Predictive Value of Preoperative and Intraoperative Neurophysiology in Evaluating Long-term Facial Function Outcome in Acoustic Neuroma Surgery

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Objective: To determine the role of neurophysiological preoperative and intraoperative parameters in providing prognostic information regarding facial nerve (FN) function at 1 year after translabyrinthine acoustic neuroma (AN) resection surgery.

Study Design: Prospective observational study in a tertiary referral center. Patients treated via translabyrinthine surgical approach for sporadic AN microresection between December 2015 and 2018.

Methods: Patients underwent preoperative (electroneurography-ENG, electromyography-EMG, and Blink Reflex-BR) and intraoperative (FN motor action potential–MAP and continuous EMG traces) neurophysiological studies. FN function was graded postoperatively at 1 year using House–Brackmann Scoring System.

Results: Sixty-two patients were included in the analysis. Mean age was 53±10 years and average tumor diameter was 23 ± 9 mm. At 1 year a normal facial function was observed in 68% of patients. In the univariate analysis a pathologic BR, low FN MAP values and ratios, and the presence of pathological neurotonic tracing (A-trains) on continuous EMG were associated with a poor facial nerve function outcome at 1 year postoperatively. Pathological preoperative BR testing and intraoperative A-trains showed a statistical significance also in the multivariable analysis, regardless of tumor size.

Conclusions: Preoperative pathological BR testing and A-train activity on intraoperative EMG are correlated with poor FN outcomes at 1 year postoperative. This may provide important prognostic information to both patients and treating neuro-otologists. In the future this may guide preoperative and postoperative patient counselling and possibly optimize timing of facial nerve reanimation in selected patients. **Key Words:** Acoustic neuroma surgery—Facial nerve—Intraoperative neuromonitoring—Preoperative and intraoperative neurophysiology.

Otol Neurotol **41:**530–536, 2020.

Facial nerve outcomes post acoustic neuroma (AN) resection is of paramount concern to both the neuro-otologist and the patient. Tumor often distorts the normal anatomical relationship of the facial nerve within the cerebellopointine angle rendering it more susceptible to intraoperative injury and postoperative dysfunction (1–6). Intraoperative electromyographic (EMG) facial nerve monitoring is the standard of care in most contemporary skull base units (7–13). It allows for early and accurate identification of the facial nerve and has been shown to improve postoperative facial nerve outcomes in lateral skull base surgery (14–22). Several neurophysiologic parameters have been proposed to predict long-term facial nerve function after AN surgery (23–36). However, its prognostic role in facial nerve outcomes remains less certain (37,38). In this study we aimed to prospectively evaluate several preoperative and intraoperative facial nerve neurophysiological parameters to establish whether they could provide accurate prognostic measure of long-term facial nerve outcome in translabyrinthine AN surgery.

METHODS

Patient Population

A prospective single-cohort observational study, of patients undergoing sporadic AN microsurgical resection via a translabyrinthine approach in a tertiary referral center was performed. All patients had an intact facial nerve preoperatively. Institutional ethics approval and prospective patient consent was obtained. Patients were recruited via the Department of Neurosciences at ASST Papa Giovanni XXIII, Bergamo, Italy, between December

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No funding was received for this work.

The authors disclose no conflicts of interest.

DOI: 10.1097/MAO.0000000000002553

2015 and December 2018. Exclusion criteria included previous AN microsurgical resection or radiation, resection by techniques other than translabyrinthine, age <18 years, patients with neurofibromatosis type 2, and preoperative facial nerve dysfunction. Epidemiological data including sex, age, and comorbidities were recorded.

Surgery

All AN microsurgery was performed by the same surgical team using a translabyrinthine technique with complete tumor resection. Anesthesia was standardized, using propofol and remifentanil to avoid interference with EMG monitoring.

