV benign paroxysmal positional vertigo, *oVEMP* ocular vestibular evoked myogenic potential, *NOS* Newcastle–Ottawa Scale, *nHL* normal hearing level, *SPL* sound pressure level

A

First Author	BPPV p13 latency (ms)	Control p13 latency (ms)	SMD	*p* value
Akkuzu (3)	14.3 ± 2.5	13.7 ± 1	0.32 ± 0.25	0.2
Yang (17)	15.0 ± 1.9	13.3 ± 0.9	1.57 ± 0.21	**< 0.001**
Korres (18)	17.3 ± 2.7	16.3 ± 1.6	0.49 ± 0.24	**0.038**
Eryaman (19)	15.8 ± 1.8	15 ± 1.1	0.57 ± 0.26	**0.025**
Longo (20)	14.8 ± 2.2	14.3 ± 1.4	0.31 ± 0.28	0.26
Singh (21)	16.2 ± 1.5	15.8 ± 1.1	0.26 ± 0.26	0.32
Kim (23)	14.3 ± 1.5	13.2 ± 1.4	0.76 ± 0.15	**< 0.001**
Sreenivasan (24)	18.3 ± 3.9	15.9 ± 1.9	0.89 ± 0.43	**0.037**
Karataş (25)	14.2 ± 1.7	14 ± 1.3	0.13 ± 0.23	0.56
Singh (26)	16.3 ± 1.5	15.8 ± 0.8	0.44 ± 0.26	0.09
			0.62 ± 0.07	**< 0.001**

B

First Author	BPPV n23 latency (ms)	Control n23 latency (ms)	SMD	*p* value
Akkuzu (3)	22.4 ± 2.4	22.1 ± 1.9	0.14 ± 0.25	0.58
Yang (17)	24.3 ± 2.3	22.6 ± 1.8	1.92 ± 0.20	**< 0.001**
Korres (18)	25.2 ± 2.9	24.6 ± 2.8	0.22 ± 0.23	0.34
Longo (20)	21.3 ± 1.8	21.4 ± 1.5	-0.06 ± 0.28	0.84
Singh (21)	24.5 ± 0.9	24.4 ± 0.7	0.10 ± 0.26	0.70
Sreenivasan (24)	28.1 ± 2.5	24.7 ± 2.9	1.22 ± 0.44	**< 0.001**
Karataş (25)	21.9 ± 2.0	21.8 ± 1.7	0.05 ± 0.23	0.81
Singh (26)	24.5 ± 0.9	24.7 ± 0.8	-0.19 ± 0.26	0.47
			0.27 ± 0.16	**0.09**

C

First Author	BPPV AR	Control AR	SMD	*p* value
Singh (21)	16.1 ± 5.1	16.3 ± 4.6	-0.03 ± 0.26	0.91
Kim (23)	22.1 ± 17.9	9.8 ± 7.6	0.80 ± 0.19	**< 0.001**
Karataş (25)	16.6 ± 12.8	16.7 ± 13.4	-0.01 ± 0.28	0.98
Singh (26)	15.7 ± 5.2	16.2 ± 4.5	-0.10 ± 0.26	0.71
			0.19 ± 0.25	**0.44**

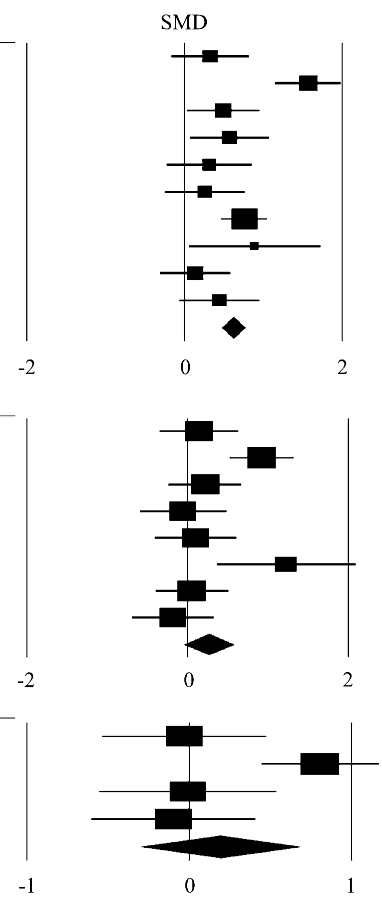

Fig. 2 Forest plot of p13 latency (**a**), n23 latency (**b**), and asymmetry ratio (AR) (**c**) of cervical vestibular evoked myogenic potential (cVEMP) comparing patients with benign paroxysmal positional vertigo (BPPV) and control patients. The latencies (ms) and AR are expressed as mean ± standard deviation

