

Brainstem Auditory Evoked Potentials' Diagnostic Accuracy for Hearing Loss: Systematic Review and Meta-Analysis

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Abstract

Objectives This study aims to perform a comprehensive review and study of diagnostic accuracy of BAEPs during MVD to predict hearing loss in studies published from January 1984 to December 2013.

Methods The PubMed/MEDLINE and World Science databases were searched. Studies performed MVD for trigeminal neuralgia, hemifacial spasm, glossopharyngeal neuralgia or geniculate neuralgia and monitored intraoperative BAEPs to prevent hearing loss. Retrospectively, BAEP parameters were compared with postoperative hearing. The diagnostic accuracy of significant change in BAEPs, which includes loss of response, was tested using summary receiver operative curve and diagnostic odds ratio (DOR).

Results A total of 13 studies were included in the analysis with a total of 2,540 cases. Loss of response pooled sensitivity, specificity, and DOR with 95% confidence interval being 74% (60–84%), 98% (88–100%), and 69.3 (18.2–263%), respectively. The similar significant change results were 88% (77–94%), 63% (40–81%), and 9.1 (3.9–21.6%).

Conclusion Patients with hearing loss after MVD are more likely to have shown loss of BAEP responses intraoperatively. Loss of responses has high specificity in evaluating hearing loss. Patients undergoing MVD should have BAEP monitoring to prevent hearing loss.

Introduction

Microvascular decompression (MVD) successfully treats trigeminal neuralgia (TGN), hemifacial spasm (HFS), glossopharyngeal neuralgia (GPN) and geniculate neuralgia (GN) by relieving vascular compression on the cranial nerve (CN) at the root exit zone (RExZ) at CN III, CN V, CN IX and nervus intermedius in TGN, HFS, GPN and GN respectively[1-3]. Damage to CN VIII by retraction at the cerebellopontine angle or brainstem ischemia directly leads to post-operative hearing loss[4]. The primary complication from surgery is hearing loss (HL) with a rate of 1-23.8%[2, 5-7]. Monitoring CN VIII utilizing intraoperative BAEPs has been shown to reduce post-operative CN VIII morbidity[8]. Clinical practice guidelines from the American Clinical Neurophysiology Society (ACNS) recommend alerting the surgeon at a significant threshold of change in the BAEPs. Significant changes are defined as a wave V latency increase ≥ 1.0 ms and/or an amplitude decrease $\geq 50\%$ [9, 10]. Although intraoperative monitoring with physician oversight remains the most effective method to prevent HL during MVD, it remains unclear when to alert the surgeon of CN VIII damage. Many studies have been performed to evaluate the usefulness of BAEPs during MVD for HFS, TGN, GPN. Our primary objective is to perform a comprehensive review of BAEP diagnostic accuracy during MVD to predict HL with attention to loss of the BAEP response and significant changes that might occur. The secondary objective is to investigate heterogeneity in the effectiveness of BAEPs for predicting HL amongst studies.

Methods

Criteria for considering studies for this review included randomized controlled trials, prospective or retrospective cohort reviews, which used BAEPs to indicate hearing loss during MVD. All studies report hearing outcomes, determined by pre and postoperative audiograms. When data or

subsets of data were presented in more than one study, the study with the most detailed data, or the study that was most recently published, was chosen. Excluded from this study are reviews, case reports, comments, editorials, and letters which did not report raw data. All studies with diagnosis of HL not directly related to MVD surgery were excluded. All studies have been published in English.

Participants :

All study participants were ≥ 18 years of age. Treatment of target conditions; TGN, HFS, GPN and GN that has become unmanageable or resistant to medication is referred for MVD. Patients underwent MVD in the period between January 1984 and December 2013. All studies performed intraoperative monitoring of BAEPs from the anesthesia to skin closure. No exclusion was given for the monitoring system used.

Target conditions :

MVD is used to treat vascular compression of cranial nerves. This study focuses on TGN, HFS, GPN and GN, but the majority of cases are either TGN or HFS in all studies. These disorders are caused by vascular compression at the root exit zone of the cranial nerves. HFS presents as tonic and clonic contractions of the muscles innervated by the facial nerve. TGN presents as intense pain on the ipsilateral side of the face.

Reference Standards:

Hearing loss was defined in several different ways among studies. One study used patient self-reporting to classify hearing loss; in this case no hearing loss was reported. All other studies used pure tone audiometry and/or speech discrimination scores to determine HL. Audiometric testing was typically conducted by an audiologist. Testing occurred pre and post operatively within a

reasonable time period. Among studies that reported a cutoff value for hearing loss, the absolute value varied.