Preoperative Imaging and Tumor size

All patients underwent a preoperative consultation with a neuro-otologist and high contrast magnetic resonance imaging (MRI) with gadolinium. Tumor size was defined as the maximum extracannicular dimension measured on a T2-weighted axial MRI centered on the cerebellopointine angle (39). This measure was performed by an experienced neuroradiologist and confirmed by a neurotologist.

Preoperative Facial Nerve Neurophysiological Studies

Preoperative neurophysiological studies of facial nerve function, including electroneurography (ENG), EMG, and Blink Reflex (BR) test, were performed and evaluated in all patients by a neurophysiologist. ENG facial nerve responses were measured on both sides via a bipolar surface stimulator placed over the stylomastoid foramen and recorded from surface electrodes placed over the orbicularis oculi and oris muscles. Facial nerve EMG responses were recorded at rest and during voluntary motion with a bipolar needle electrode placed in the frontalis, orbicularis oculi, and oris muscles on both sides (40). The BR is the electrical correlate of the clinically evoked corneal reflex and has three components, an early R1 and two later R2 responses (41). The R1 response represents the disynaptic reflex pathway between the sensory nucleus of the fifth cranial nerve and the ipsilateral facial nucleus in the pons and provides indirect information about the entire facial nerve anatomical course. The R2 responses represent the polysnaptic reflex ipsilateral and controlateral. BR was elicited at the supraorbital nerve with a bipolar surface stimulator electrode on both sides and recorded from surface electrodes placed over the orbicularis oculi muscles, with the patient lying down in a quiet room with eyes closed (40). The evoked muscle action potentials (R1 and R2) were elicited for three consecutive times for each patient. The responses were defined pathologic if the stimulation of the affected side resulted in an absence of the ipsilateral R1 response or a delay in latency of responses (>12 ms R1; >33 ms R2) (41).

Intraoperative Neurophysiological Facial Nerve Monitoring

Both stimulated and continuous EMG monitoring was performed by a neurophysiologist with expertise in intraoperative monitoring. Three EMG needle electrodes channels were placed subdermally to monitor the orbicularis oculi, the orbicularis oris, and the mentalis muscles. Direct electrical stimulation of the facial nerve by a concentric bipolar probe with stimulus intensity from 0.05 mA to 0.7 mA and duration of 200 μs was used to assess the FN muscle action potential (MAP) amplitude response (42). Stimulus intensity was gradually increased to achieve the supramaximal response. The facial nerve MAP amplitude values were evaluated at least at three time points of the surgery—at the first intraoperative finding of the facial nerve (MAP 1), at the brainstem/cisternal segment (MAP II), and at the IAC meatus (MAP III) after tumor removal (20,22,29,31). Ratios comparing different MAP amplitudes were calculated including MAP II/ MAP 1 (Ratio 1) and MAP II/ MAP III (Ratio 2) (32). Attempts to standardize stimulated EMG responses were made as variations in response amplitude can occur due to a number of mitigating intraoperative factors. The operating surgeon suctioned cerebrospinal fluid (CSF) from the field immediately before stimulation, ensured the probe was contacting only the FN, used identical probe orientation, and attempted to stimulate in a standardized location on all cases. All stimulated FN MAP were repeated twice, to validate the ensure accurate responses. For the final analysis, the channel with the greatest response amplitude value was used (31,32). Continuous EMG monitoring was examined for ''A-train'' activity. This is a specific electromyography (EMG) pattern of prolonged neurotonic discharge (more than 10 seconds) that represents potential axonal loss and has a high correlation with postoperative facial nerve dysfunction (22,25–28).

Outcome Measures

The primary clinical end point was postoperative FN outcome. Clinical FN examination was completed using the House–Brackman (H–B) grading (43) at three defined points—day of postoperative discharge, 7 days postoperative, and 1 year postoperative. The postoperative FN grading was evaluated by a clinician independent of the surgical team, blinded to the neurophysiology results. Facial nerve outcomes were further subdivided into two categories—''Good facial nerve outcome'' (H-B 1–2) representing minimal or no FN dysfunction and ''Poor facial nerve outcome'' (H-B 3–6) representing significant postoperative FN dysfunction. Patients with poor FN outcome received physical therapy and ocular protective measures, including lubrication and overnight eyelid tape application to ensure closure. Gold weight and temporary tarsorrhaphy was performed in selected patients at the clinician's discretion. Postoperative facial nerve outcomes were compared to preoperative and intraoperative neuro-physiological findings to determine if specific EMG results prognosticate poor facial nerve outcome.