control patients ($p < 0.01$). A forest plot comparing n23 latency of BPPV and control patients is shown in Fig. 2b. The SMD ± SE for n23 latency of patients with BPPV compared with control patients was 0.27 ± 0.16. The n23 latency of patients with BPPV was more prolonged than that of control patients, but the difference was not statistically significant ($p = 0.09$). A forest plot comparing the AR of BPPV and control patients is shown in Fig. 2c. The SMD ± SE for AR of patients with BPPV compared with control patients was 0.19 ± 0.25. The AR of patients with BPPV was larger than that of control patients, but the difference was not statistically significant ($p = 0.44$).

cVEMP parameters for the affected and the non-affected ears in patients with BPPV

A forest plot showing a comparison of p13 latency for the affected ear and the non-affected ear in patients with BPPV is shown in Fig. 3a. The SMD ± SE for p13 latency of the affected ear compared with that of the non-affected ear was 0.16 ± 0.09. The p13 latency of the affected ear was more prolonged than that of the non-affected ear, but the difference was not statistically significant ($p = 0.07$). A forest plot showing a comparison of n23 latency between the affected ear and the non-affected ear in patients with BPPV is shown in Fig. 3b. The SMD ± SE for n23 latency of the affected ear compared with that of the non-affected ear was 0.14 ± 0.12. The n23 latency of the affected ear was more prolonged than that of the non-affected ear, but the difference was not statistically significant ($p = 0.24$).

oVEMP parameters between patients with BPPV and control patients

A forest plot showing a comparison of n1 latency between BPPV and control patients is shown in Fig. 4a. The SMD ± SE for n1 latency of patients with BPPV compared with control patients was 0.58 ± 0.16. The n1 latency of patients with BPPV was significantly more prolonged than that of the control patients ($p < 0.01$). A forest plot comparing p1 latency of BPPV and control patients is shown in Fig. 4b. The SMD ± SE for p1 latency of patients with BPPV compared with control patients was − 0.16 ± 0.15. The p1 latency of patients with BPPV was more prolonged than that of control patients, but the difference was not statistically significant ($p = 0.45$). A forest plot comparing the AR of BPPV and control patients is shown in Fig. 4c. The SMD ± SE for AR of patients with BPPV compared with control patients was 1.19 ± 0.36. The AR of patients with BPPV was significantly larger than that of control patients ($p < 0.01$).

oVEMP parameters for the affected and the non-affected ears in patients with BPPV

A forest plot showing a comparison of n1 latency for the affected ear and the non-affected ear in patients with BPPV is shown in Fig. 5a. The SMD ± SE for n1 latency of the affected ear compared with that of the non-affected ear was 0.22 ± 0.14. The n1 latency of the affected ear was more prolonged than that of the non-affected ear, but the

A

First Author	Affected ear p13 latency (ms)	Non-affected ear p13 latency (ms)	SMD	*p* value
Yang [17]	15.0 ± 1.9	13.8 ± 2.0	0.63 ± 0.27	**0.017**
Korres [18]	17.3 ± 2.7	17.2 ± 1.9	0.05 ± 0.30	0.88
Eryaman [19]	15.8 ± 1.8	15.7 ± 1.6	0.02 ± 0.27	0.95
Longo [20]	14.8 ± 2.2	14.6 ± 1.2	0.13 ± 0.33	0.70
Singh [21]	16.2 ± 1.5	15.7 ± 0.8	0.37 ± 0.26	0.26
Yetiser [22]	17.3 ± 3.9	17.3 ± 3.0	0.00 ± 0.47	1.0
Yetiser	17.4 ± 3.0	17.4 ± 3.0	-0.02 ± 0.19	0.92
Yetiser	19.2 ± 3.9	18.2 ± 4.1	0.27 ± 0.34	0.42
Sreenivasan [24]	18.3 ± 3.9	16.3 ± 1.5	0.69 ± 0.47	0.14
Karataş [25]	14.2 ± 1.7	14.7 ± 1.8	-0.29 ± 0.24	0.23
Singh [26]	16.3 ± 1.5	15.8 ± 1.1	0.40 ± 0.26	0.12
			0.16 ± 0.09	**0.07**