Literature Search:

A systematic literature search was performed through the PubMed/MEDLINE and World Science databases to identify articles on the diagnostic value of BAEPs for the detection of HL after MVDs. All the eligible studies were published through February 14, 2014. The following keywords were used: “auditory evoked response , auditory evoked potentials, brainstem auditory evoked potentials, brainstem auditory evoked response, Intraoperative monitoring, or Intraoperative neurophysiological monitoring” and “microvascular decompression, or MVD” and “hemifacial spasm, HFS, trigeminal neuralgia, TGN, tic douloureux, geniculate neuralgia, GN, nervus intermedius neuralgia, or glossopharyngeal neuralgia”. The list of articles was supplemented via extensive cross-checking of the reference lists. There was no limitation on the sample size of the every single study. When there were multiple articles by the same group based on similar patients and using similar detection methods, only the largest or the most recent article was included. Our search criteria as well inclusion and exclusion criteria was optimized to minimize and prevent sources of bias common in observational studies[11].

Data extraction and analysis:

Two investigators (PDT, GCC) independently extracted relevant data on the design and results of each study using a standardized form. We extracted data from selected articles, which included first authors, year of publication, study population, region, diagnostic cut off point and time, and methods quality. The authors met and compared the articles each had excluded and reconciled

differences. A final list of articles that met the study inclusion criteria was assembled. Hearing loss after the procedure was the primary outcome recorded from the studies. The authors' comprehensive data was included in the analysis, which was published in October 2014.

We extracted data on the number of: True positives (TP), i.e. patients with hearing loss identified by both the reference and index tests; False negatives (FN), i.e. patients with hearing loss identified by the reference test, but as safe by the index test; True negatives (TN), i.e. patients without hearing loss confirmed by both the reference and index tests; False Positives (FP), i.e. patients without hearing loss confirmed by the reference test, but identified with hearing loss by the index test.

The data was used to construct 2x2 tables. For each individual study, predictive value including sensitivity, specificity of changes in BAEPs to identify HL was calculated after categorizing patients into no change (NC), significant change (SC), transient loss (TL) and persistent loss (PL) based on changes in BAEPs during MVD. BAEP waveform changes in latency and amplitude are dynamic during MVD, secondary to the degree of retraction and/or compression affecting the auditory nerve or its vasculature. Hence we felt that categorizing the changes which incorporated the current alarm criteria may be helpful in understanding the value of BAEPs during MVD. Patients who experienced persistent wave V peak absolute latency increase ≥ 0.5 ms and/or an amplitude reduction $\geq 50\%$ and did not have loss of wave form during MVD were reported a *significant change* (SC). [9, 12] . Loss of waveform (LW) was defined as a wave V latency increase ≥ 12 ms and/or 100% amplitude loss. The loss of Wave V of BAEP was further subdivided into persistent loss (PL) and transient loss (TL). In transient loss (TL), patients' wave V latency and amplitude returned to insignificant deviations from baseline by operative closure. In persistent loss, patients wave V remained at LW criteria by operative closure.

Assessment of methodological quality:

The review authors used the QUADAS 2 tool to assess the susceptibility to bias of the included studies. The methodological quality of the included studies was assessed independently by two review authors and disagreement was resolved by mutual consultation.

Statistical analysis:

We used Open Meta-Analyst and Stata 13 (metandi command) for the statistical analyses. The primary analysis of this review was to fit the data into a HSROC model using the bivariate model.(what does HSROC gives us and why HSROC, any citations). We were also able to obtain pooled sensitivity and specificity through the same bivariate model used in generating the HSROC. For pooled estimates of diagnostic odds ratio (DOR), we used the Der-Simonian Laird random effects meta-analysis.

We did not include datasets in the pooled analysis if either $TP+FN = 0$, or $TN+FP = 0$ because it was not possible to accurately estimate sensitivity or specificity. In other instance, we handled zero cell counts by adding a 0.5 continuity correction to the study data(citation).

