Transcranial motor evoked potential alarm criteria to predict foot drop injury during lumbosacral surgery

Arvydas Tamkus, M.D., Ph.D.
- Title: Vice President of Risk Management, Quality Assurance, and Clinical Research
- Affiliation: Nuvasive Clinical Services (formerly Biotronic NeuroNetwork)
- Email: ArvydasT@nuvasive.com

Kent S. Rice, M.S.
- Title: Senior Manager Education and Training
- Affiliation: Nuvasive Clinical Services (formerly Biotronic NeuroNetwork)
- Email: Kent.Rice@nuvasive.com

Gregory Hoffman, M.D.
- Title: Gregory Hoffman, M.D.
- Affiliation: Orthopaedics Northeast and Parkview Hospital
- E-mail: ghoffman@orthone.com

Corresponding Author:
Arvydas Tamkus, M.D., Ph.D., D.ABNM
812 Avis Drive
Ann Arbor, MI 48108
Phone: 734-717-5632
Fax: 734-622-0452
E-mail: ArvydasT@nuvasive.com

The manuscript submitted does not contain information about medical device(s)/drug(s).
No funds were received in support of this work.
Relevant financial activities outside the submitted work: employment.
ABSTRACT:

Study Design: Retrospective cohort analysis.

Objective: This study aims to investigate whether waveform alterations in transcranial motor evoked potentials (TCMEP) can reliably predict postoperative foot drop.

Summary of Background Data: Nerve injury leading to foot drop is a potential complication of lumbosacral surgery. Very limited data exist on the use of intraoperative TcMEPs to identify iatrogenic foot drop.

Methods: We retrospectively reviewed neuromonitoring data from 130 consecutive spine surgeries with instrumentation involving L4-S1. TCMEP waveform analysis included amplitude (A), area under the curve (AUC), latency (L), and duration (D). Patient outcomes were correlated with neuromonitoring results. Intraoperative alert criteria were established based on observed intraoperative changes.

Results: Three patients developed severe foot drop with a muscle weakness functional grade ranging from 0/5 to 3/5. Two patients developed a mild foot drop with functional grade 4/5. Twenty-three patients had preoperative weakness in an L5 distribution. One-hundred and two patients who had neither preoperative nor postoperative neurological complications served as a control group. Amplitude significantly decreased in patients with a severe postoperative deficit (p=0.005) as did AUC and duration (p<0.05). Intraoperative alert criteria defined as a >65% decrease in AUC resulted in a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 100%, 91.4%, 12%, and 100%, respectively. When defining an alert criteria as a >50% decrease in amplitude, sensitivity, specificity, PPV, and NPV were 100%, 87.9%, 8.8%, and 100%. Conclusions: Reduction of TCMEP waveform associated with postoperative severe foot drop can be detected during lumbar surgery. Other
waveform parameters such as AUC may predict foot drop better than the amplitude. Additional examinations in larger samples of foot drops are needed to validate these alert threshold findings.

**Key Words:** Intraoperative neurophysiologic monitoring, foot drop, alarm criteria, transcranial motor evoked potentials, area under the curve.

**Level of Evidence:** 4
Introduction

New neurological deficits are the most concerning complication associated with spine surgery. Hamilton et al reported overall new neurologic deficit in spine surgery of 1% (1064/108,419) based on a SRS Morbidity and Mortality database study\(^1\). Iatrogenic nerve injury has been described in many studies with the reported rates varying from 0.8% to 10%\(^1-9\) with a common deficit being a foot drop\(^9\).

Foot drop, a significant weakness of ankle and toe dorsiflexion is a gait impairing, life-style affecting condition. Tibialis anterior (TA), extensor hallucis longus (EHL) and extensor digitorum longus (EDL) are the muscles that participate in ankle dorsiflexion. They are innervated by deep peroneal nerve which originates in ventral rami of L4-S1 spinal nerve roots. Contribution of these nerve roots is not equal. Schirmer et al reported that TA is primarily innervated by L5 and L4 nerve roots - 44.5% and 35.6% respectively with some contribution from S1 – 19.5\(^{10}\). During lumbar spine surgery nerve roots may suffer direct trauma from the surgical instrument or be stretched. Nerve perfusion and axoplasmic flow from perikaryon down the axon may be interrupted and palsy may occur. Extent of the palsy depends on the severity of the injury and the nerve roots involved.