B

First Author	Affected ear n23 latency (ms)	Non-affected ear n23 latency (ms)	SMD	*p* value
Yang [17]	24.3 ± 2.3	23.0 ± 2.4	0.56 ± 0.26	**0.034**
Korres [18]	25.2 ± 2.9	25.1 ± 1.6	0.04 ± 0.30	0.89
Longo [20]	21.3 ± 1.8	21.4 ± 1.5	-0.08 ± 0.33	0.82
Singh [21]	24.5 ± 0.9	24.6 ± 0.8	-0.13 ± 0.26	0.62
Yetiser [22]	23.9 ± 4.5	24.7 ± 3.5	-0.20 ± 0.47	0.67
Yetiser	27.1 ± 3.1	26.3 ± 3.3	0.28 ± 0.19	0.15
Yetiser	26.2 ± 4.3	26.5 ± 3.9	-0.09 ± 0.33	0.80
Sreenivasan [24]	28.1 ± 2.5	25.1 ± 1.7	1.42 ± 0.51	**< 0.001**
Karataş [25]	21.9 ± 2.0	22.4 ± 2.2	-0.24 ± 0.24	0.32
Singh [26]	24.5 ± 0.9	24.3 ± 0.6	0.29 ± 0.26	0.26
			0.14 ± 0.12	**0.24**

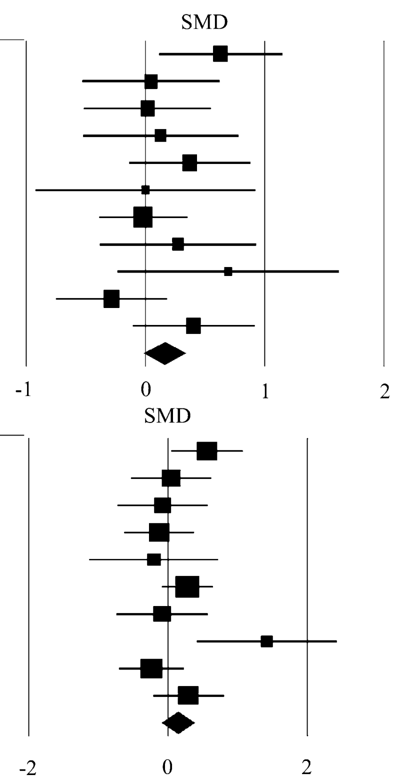

Fig. 3 Forest plot of p13 latency (**a**) and n23 latency (**b**) comparing the affected ear and the non-affected ear in patients with benign paroxysmal positional vertigo (BPPV). The latencies (ms) are expressed as mean ± standard deviation. "Asterisk" Yetiser et al. divided patients into three groups by age; patients' age of < 30, 31–50, and > 50 years

A

First Author	BPPV n1 latency (ms)	Control n1 latency (ms)	SMD	*p* value
Kim [23]	10.6 ± 0.9	9.7 ± 1.1	0.89 ± 0.16	**< 0.001**
Singh [7]	11.6 ± 1.3	11.3 ± 1.1	0.29 ± 0.28	0.30
Singh [26]	11.6 ± 1.3	11.4 ± 1.1	0.24 ± 0.28	0.40
Dabbous [27]	15.8 ± 1.8	10.0 ± 0.9	0.66 ± 0.23	**< 0.001**
			0.58 ± 0.16	**< 0.001**

B

First Author	BPPV p1 latency (ms)	Control p1 latency (ms)	SMD	*p* value
Singh [7]	22.4 ± 2.4	22.1 ± 1.9	-0.35 ± 0.29	0.23
Singh [26]	24.3 ± 2.3	22.6 ± 1.8	-0.26 ± 0.28	0.36
Dabbous [27]	25.2 ± 2.9	24.6 ± 2.8	0.12 ± 0.22	0.59
			-0.16 ± 0.15	**0.45**

C

First Author	BPPV AR	Control AR	SMD	*p* value
Kim [23]	19.4 ± 15.7	14.4 ± 11.3	0.35 ± 0.18	0.051
Singh [7]	48.8 ± 27.3	13.4 ± 6.9	1.86 ± 0.32	**< 0.001**
Singh [26]	36.8 ± 18.3	18.4 ± 6.9	1.30 ± 0.30	**< 0.001**
Dabbous [27]	37.5 ± 22.1	14.4 ± 8.8	1.38 ± 0.29	**< 0.001**
			1.19 ± 0.36	**0.001**