Heterogeneity:

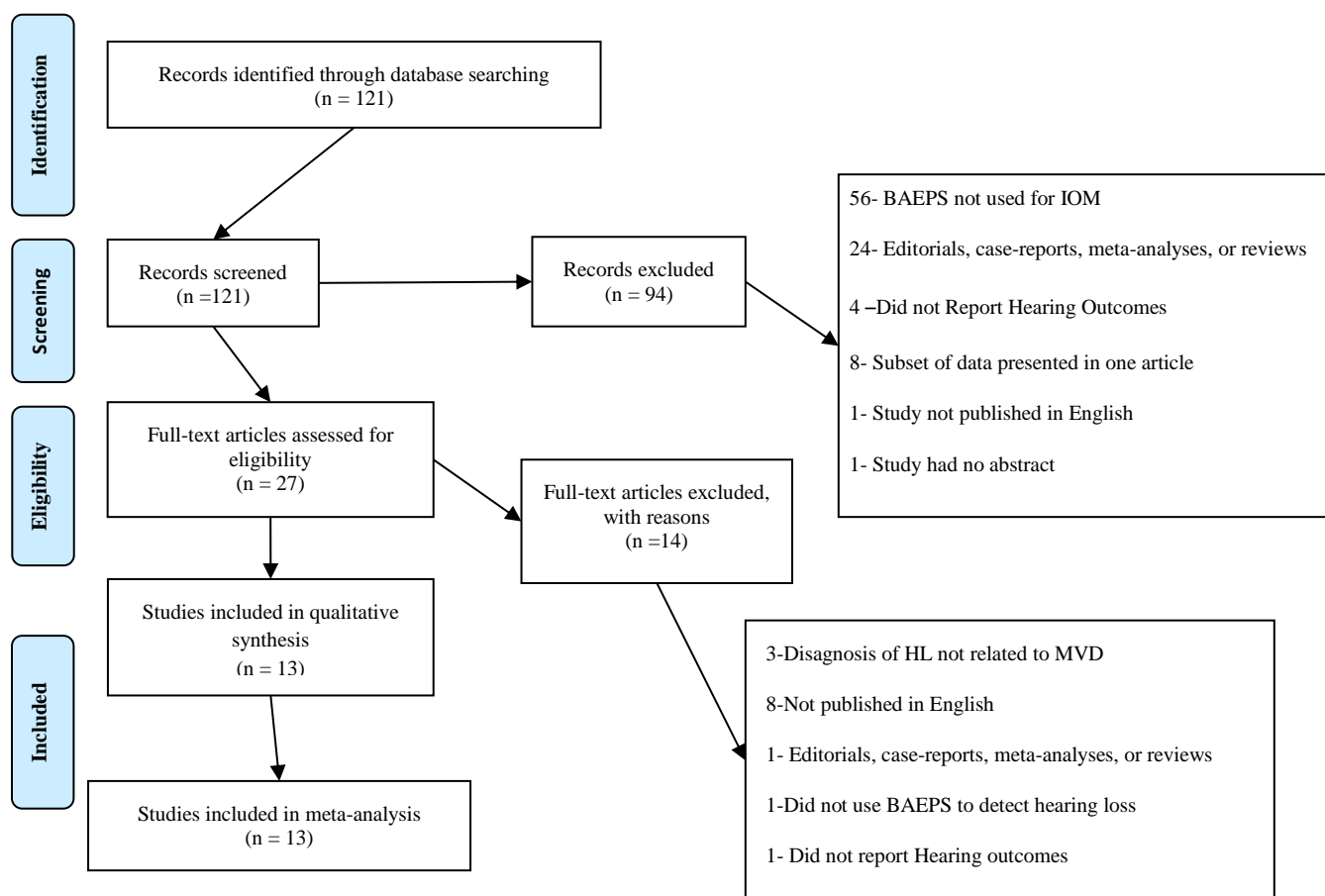
Heterogeneity among included studies is assessed by using the Cochrane Q statistic and quantified with the I^2 lying between 0 and 100%. In general, $I^2 (>50\%)$ shows that heterogeneity among studies produce some impact, whereas $I^2 (<50\%)$ shows that homogeneity is good for the reliability of meta-analysis.

Results

Results of the Search

The electronic search yielded a total of 121 records (Figure 1). We rejected 94 studies as they did not meet inclusion criteria. Of the two authors who screened the results, one author selected 25 studies for potential inclusion and one author selected 40 studies. After disagreements were discussed between authors, we obtained the full-text copies of 27 studies. Of these, 14 studies were excluded for reasons stated in the flow diagram and 13 studies met the inclusion criteria for our review since they used an appropriate index and reference test in patients having MVD surgery.