Statistical Analysis

Statistical analysis was performed with Stata software (release 14, StataCorp). Continuous variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), according to data distribution. The normality assumption was evaluated with the Shapiro–Wilk test based on skewness and kurtosis. Comparisons between two groups were performed using the unpaired Student t test or the Mann–Whitney test, based on the different assumptions. Preoperative and intraoperative characteristics potentially associated with FN at 1 year follow-up were first identified at a univariate level yielding odds ratios (ORs) with 95% confidence intervals (CIs). Positive (PPV), and negative (NPV), predictive values were also estimated, defining the probability of having, or not, a facial nerve impaired function in a subject with positive, or negative, result in preoperative/intraoperative characteristics. All statistical tests used the 5% level of significance, and all p values were two-tailed. Multivariable logistic regression analyses were also performed, exploring the different contribution of identified characteristics taking into account model stability.

RESULTS

Patient Population

A total of 86 patients underwent translabyrinthine AN resection during the study period, with 74 patients meeting the inclusion criteria. Three patients had an intraoperative facial nerve transection during tumor dissection and underwent immediate facial nerve reanimation and were therefore excluded. A further nine patients were excluded due to failure to complete the relevant neurophysiological testing or failure to attend long-term follow-up. As a result, data of 62 patients were included in the final study analysis. Mean age of study participants was 53 ± 10 years (age range 33–73 yr) and 59.6% (n = 37) were female. Average AN tumor diameter, as measured on MRI, was 23 ± 9 mm. Thirty-one patients (50%) had a tumor size between 10 and 19 mm; 22 patients (35.4%) between 20 and 29 mm, and 9 patients (14.5%) had a tumor >29 mm (Table 1).

Postoperative FN Outcomes

Long-term FN outcomes are reported in Table 1. At 1 year postoperatively, good postoperative FN outcomes were observed in 67.7% of patients (n = 42). No H-B grade VI was observed at 1 year follow-up. Compared with the H-B evaluation on day 7 after the surgery, 87% of the whole sample spontaneously improved by I or II grades at H-B Grading Score at 1 year. The tumor size correlated with the H-B grading score at 1 year follow-up ($p = 0.002$).

Preoperative FN Neurophysiology

A pathologic preoperative BR test was observed in 46.7% (n = 29) of the patients. These patients had a tumor size of 27.9 mm (SD = 9.6) that was significantly greater compared with that of patients with normal BR (18.7 mm; SD = 4.9; $p < 0.001$). Poor FN outcome at 1 year was observed in 55% (n = 34) of patients with a pathologic BR, compared with only 12% (n = 7) of patients with normal preoperative neurophysiology (Fig. 1).

Intraoperative Neurophysiological Results

Facial Nerve Mean Action Potential (FN MAP)

The FN MAP amplitude was examined at three time points: MAP I at the first finding of the nerve during surgery, MAP II at the brainstem, and MAP III at the IAC meatus after tumor removal (Fig. 2, A and B). Only MAP I and MAP II were compared to FN outcomes, given MAP III only measures the distal FN response. The median values for MAP I and MAP II were 1200 μV (1,500–800 μV; iqr 700 μV) and 800 μV (1,200–400 μV; iqr 800 μV), respectively. Subjects with good FN function at 1 year demonstrated a statistically significant higher median MAP I than patients with poor FN outcomes (1,200 μV (1,500–1,000 μV; iqr 500 μV) vs 650 μV (1,000–400 μV; iqr 600 μV), $p < 0.001$). Similarly, median MAP II values at 1 year after surgery were significantly greater in patients with good FN outcomes compared with poor FN outcomes (1,100 μV (1,500–800 μV; iqr 700 μV) vs 175 μV (450–50 μV; iqr 400 μV), $p < 0.001$).