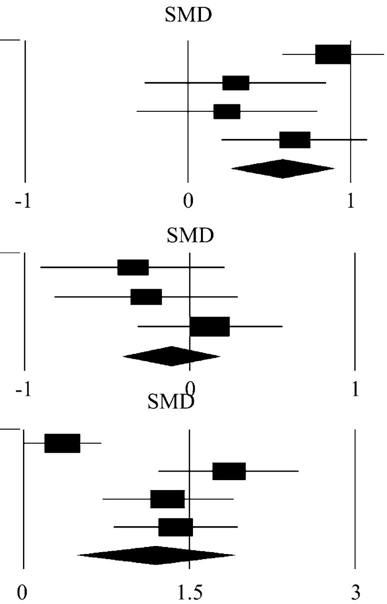

Fig. 4 Forest plot of n1 latency (**a**), p1 latency (**b**), and asymmetry ratio (AR) (**c**) of ocular vestibular evoked myogenic potential (oVEMP) comparing patients with benign paroxysmal positional vertigo (BPPV) and control patients. The latencies (ms) and AR are expressed as mean ± standard deviation

A

First Author	Affected ear n1 latency (ms)	Non-affected ear n1 latency (ms)	SMD	*p* value
Seo [15]	10.5 ± 0.5	10.3 ± 0.9	0.27 ± 0.42	0.52
Singh [7]	11.6 ± 1.3	11.4 ± 1.1	0.17 ± 0.28	0.56
Singh [26]	11.6 ± 1.3	11.5 ± 1.3	0.13 ± 0.28	0.63
Dabbous [27]	10.9 ± 2.2	10.4 ± 1.6	0.31 ± 0.23	0.17
			0.22 ± 0.14	**0.11**

B

First Author	Affected ear p2 latency (ms)	Non-affected ear p2 latency (ms)	SMD	*p* value
Seo [15]	16.5 ± 0.8	16.7 ± 0.8	-0.25 ± 0.42	0.55
Singh [7]	16.1 ± 2.0	16.0 ± 1.5	0.07 ± 0.28	0.80
Singh [26]	16.1 ± 2.0	16.1 ± 1.5	0.01 ± 0.28	0.98
Dabbous [27]	15.4 ± 3.1	14.5 ± 2.0	0.38 ± 0.23	0.09
			0.14 ± 0.14	**0.32**

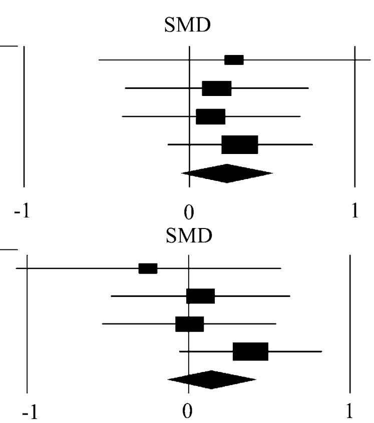

Fig. 5 Forest plot of n1 latency (**a**) and p1 latency (**b**) comparing the affected ear and the non-affected ear in patients with benign paroxysmal positional vertigo (BPPV). The latencies (ms) are expressed as mean ± standard deviation

difference was not statistically significant ($p = 0.11$). A forest plot showing a comparison of p1 latency between the affected ear and the non-affected ear in patients with BPPV is shown in Fig. 5b. The SMD ± SE for p1 latency of the affected ear compared with that of the non-affected ear was 0.14 ± 0.14. The p1 latency of the affected ear was more prolonged than that of the non-affected ear, but the difference was not statistically significant ($p = 0.32$).

Evidence level of each study

The results of the NOS scoring of each article are presented in Tables 1 and 2. Eleven studies were graded as 7 (of 9), two studies were graded as 6 (of 9), and one study was graded as 5 (of 9). We considered the articles enrolled in our study to be of high quality, and they did not diminish the quality of the present meta-analysis.