Figure 1. Results from searching studies for inclusion in the review



Methodological quality of included studies

Methodological quality is presented in Figure 1. Characteristics of included studies are presented in Tables 2 and 3.

Patient selection was unclear in one study due to unclear exclusions of patients, and high risk in one study due to non-random or consecutive sampling of patients. Seven out of thirteen studies had a high risk index test because they did not specify a threshold or cut-off value for significant changes, commonly referred to as alarm criteria. The reference standard risk of bias was unclear in three studies because no cut-off value was used to classify hearing loss. The risk was high in three studies, two were unlikely to correctly classify the target condition and one interpreted results of the reference standard with knowledge of the index test. Flow and timing had an unclear risk in two studies because the time interval between the index test and reference standard was not specified and a high risk in four studies. Three studies did not include all patients in their analysis and one did not give the reference standard to all patients. One study had a high applicability concern because some patients in the analysis did not undergo MVD. One study had a high applicability concern because not all patients received the index test. The reference standard applicability was unclear in two studies because hearing loss criteria was not reported as PTA or SDS scores. The reference standard applicability was of high concern in one study because patients subjectively requested auditory tests.

Findings

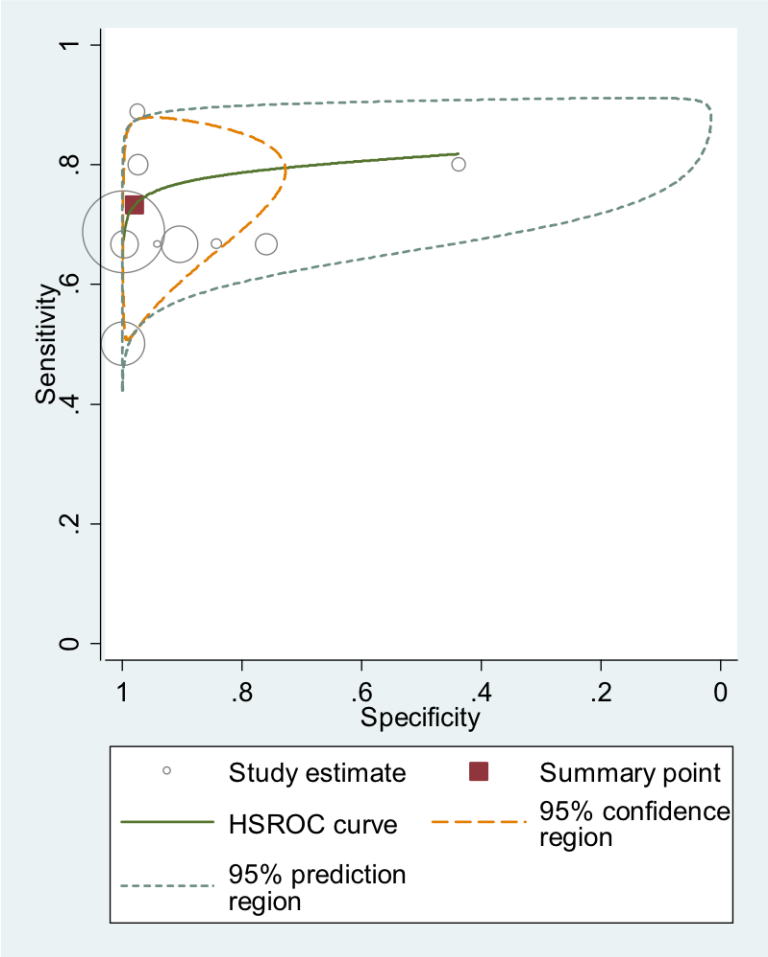
Total incidence of hearing loss in our study is 2.20%. Among patients who had no change in BAEPs, any changes, significant changes, loss of response, transient loss or permanent loss; the hearing loss rate was 0.46%, 7.96%, 2.32%, 5.21%, 24.00% and 49.30% respectively. Only Thirumala 2014 reported transient losses with hearing loss[13]. All studies used BAEPs to predict hearing loss intraoperatively. Alarm criteria were specified prior to surgery in 6 studies

and in the 7 others were determined during the course of study. Some studies were excluded from the statistical analysis because no patients experienced significant changes, or loss of response predictive of hearing loss. Only one study adopted the diagnostic accuracy paradigm in their analysis (Thirumala 2014) and the other studies reported outcomes to show how BAEPs may be interpreted. In the analysis, Loss of BAEP response and relationship to hearing loss, the excluded studies were Bond 2010, Huang 2009 and Radtke 1991. In the second analysis, Radtke 1991 was added back.