Intraoperative neurophysiologic monitoring (IONM) is commonly used during lumbar spine surgery to detect and prevent intraoperative iatrogenic neurological complications. Free-run electromyography (EMG), triggered EMG and somatosensory evoked potentials (SSEP) are the modalities frequently utilized. Free-run EMG provides useful warnings to mechanical manipulations of the nerve roots, but has a very low positive predictive value\(^{11}\). SSEPs are reported to be insensitive to a single nerve root injury because of the multilevel distribution\(^{12}\).

Considering the limitations of SSEP and EMG monitoring alone some authors did suggest that TCMEPs could be considered for monitoring lumbosacral roots. Mok et al. in a pig study
demonstrated that ligation of L5 nerve root caused at least 50% decrease in TCMEP amplitude of TA muscle. Valone et al. in pig study demonstrated differences in changes in L5 nerve root TCMEP amplitude comparing compressive forces of 1 Newton and 2 Newton. In neither of these studies could clinical correlation be established. Lieberman et al. in a study of lumbar surgeries involving pedicle subtraction osteotomies found TcMEPs to be sensitive to nerve root injury, but limited number of subjects precluded them from establishing precise threshold values.

To our knowledge there are no clinical studies analyzing IONM method including TCMEP monitoring to predict and potentially prevent foot drop complication during lumbar spine surgery. Our goal was to determine if TCMEP waveform alterations could predict foot drop and thereby provide potential warning criteria for intraoperative detection of foot drop.

**Materials and Methods**

This study was granted IRB exemption status as an anonymous retrospective review by the Western Institutional Review Board. We retrospectively reviewed data from 130 consecutive spine cases involving L4-S1 spine levels. Patient demographic and IONM data including any changes were collected and evaluated.

IONM including TCMEP, EMG and SSEP was performed. SSEPs were recorded using posterior tibial (PTN) and ulnar nerve stimulation. Free-run EMG was recorded from the muscles corresponding with the myotomes of the surgical levels. Pedicle screw testing was performed as previously described. Because of low predictive value of SSEP and EMG for nerve root function, we primarily focused on analysis of TCMEP.
TCMEPs were performed with an Xltek Protektor (Natus, San Carlos, CA) using stimulation at C3 and C4 scalp locations (international 10-20 system) and a train of 7-9 pulses of 0.5 milliseconds duration. Stimulation was set at the intensity needed to record responses from all muscle groups with single-train stimulation. Separate muscle TCMEP thresholds were not set. TCMEP stimulation intensity was routinely increased during the surgery to accommodate for anesthetic fade in any monitored muscles. Facilitation techniques such as multi-train sequences and changes in inter-stimulus period were used as necessary. Stimulus intensity was documented. TCMEP recordings included the following muscles: Tibialis Anterior – Extensor Hallucis Longus (TA-EHL), Gastrocnemius (GN) and Abductor Hallucis (AH). Multiple TCMEP traces were recorded during each trial to confirm repeatability.

TCMEP waveform parameter analysis included waveform amplitude (A), area under the curve (AUC), latency (L) and duration (D). The waveform with the highest amplitude within the same trial was selected to measure these waveform parameters. A working definition for intraoperative alert criteria was attempted for the TCMEP waveform parameters measured.

Balanced anesthesia was used with ≤0.5MAC of inhalational agent, propofol and narcotic.