Discussion

In the pathophysiology of BPPV, the otoconia consisting of calcium carbonate crystals are dislodged from the utricular macula and migrate into the lumen of the semicircular canals [2, 30]. In this hypothesis, it is suggested that the degeneration of the utricular macula causes the detachment of otoconia. Akkuzu et al. proposed that the degeneration process may occur in the saccular macula as well as the utricular macula [3]. Gacek et al. also reported a loss of cell count in saccular macula as well as in the inferior vestibular nerve in postmortem temporal bone examination of patients with BPPV [4, 31]. Therefore, VEMPs in patients with BPPV may show abnormal otolithic function even during patients are in the head position which does not induce the vertigo.

In the present study, p13 latency of cVEMP in patients with BPPV was significantly prolonged compared to control patients. This result indicated that saccular dysfunction may occur in patients with BPPV. In addition, our results showed prolonged n23 and larger AR in patients with BPPV compared to control patients; however, there was no significant difference in n23 and AR between BPPV and control patients. To analyze the mean values of cVEMP parameters, the data of patients who showed absence of a meaningful waveform were excluded in the articles enrolled in the present meta-analysis. The absence may reflect saccular dysfunction and cannot be calculated together with the data of patients who showed cVEMP waveforms; therefore, the difference may be diminished by excluding these patients. There were a few cases that showed absent response in control patients in articles enrolled in the present study. Furthermore, in the analysis of AR, only four articles were enrolled in our study. More studies may be needed to achieve statistical significance.

Furthermore, n1 latency and AR of oVEMP in patients with BPPV showed significantly larger values compared to control patients in the present study. This result indicated that utricular dysfunction as well as saccular dysfunction may occur in patients with BPPV. oVEMP originates from the utricle via the superior vestibular nerve and reflects the utricular function [11, 32]. Originally, degeneration of the utricular macula was demonstrated in patients with BPPV [33], and utricular dysfunction was indicated in BPPV. Singh et al. reported that patients with BPPV showed a smaller peak-to-peak amplitude and AR in oVEMP than control patients [7]. Furthermore, Takeda et al. reported reduced vestibulo–ocular reflex gain in patients with BPPV using eccentric rotation [34]. These previous articles indicated that utricular dysfunction could exist in patients with BPPV and agree with our results.

Previously, it was proposed that calcium metabolism played an important role in the maintenance of otoconia [35], and abnormal calcium metabolism could relate to the etiology of BPPV. Kahraman et al. reported that patients showed abnormal calcium metabolism at the first visit more than at follow-up visits, including lower ionized calcium, corrected by pH and 25-hydroxyvitamin D and higher parathormone [36]. In our study, p13 and n23 latencies of cVEMP and n1 and p2 latencies of oVEMP in the affected and the non-affected ears of patients with BPPV did not show significant differences. The degeneration may be caused by the systemic condition, including calcium homeostasis [35]. If the degeneration of the saccular and utricular maculas occur in BPPV, these degenerations may occur in both ears of patients with BPPV, and our results agreed with this hypothesis. The degeneration of otolithic organs may be caused by abnormal calcium metabolism; therefore, it will be necessary to investigate VEMP values of patients with abnormal calcium metabolism.

As mentioned above, the cVEMP of patients with BPPV indicated that saccular dysfunction may exist in BPPV. However, the differences in the VEMP parameters between the BPPV and control patients was too small, and there was no significant difference between the affected ear and the non-affected ears in BPPV patients. Hence, we suggest that VEMPs was not suitable for clinical application, including the prediction of prognosis or severity of BPPV. Sometimes patients feel severe dizziness right after vertigo attack as well as during recovery period. If such an abnormal sensation is caused by otolithic dysfunction, these patients show abnormal VEMP value. Further research will be required to investigate the otolithic function along the time course of BPPV.

This study has several limitations. First, there is publication bias in this analysis. The funnel plot of the analysis of the differences in p13 and n23 latencies of cVEMP and p2 latency of oVEMP between BPPV and control patients does not show publication bias ($p=0.44$, $p=0.94$, $p=0.084$, Egger's test, respectively, data not shown). In addition, the funnel plot of the analysis of differences in p13 and n23 latencies of cVEMP and n1 and p2 latencies of oVEMP in the affected and the non-affected ears also does not show publication bias ($p=0.30$, $p=0.67$, $p=0.78$, $p=0.095$, Egger's test, respectively, data not shown). However, in the funnel plot of the analysis of differences in AR of cVEMP and oVEMP between BPPV and control patients, Egger's test of the intercept suggests publication bias ($p=0.027$, $p=0.015$, respectively, data not shown). Furthermore, the funnel plot of the analysis of differences in n1 latency of oVEMP between BPPV and control patients shows publication bias ($p=0.017$, Egger's test, data not shown). The number of articles presenting AR of BPPV and control patients and oVEMP values is relatively small, and this may have caused publication bias. Second, the articles that were enrolled in the present study include various characteristics such as patients' profile, type of BPPV, and VEMP threshold. In particular, the cVEMP threshold is slightly different in each article (Tables 1, 2). The cVEMP threshold employed in each article is within an acceptable range regarding the appropriate threshold that was previously proposed [9, 12]. However, these differences may affect the results; therefore, we have applied a random effect model for the meta-analysis.