Loss of BAEP response and relationship to hearing loss (10 studies)

Study sensitivities ranged from 50% to 90%, while specificities ranged from 44% to 100%. Combining data from all studies using the bivariate model, loss of BAEP response exhibited strong specificity (average [95% CI]: 98% [88%, 100%]) but weaker sensitivity (average [95% CI]: 74% [60%, 84%]). A graph of the estimated SROC along with the summary point, 95% confidence ellipse and prediction ellipse for BAEPs is shown in Figure 2.

Figure 2 SROC of HL
A.



B.

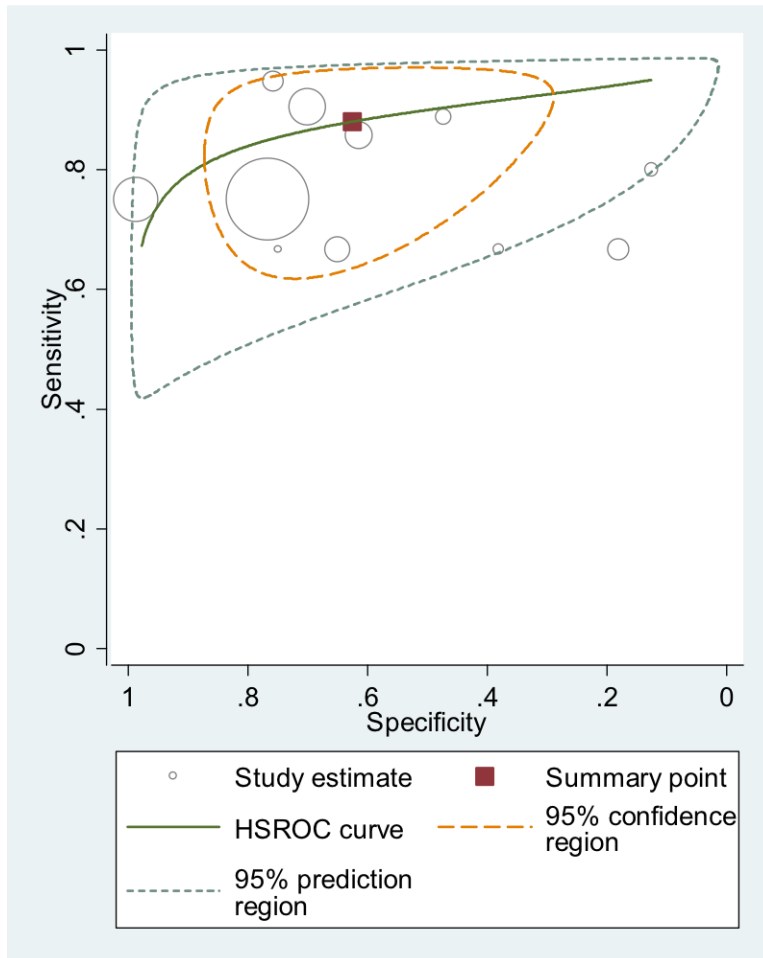


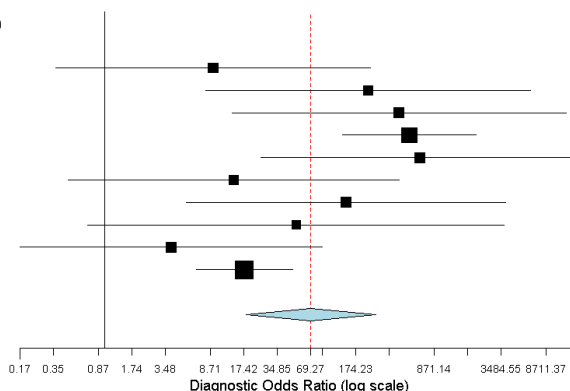
Figure 2. SROC for HL in (A) patients with loss of BAEP response and (B) patients with a significant change of BAEP response. The size of the study estimate circle indicates study effect size.

A pooled random effects estimate of diagnostic odds ratio for individual studies of patients with hearing loss with loss of BAEP response was 69.3 [18.2 - 263]. This indicates that the odds of observing loss of BAEP response among those with hearing loss are 69 times higher than those without hearing loss. Figure 3 shows a forest plot of diagnostic odds ratios (DOR) for the individual studies, with substantial heterogeneity of 63%.