TABLE 1. *Tumor size distribution*

Tumor Size (mm)	Total Sample N = 62	Poor FN Outcome N = 20 (32%)	Good FN Outcome N = 42 (68%)
10–19	31	3	28
20–29	22	11	11
≥30	9	6	3

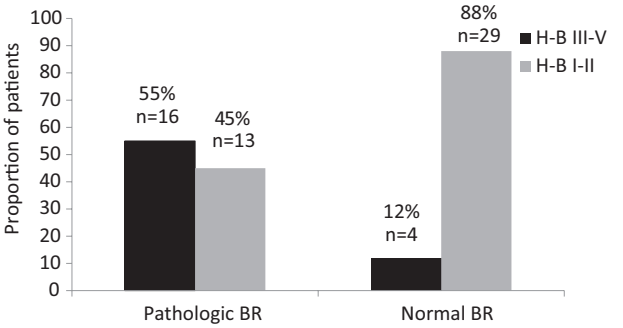


FIG. 1. Distribution of H-B Grading Score at 1 year after surgery across preoperative Blink Reflex test groups. BR indicates Blink Reflex; H-B, House and Brackman Grading Score; n, number of subjects.

FN MAP Ratios

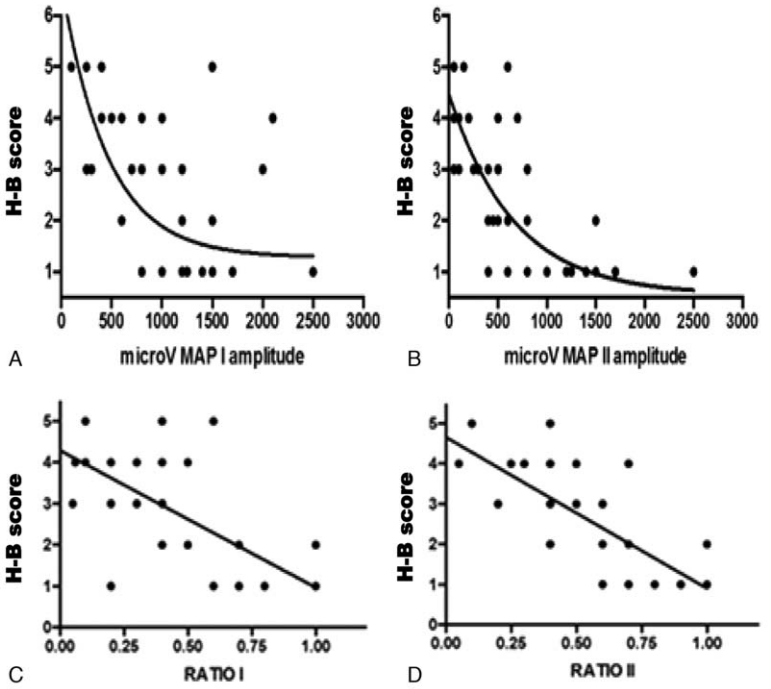
Ratio I (Brainstem MAP amplitude/First stimulation MAP amplitude) and Ratio II (Brainstem MAP/IAC MAP amplitude post tumor removal) were also analyzed in this study. Subjects with good FN outcomes at 1 year showed median values for Ratio I and Ratio II significantly higher than those with H-B grade ≥ III (Ratio I: 0.8 vs 0.3 and Ratio II: 0.8 vs 0.4; $p < 0.001$). When the relationship between Ratio I-Ratio II and H-B Grading Score at 1 year was evaluated, a linear relationship was observed (Fig. 2, C and D).