Acknowledgements The authors would like to thank Enago (www.enago.jp) for the English language review.

Author contributions RO conceived and designed the study and wrote the paper. RO, TI, and YT collected and analyzed the data. TS, KO, YO, and HI reviewed and revised the manuscript.

Funding None.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest.

References

1. Imai T, Takeda N (2017) Committee for standards in diagnosis of Japan Society for equilibrium research. Classification, diagnostic criteria and management of benign paroxysmal positional vertigo. Auris Nasus Larynx 44:1–6
2. Parnes LS, McClure JA (1992) Free-floating endolymph particles: a new operative finding during posterior semicircular canal occlusion. Laryngoscope 102:988–992
3. Akkuzu G, Akkuzu B, Ozluoglu LN (2006) Vestibular evoked myogenic potentials in benign paroxysmal positional vertigo and Meniere's disease. Eur Arch Otorhinolaryngol 263:510–517
4. Gacek RR (2003) Pathology of benign paroxysmal positional vertigo revisited. Ann Otol Rhinol Laryngol 112:574–582
5. Murofushi T, Curthoys IS (1997) Physiological and anatomical study of click-sensitive primary vestibular afferents in the guinea pig. Acta Otolaryngol 117:66–72
6. Murofushi T, Curthoys IS, Topple AN, Colebatch JG, Halmagyi GM (1995) Responses of guinea pig primary vestibular neurons to clicks. Exp Brain Res 103:174–178
7. Singh NK, Barman A (2015) Efficacy of ocular vestibular-evoked myogenic potential in identifying posterior semicircular canal benign paroxysmal positional vertigo. Ear Hear 36:261–268
8. Rosengren SM, Welgampola MS, Colebatch JG (2010) Vestibular evoked myogenic potentials: past, present and future. Clin Neurophysiol 121:636–651
9. Colebatch JG, Halmagyi GM, Skuse NF (1994) Myogenic potentials generated by a click-evoked vestibulocollic reflex. J Neurol Neurosurg Psychiatry 57:190–197
10. Murofushi T, Halmagyi GM, Yavor RA, Colebatch JG (1996) Absent vestibular evoked myogenic potentials in vestibular neurolabyrinthitis. An indicator of inferior vestibular nerve involvement? Arch Otolaryngol Head Neck Surg 122:845–848
11. Fife TD, Colebatch JG, Kerber KA, Brantberg K, Strupp M, Lee H, Walker MF, Ashman E, Fletcher J, Callaghan B, Gloss DS 2nd (2017) Practice guideline: cervical and ocular vestibular evoked myogenic potential testing: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology. Neurology 89:2288–2296
12. Node M, Seo T, Miyamoto A, Adachi A, Hashimoto M, Sakagami M (2005) Frequency dynamics shift of vestibular evoked myogenic potentials in patients with endolymphatic hydrops. Otol Neurotol 26:1208–1213
13. Rauch SD (2006) Vestibular evoked myogenic potentials. Curr Opin Otolaryngol Head Neck Surg 14:299–304
14. Murofushi T, Shimizu K, Takegoshi H, Cheng PW (2001) Diagnostic value of prolonged latencies in the vestibular evoked myogenic potential. Arch Otolaryngol Head Neck Surg 127:1069–1072
15. Seo T, Saka N, Ohta S, Sakagami M (2013) Detection of utricular dysfunction using ocular vestibular evoked myogenic potential in patients with benign paroxysmal positional vertigo. Neurosci Lett 550:12–16
16. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P (2009) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
17. Yang WS, Kim SH, Lee JD, Lee WS (2008) Clinical significance of vestibular evoked myogenic potentials in benign paroxysmal positional vertigo. Otol Neurotol 29:1162–1166
18. Korres S, Gkoritsa E, Giannakakou-Razelou D, Yiotakis I, Riga M, Nikolpoulos TP (2011) Vestibular evoked myogenic potentials in patients with BPPV. Med Sci Monit 17:CR42–CR47
19. Eryaman E, Oz ID, Ozker BY, Erbek S, Erbek SS (2012) Evaluation of vestibular evoked myogenic potentials during benign paroxysmal positional vertigo attacks; neuroepithelial degeneration? B-ENT 8:247–250
20. Longo G, Onofri M, Pellicciari T, Quaranta N (2012) Benign paroxysmal positional vertigo: Is vestibular evoked myogenic potential testing useful? Acta Otolaryngol 132:39–43
21. Singh NK, Sinha SK, Rajeshwari G, Kumari A (2014) Are cervical vestibular evoked myogenic potentials sensitive to changes in vestibular system associated with benign paroxysmal positional vertigo? Hear Balance Commun 12:20–26
22. Yetiser S, Ince D, Gul M (2014) An analysis of vestibular evoked myogenic potentials in patients with benign paroxysmal positional vertigo. Ann Otol Rhinol Laryngol 123:686–695
23. Kim EJ, Oh SY, Kim JS, Yang TH, Yang SY (2015) Persistent otolith dysfunction even after successful repositioning in benign paroxysmal positional vertigo. J Neurol Sci 358:287–293
24. Sreenivasan A, Sivaraman G, Parida PK, Alexander A, Saxena SK, Suria G (2015) The clinical utility of vestibular evoked myogenic potentials in patients of benign paroxysmal positional vertigo. J Clin Diagn Res 9:MC01–MC3.
25. Karata A, Yüce T, Çebi IT, Acar Yüceant G, Hacı C, Salviz M (2016) Evaluation of cervical vestibular-evoked myogenic potential findings in benign paroxysmal positional vertigo. J Int Adv Otol 12:316–320
26. Singh NK, Apeksha K (2016) Efficacy of cervical and ocular vestibular-evoked myogenic potentials in evaluation of benign paroxysmal positional vertigo of posterior semicircular canal. Eur Arch Otorhinolaryngol 273:2523–2532
27. Dabbous AO, El-Shennawy AM, Medhat MM, Kandil MT (2019) Assessment of the utricular function in posterior canal benign paroxysmal positional vertigo patients before and after canalith repositioning maneuvre and its relation to residual dizziness. Hearing Balance Commun 17:91–106
28. Li MW, Houlden D, Tomlinson RD (1999) Click evoked EMG responses in sternocleidomastoid muscles: characteristics in normal subjects. J Vestib Res 9:327–334
29. Nakayama M, Epley JM (2005) BPPV and variants: improved treatment results with automated, nystagmus-based repositioning. Otolaryngol Head Neck Surg 133:107–112
30. Imai T, Takeda N, Uno A, Morita M, Koizuka I, Kubo T (2002) Three-dimensional eye rotation axis analysis of benign