Figure 3. Forest Plots of HL

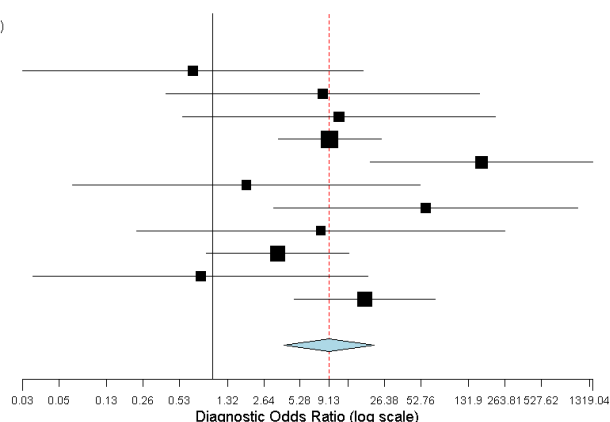
A.

Studies	Estimate (95% C.I.)	(TP * TN)/(FP * FN)
Bricolo 2004	9.29 (0.36, 237.06)	63/0
Brock 2004	225.00 (7.92, 6391.59)	148/0
James 2005	425.00 (13.67, 13210.21)	254/0
Jo 2011	528.07 (133.57, 2087.72)	12496/20
Lee 2013	655.00 (24.61, 17432.12)	654/0
Lee(2) 2009	14.14 (0.47, 424.67)	16/0
Ramnarayan 2006	143.00 (5.34, 3830.20)	142/0
Rizvi 1999	51.00 (0.70, 3710.31)	8/0
Sindou 1992	3.92 (0.17, 88.15)	28/0
Thirumala 2014	17.67 (6.58, 47.44)	2744/147
Overall (I²=63%, P< 0.01)	69.27 (18.25, 262.97)	16553/167



B.

Studies	Estimate (95% C.I.)	(TP * TN)/(FP * FN)
Bricolo 2004	0.68 (0.03, 17.47)	15/0
Brock 2004	8.12 (0.41, 161.28)	72/0
James 2005	11.10 (0.56, 219.53)	234/0
Jo 2011	9.25 (3.46, 24.71)	13065/1325
Lee 2013	167.74 (19.99, 1407.27)	969/4
Lee(2) 2009	1.89 (0.07, 51.92)	8/0
Ramnarayan 2006	58.15 (3.21, 1054.34)	450/0
Rizvi 1999	7.80 (0.23, 262.81)	6/0
Radtke 1991	3.43 (0.88, 13.38)	390/105
Sindou 1992	0.79 (0.03, 19.27)	8/0
Thirumala 2014	18.16 (4.72, 69.92)	2888/130
Overall (I²=42%, P=0.07)	9.13 (3.86, 21.63)	18105/1564



Forest Plot for HL in (A) patients with loss of BAEP response and (B) patients with a significant change of BAEP response. CI= Confidence interval; TP= true positive; TN= true negative; FP= False Positive; FN = False Negative

Loss of BAEP response or significant changes and their relationship with hearing loss (11 studies)

Study sensitivities ranged from 67% to 91%, while specificities ranged from 14% to 99%.

Combining data from all studies using the bivariate model, loss of BAEP response or significant change exhibited strong specificity (average [95% CI]: 88% [77%, 94%]) but weaker sensitivity

(average [95% CI]: 63% [40%, 81%]). A graph of the estimated SROC along with the summary point, 95% confidence ellipse and prediction ellipse for BAEP is shown in Figure 2.

A pooled random effects estimate of diagnostic odds ratio for individual studies of patients with hearing loss with loss of BAEP response or significant change was 9.1 [3.9 – 21.6].

This indicates that the odds of observing loss of BAEP response or significant BAEP change among those with hearing loss are 9.1 times higher than those without hearing loss. Figure 3 shows a forest plot of diagnostic odds ratios (DOR) for the individual studies, with mild-moderate heterogeneity of 43%.

Included in the appendix, patients with post-operative hearing loss or impairment have a 7.79 higher DOR of losing BAEPs or having a significant change. The pooled sensitivity for these studies was improved compared to only hearing loss, but the specificity was lower. Hearing impairment was associated with loss of response at a DOR of 4.233. The sensitivity was below random and the specificity was high.