A Trains on Continuous EMG Trace

The presence or absence of pathologic EMG activity (A-trains) during the tumor dissection had a noteworthy association with long-term FN outcome. Pathologic intraoperative EMG discharges were observed in 30 patients (48.3%). Poor FN function at 1 year was present in 60% (n = 18) of patients with A-trains compared with 9.4% (n = 3) with normal continuous EMG trace (Fig. 3). Pathologic intraoperative EMG discharges correlated with poor FN outcomes at 1 year postsurgery, with a negative predictive value (NPV) of 91% (95% CI 75–98%).

Univariate and Multivariable Analysis

Univariate analysis was performed to investigate the association between preoperative and intraoperative neurophysiological tests and long-term FN outcome.



MAP I (Panel A - R^2 40%; p < 0.001); MAP II (Panel B - R^2 67%; p < 0.001); Ratio I (Panel C - R^2 68%; p < 0.001); Ratio II (Panel D - R^2 76%; p < 0.001)

FIG. 2. Association between facial nerve MAP I, MAP II, Ratio I and Ratio II and H-B grading score at 1 year. MAP I (*A*, R^2 40%; $p < 0.001$); MAP II (*B*, R^2 67%; $p < 0.001$); Ratio I (*C*, R^2 68%; $p < 0.001$); Ratio II (*D*, R^2 76%; $p < 0.001$. H-B indicates House and Brackman Grading Score; MAP I, motor action potential at the first finding of the nerve during surgery; MAP II, motor action potential at the brainstem after tumor removal; RATIO I, MAP II amplitude value/MAP I amplitude value; RATIO II, MAP II amplitude value/MAP III amplitude—at the internal auditory canal meatus after tumor removal).

Pathologic BR, low MAP I, and II FN amplitude values and the presence of A-trains, all were associated with a poor FN function outcome at 1 year after surgery (Table 2). We should acknowledge that MAP I and II odds ratios were just slightly lower than one, though precise and statistically significant. Then, we performed multivariable analyses considering univariate-level results, clinical expertise, and model stability according to sample size, events-per-variable, and multicollinearity. Specifically, MAP II, if included in a model with Blink Reflex test and A-train activity, compromised the stability of the model. Thus, it was not included.

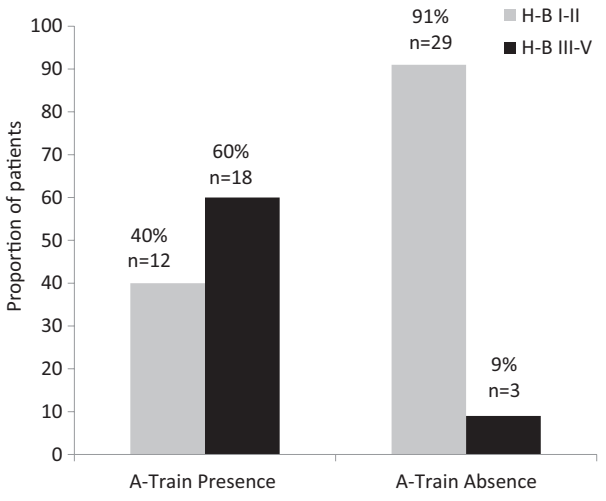


FIG. 3. Association between prolonged A-Train activity (presence/absence) and H-B grading score at one year follow up. H-B indicates House and Brackman Grading Score; n, number of subjects.

TABLE 2. *FN function and preoperative/intraoperative characteristics: univariate analyses*

	OR (95% CI) Unadjusted	*p*
Age	0.98 (0.93; 1.04)	0.557
Male sex[a]	0.98 (0.33; 2.91)	0.971
Blink reflex test[b]	8.92 (2.49; 31.97)	0.001
A-train activity[c]	12.64 (3.14; 50.79)	<0.001
MAP I	0.997 (0.996; 0.999)	0.001
MAP II	0.991 (0.985; 0.996)	0.001
Tumor size	1.13 (1.05; 1.23)	0.002

Reference categories:.
[a]male versus female.
[b]Pathologic versus nonpathologic.
[c]Pathologic versus nonpathologic intraoperative EMG discharges.
CI indicates confidence interval; OR, odds ratio; PPV, positive predictive value.