paroxysmal positioning nystagmus. ORL J Otorhinolaryngol Relat Spec 64:417–423
31. Gacek RR, Gacek MR (1998) Update on the pathology and management of benign paroxysmal positional vertigo. Otorhinolaryngol Nova 8:235–244
32. Curthoys IS, Iwasaki S, Chihara Y, Ushio M, McGarvie LA, Burgess AM (2011) The ocular vestibular-evoked myogenic potential to air-conducted sound; probable superior vestibular nerve origin. Clin Neurophysiol 122:611–616
33. Dix MR, Hallpike CS (1952) The pathology, symptomatology and diagnosis of certain common disorders of the vestibular system. Ann Otol Rhinol Laryngol 61:987–1016
34. Takeda N, Nishiike S, Kitahara T, Kubo T, Ogino H, Koizuka I (1997) Clinical features and utricular dysfunction in patients with benign paroxysmal positional vertigo. Nihon Jibiinkoka Gakkai Kaiho 100:449–456
35. Hughes I, Thalmann I, Thalmann R, Ornitz DM (2006) Mixing model systems: using zebrafish and mouse inner ear mutants and other organ systems to unravel the mystery of otoconial development. Brain Res 1091:58–74
36. Kahraman SS, Ozcan O, Arli C, Ustun I, Erduran R, Akoglu E, Gokce C (2016) Calcium homeostasis during attack and remission in patients with idiopathic benign paroxysmal positional vertigo. Otol Neurotol 37:1388–1392