Discussion

Patients who experience peri operative loss of BAEP responses are 69 times more likely to experience HL. The pooled specificity across studies was high (98%) but the sensitivity was low (74%). The higher specificity of hearing loss in patients with BAEP loss indicates that, in some patients, recovery of BAEPs is desirable but not always achievable. The lower sensitivity could be secondary to the fact that when there is a loss of the response the surgical procedure is in most cases stopped until there is a recovery of the BAEP wave form. The therapeutic effect of surgical pause might have prevented hearing loss in many patients. Loss of BAEP response is often associated with unknown excessive stretch of CN VIII. Increasing the stretch of the axons

of CN VIII results in temporal dispersion of the wave forms resulting in a loss of amplitude[14]. If the stretch is prolonged, there is a risk for permanent injury. Loss of BAEP response can also be caused by changes in blood flow to the nerve, brain stem or direct trauma to the cranial nerve complex [15-18]. Loss of BAEP response can occur without loss of auditory function. This may result when be temporal dispersion without a conduction block in the auditory pathway or another hearing pathway not measured with BAEPs persists[19].Our analysis could not fully separate the patients who experience transient loss of BAEP responses with hearing loss, because many studies did not identify transient losses. Transient loss of response has a lower chance of hearing loss[13], compared to a permanent loss of response.

Patients who experience peri operative significant changes are nine times more likely to experience hearing loss. The sensitivity (63%) of significant changes is lower compared to the high specificity (88%). The strong specificity could be secondary to including patients with loss of BAEP responses in the analysis. Significant changes are meant to be an alarm during MVD so the surgeon can be aware of inadvertent auditory nerve stretch. The varied alarm criteria adopted in clinical practice may result in a weaker sensitivity and varied therapeutic interventions. The ACNS and ASNMM recommend an alarm at a 1.0 ms or 10%, respectively, increase in latency of wave V and/or a decrease in the amplitude greater than 50% [9, 10]. The therapeutic effect of adjusting the retraction on the auditory nerve might be variable as the studies in this paper used multiple, different alarm criteria

Overall incidence of hearing loss in our study was 2.20%. Hearing loss rates may vary by condition. Hearing loss has been evaluated using multiple criteria, with some using PTA alone and some using both PTA/SDS. Patients with any significant change in hearing were seven times more likely to experience significant change in BAEPs during the procedure. The clinical

relevance of the analysis is difficult to interpret as the hearing loss and hearing impairment are variably defined. The studies Jo 2011, Lee Jo 2013, Lee 2009, Ramnarayan 2006, Sindou 1992, and Radtke 1991 all reported PTA thresholds below 30 dB with an average of 20 dB. This hearing loss may be amenable to hearing aids and not as important in clinical practice. In addition the alarm criteria are varied among studies with different therapeutic interventions.

Although the current study showed strengths based on comprehensive literature review, with quality assessment using the QUADA-2, there are several limitations that must be addressed. Most importantly, it is crucial to acknowledge the fact that a search bias may have existed owing to the difficulty associated with acquiring every possible study assessing use of BAEP during MVD. Also, owing to study design, our analysis is at risk of publication bias because of dependence on currently published data on the topic of investigation; however, our analysis via funnel plot (Supplementary Figure α) provides evidence of such bias in the current study. Statistically significant heterogeneity was observed among loss of response study specificity. Owing to the design of this study, it was difficult to assess every possible factor for such a result because of data pooling from diverse sources.

Conclusion

BAEPs are essential to preventing and predicting HL after MVD. Across all studies an increase in latency or decrease in amplitude increases the DOR for hearing loss. Despite recommendations from the ACNS/ASNM, significant changes are not universally defined. Without universal adoption, heterogeneity amongst studies and institutions will remain high. As loss of BAEPs during the procedure can be a specific marker of hearing loss allowing for perioperative intervention with novel treatment pathways directed to these patients.

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Table 2. Study Profile and Characteristics.