TABLE 3. *FN function: multiple logistic regression*

	Model 1		Model 2		Model 3	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Blink reflex test	8.20 (1.96; 34.41)	0.004	7.05 (1.44; 34.56)	0.016	5.54 (1.25; 26.69)	0.033
A-train activity	11.72 (2.59; 52.96)	0.001	11.59 (2.15; 62.51)	0.004	9.81 (2.11; 45.65)	0.004
MAP I	—		0.998 (0.996; 0.999)	0.014	—	
MAP II	—		—		—	
Ratio I	—		—		—	
Ratio II	—		—		—	
Tumor size	—		—		1.05 (0.96; 1.16)	0.275
PPV (95% CI)	72% (46–90%)		75% (51–91%)		72% (46–90%)	
AUC (95% CI)	86% (77–94%)		91% (83–98%)		88% (79–96%)	

AUC indicates area under the curve; CI, confidence interval; OR, odds ratio; PPV, positive predictive value.

Similarly, we could not include Ratio I and Ratio II, since a very small estimate was previously reported with wide confidence intervals. Therefore, we considered three models separately, i.e., 1) both preoperative and intraoperative parameters in terms of Blink Reflex test and A-train activity, 2) MAP I along with Blink Reflex test and A-trains, 3) Blink Reflex test and A-train activity controlling for tumor size. Estimates and diagnostic accuracy are reported in Table 3. These models provided similar results in terms of positive predictive value (about 70%) and diagnostic accuracy (AUC about 90%). Both Blink Reflex test and A-train activity were likely to be strong predictors of long-term FN function evaluated with the H-B score, showing their effect holding all other predictors constant (Table 3), though the limited sample size affected estimates reliability. Previous evidence showed the need of a sample size of at least 100 subjects to take into account all key factors in a multivariable model. For instance, controlling for tumor size, Blink Reflex test, and A-train activity showed odds ratios of 5.54 (95% CI 1.25; 26.69, $p = 0.033$) and 9.81 (95% CI 2.11; 45.65, $p = 0.004$), respectively.

DISCUSSION

Management of AN has been revolutionized in the modern surgical era. Earlier tumor detection with the introduction of MRI imaging, in conjunction with a greater understanding of natural history of AN, has led to increased tumor observation. Surgery has also evolved, with significant reductions in mortality, and thus the focus of skull base surgery has shifted to minimizing morbidity. The aim of AN surgery is now complete tumor resection, with every effort to maintain good postoperative facial function. Facial nerve dysfunction is cosmetically disfiguring and results in significant impairment to activities of daily living (44). Intraoperative cranial nerve monitoring is the standard of care in contemporary skull base surgery, and has been shown to assist in FN identification and postoperative outcomes. However, whether preoperative or intraoperative electrophysiological studies can predict long-term FN outcomes remains largely unknown. The benefits of potential FN electroprognostic tests are multiple including tailored preoperative and postoperative counselling, revised treatment paradigms, and early facial nerve reanimation in appropriate patients. To the author's knowledge this is the first study examining both preoperative and intraoperative neurophysiological parameters as possible reliable predictors of long-term facial nerve outcome in patients undergoing translabyrinthine AN surgery.

In this study, preoperative neurophysiological testing was performed including Blink Reflex (BR) testing in conjunction with facial nerve EMG and ENG. The BR is the only preoperative neurophysiological parameter that has shown promise in FN prognostication. In 2002, Darrouzet et al evaluated the difference in latency of BR in AN and FN outcomes. They reported that patients with a high ΔR1 on BR had a poor FN outcome. There was no association with high ΔR1 on BR and AN size, but an association with FN tumor adherence (45). They hypothesized that pathologic preoperative BR could be the indirect expression of a preexistent axonal suffering, possibly due to an unfavorable anatomical relationship between the facial nerve and the tumor, and thus play an important role in predicting the long-term FN function. This study supported the supposition that pathological preoperative BR testing may confer poor long-term FN outcomes. Indeed, poor FN outcome at 1 year was observed in 55% of patients with a pathologic BR, compared with only 12% of patients with normal preoperative neurophysiology.