Author (pub yr)	Study Design	Condition	Alarm Criteria	HL Criteria	Baseline BAEP	Length of F
Bond,2010	Retrospective Cohort	TGN	Yes, transient changes of absolute or IPL in excess of 10% baseline value	Self-reporting	Yes (after anesthesia)	Not Stated
Bricolo,2004	Retrospective Cohort	HFS	Yes, >0.5ms delay in the peak of Wave V, or if there were marked changes in amplitude or form of wave I or V	Mild 26-40dB, Moderate 41-55, Intermediate 56-70, Severe 71-90, Profound >90	Yes (after anesthesia)	Before Discharge
Brock 2004	Retrospective Cohort	TGN	No, scores were considered abnormal if the abs. or IPL exceeded baseline by 2.5 standard deviations	Slight 20-30dB, Moderate 35-40, Severe hypoacusia or anacusia	Yes, (after anesthesia)	Not Stated
Huang,2009	Retrospective cohort	HFS	No, >50% wave V amplitude decrease	Not Stated	Yes (after anesthesia)	Not Stated
James,2005	Retrospective cohort	HFS/TGN/CPA Surgery	Yes, a 1.0 ms latency increase or 50% amplitude decrease of wave V	PTA cutoff 50 dB, SDS cutoff 50%	Yes (after anesthesia)	Immediately Post and upon discharge
Jo,2011	Retrospective cohort	HFS	Yes, a 1.0 ms latency increase or 50% amplitude decrease of wave V	PTA cutoff 15 dB, SDS >20%	Yes (before anesthesia)	3-10 days Post-O
Lee Jo,2013	Retrospective Cohort	HFS	No, >0.5ms delay in the peak of Wave V, or if there were marked changes in amplitude or form of wave I or V	PTA cutoff 15 dB, SDS >20%	Yes (before anesthesia)	2-13 days Post-op
Lee,2009	Retrospective Cohort	HFS	No, 0.4ms (watch), 0.6 ms (warn), 1.0 ms (critical) wave V latency delay, and a 50% amplitude reduction with a latency increase	Cutoff >25 dB	Yes (after anesthesia)	3-10 days Post-O

Ramnarayan,2006	Retrospective Cohort	TGN	No, greater than 3 standard deviations over the normal mean value latency of wave V ($4.77 \pm .23\text{ms}$)	>20 dB	Yes (after anesthesia)	48 Hours
Rizvi,1999	Retrospective Cohort	TGN	No, increase in IPL of 1.5 ms or an increase more than 3 standard deviations	No Cut Off Value, Given Distribution shows no major changes	Yes (after anesthesia)	N/A
Radtke,1991	Retrospective Cohort	HFS,TGN	No, wave V latency increase $\geq 1.0\text{ms}$ or rapid changes $>0.1\text{ms/min}$	>30 dB	Yes (before anesthesia)	Immediately Post and 1 month out
Sindou,1992	Retrospective Cohort	HFS,TGN	Yes, 1 ms in 10 minutes or drastic modification, for voltage a decrease in amplitude of wave V $>50\%$	>20 dB	Yes (after anesthesia)	Immediately Post
Thirumala,2014	Retrospective Cohort	HFS,TGN,GN,GPN	Yes, , a 1.0 ms latency increase or 50% amplitude decrease of wave V	<50% SDS. >50dB PTA	Yes (after anesthesia)	1-90 Days Post C

Table 2. Study Profile and Characteristics. HFS= Hemifacial Spasm, TGN= trigeminal neuralgia, GN= geniculate neuralgia, GPN= glossopharyngeal neuralgia, SDS= Speech Discrimination Score, PTA= Pure Tone Audiometry. IPL= interpeak latency

Table 3. Patient Demographics

Author (pub, yr)	Sample size for analysis	Patient Age (Avg)	Hearing Loss	Hearing Impairment	BAEP Changes	Significant Changes	Transient Loss	Per
Bond,2010	119	60	0	0	0	---	---	
Bricolo,2004	84	53	1	8	8	3	2	
Brock, 2004	45	55.5	4	7	7	3	---	
Huang,2009	36	N/A	0	1	0	---	---	
James,2005	130	N/A	0	3	3	1	---	
Jo,2011	1156	48.7	20	26	24	12	---	
Lee Jo,2013	331	N/A	4	7	3	1	---	
Lee,2009	22	61	1	2	3	2	---	
Ramnarayan,2006	75	N/A	2	7	9	7	---	
Rizvi,1999	9	N/A	1	3	4	3	---	
Radtke,1991	261	53.9	0	9	6	2	3	
Sindou,1992	34	51	2	6	6	1	2	
Thirumala,2014	238	52.41	21	0	19	5	5	
Total	2540	51	56	79	92	40	12	

Table 3. Patient Demographics. A N/A indicates data was not collected on age. For BAEP changes, a line of --- indicates data was not recorded.

Several studies did not comment on transient losses and their difference from significant changes or permanent loss. In the studies Bond 2010 and Huang 2009, no change in BAEP was recorded and therefore there can be no discrimination between BAEP change categories.