When results were controlled for tumor size, a known poor prognostic factor for FN outcome, pathological preoperative BR testing still conferred a greater likelihood of poor FN outcomes. Additionally, in combination with A-trains on intraoperative EMG trace, pathological preoperative BR testing provided a PPV of 72% for poor FN outcomes.

Introperative cranial nerve monitoring (ICNM) is widely used in modern neuro-otology practice. Since the introduction of ICNM in the late 1980s it has become standard of care for most AN surgeons and its use is supported by multiple AN surgery guidelines. The use of intraoperative neurophysiological parameters for

prognostification is less well defined (46). In the 2018 Congress of Neurological Surgeons Systematic Review on ICNM in AN Surgery identified high FN MAP post tumor resection at the brainstem and IAC and low stimulus threshold, used alone or in combination, as predictive of ''good'' postoperative FN outcome (37). However, it was observed that patients with low amplitude ratios or absence of electrical responses after tumor removal did not always develop a permanent facial nerve palsy, limiting the use of ICNM for prognostic purposes. This study supported this finding, with lower MAP values, alone and as ratios, failing to show a reliable likelihood of poor FN outcomes at 1 year postoperatively based on clinical H-B scoring. In addition, in concordance with the recently published systematic review, these parameters seem too variable to be used in clinical practice as consistent predictors of long-term facial nerve outcome. This lack of predictive specificity might be due to the wide range of intraoperative factors and variables affecting FN MAP and the lack of differentiation on neurophysiology between neuropraxia and permanent neural damage.

Pathological neurotonic discharges on continuous EMG tracing, termed A-trains, have been previously shown to correlate with the severity of postoperative facial nerve palsy (38). Prell et al. published their findings showing that an A-train time >10 seconds was associated with a ≥ 2 grade deterioration in H-B Grading Score, with a sensitivity of 57% and a specificity of 81% (36–38). Our results supported these findings, with A-trains on continuous EMG trace associated with a negative predictive value (NPV) of 91% (95% CI 75–98%) for poor FN outcome postoperatively at 1 year. However, units should be cautioned regarding the high rate of false-positive results of A-trains on EMG tracing, as interpretation of pathologic discharges requires specific neurophysiologic expertise (37,38,47).

Limitations of this study include the small sample size and the absence of the facial nerve motor evoked potentials (FMEP) amplitude ratio values in the analysis. FMEP used multipulse transcranial electric stimulation of the motor bulbar neurons to examine the complete facial nerve pathway without the need for direct neural stimulation (33–36). Nevertheless, the routine use of this adjunctive neurophysiological intraoperative technique in our experience is limited. Like all neurophysiological testing, FMEP has limitations, with unwanted head movements, direct peripheral facial nerve, or facial musculature stimulation eliciting aberrant responses (48).

CONCLUSION

Preoperative and intraoperative neurophysiological testing is an evolving area in modern AN surgical practice. Pathological results on preoperative BR testing and A-trains on intropeative EMG tracing may allow skull base surgeons to provide prognostic information to patients regarding long-term FN outcomes. Additionally, this testing may allow surgeons to provide detailed postoperative counselling in the setting of postoperative FN dysfunction and intact FN intraoperatively. Ultimately, further validation of these results may guide the timing of facial nerve reanimation in selected patients and potentially further reduce the morbidity of translabyrinthine AN surgery.

Acknowledgments: The authors thank Luca Longhi, MD, for revising the article and Dr Cristina Crocamo (Department of Medicine and Surgery, University of Milano Bicocca, Italy) for assistance with statistical analysis.

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