Statistical analysis was performed using JMP v13.0 (SAS Institute, Inc., Cary, NC). Each recorded myotome was analyzed separately, for a total of 260 myotomes. A, AUC, L, and D were compared between three groups of myotomes, those without any new postoperative deficit (n=255), those with a new mild postoperative deficit (n=2), and those with a severe postoperative deficit (n=3). Independent samples t-tests were used to compare mild and severe deficit myotomes to those without a new postoperative deficit. Statistical significance was defined at p<0.05.
Results

All 130 patients underwent posterior lumbar spine surgery with instrumentation involving L5 spine level. Patient demographics are presented in Table 1. The 102 patients who did not have any preoperative or postoperative neurological complications in L5 distribution served as a control group. Of 23 patients (17.7%) who had pre-operative weakness with dorsiflexion of the foot, none had any new or worsened deficit. Of the other 107 patients with no preoperative motor deficit, five patients developed a new foot drop. Thus, the rate of a new foot drop injury in this study was 3.8%. Three patients developed severe foot drop with a muscle weakness functional grade ranging from 0/5-3/5. Two patients developed a mild foot drop with the functional grade 4/5. Both patients with mild weakness had a complete recovery within 3 months after surgery. Patients with severe foot drop had only partial recovery at the three month follow up.

Compared to myotomes with no new postoperative deficit, amplitude significantly decreased (p=0.005) as did waveform duration and area under the curve (p<0.05) in patients with a new severe postoperative deficit. There was no observed change in latency and no difference compared to non-deficit myotomes (p=0.510). Amplitude, area under the curve, and duration percentage change from baseline in severe deficit myotomes compared to those without a new postoperative deficit were all also statistically significant (p<0.05) Aggregate and patient-level information on changes between the groups on these parameters are included in Table 2. There was no difference in TCMEP waveform parameters comparing control and patients with mild postoperative foot drop. Note that on average there was an increase in amplitude and AUC at the end of the surgery in most patients in the control group. This could mainly be attributed to routine increase of stimulation intensity to compensate for a fade in other muscles, primarily gastrocnemius.
Based on the individual patient data we attempted to empirically select the potential warning criteria. Intraoperative alert criteria defined as a >65% decrease in AUC resulted in a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 100%, 91.4%, 12%, and 100% (ASIA 0-2), respectively. When defining an alert criteria as a >50% decrease in amplitude, sensitivity, specificity, PPV, and NPV were 100%, 87.9%, 8.8%, and 100% (ASIA 0-2). When defining an alert criteria as a >20% decrease in duration, sensitivity, specificity, PPV, and NPV were 67.7%, 84.4%, 4.8%, and 99.5% (ASIA 0-2). Mild (-1 ASIA grade) foot drops were not able to be detected using the aforementioned alert criteria.

Other IOM modalities did not warrant warnings about pending foot drop injury in any of these five patients with the new foot drop: PTN SSEP waveforms were stable and pedicle screw testing did not show any abnormal values. Free-run EMG activity was reported in 4/5 patients however EMG from the muscles with new weakness was reported in only 2/5 patients. Furthermore free run EMG was reported in 56.9% (58/102) patients in the control group.

In comparing results of patients with preoperative weakness with to those without, we found that there was a statistically significant AUC reduction from the baseline (-1927.6 µV/ms; p<0.05) for patients with known preoperative weakness which may be related to anesthetic fade as none of those patients experienced worsened postoperative deficits. We also compared baseline TCMEP waveform characteristics of the control group versus patients with known preoperative TA-EHL weakness. Patients with preoperative weakness exhibited progressively lower amplitudes and AUC decreasing more with the higher degree of weakness. However no statistically significant differences were found. Data are presented in Table 3.
Although not statistically significant average stimulation intensity used for opening baselines was higher in patients with preoperative weakness (164.8 ± 39.8 mA) than in the control group (158.2 ± 58.2 mA). Figure 1 shows the effect of increasing stimulus intensity on TCMEP waveform parameters for a patient with preoperative 3/5 grade weakness. In this patient signal duration increased by 205%, AUC – by 185% and amplitude by 120% when stimulus intensity was increased from 125mA to 185mA.

Discussion

Reduction of the muscle-recorded TcMEP amplitude is commonly used to assess the function of motor pathways and to detect pending injury. Different authors suggested a wide range of alarm criteria ranging from 50% to 100%. Mok et al in a pig study reported statistically significant 457µV amplitude and 67.08% (range 51.9%-83.1%) mean percent reduction of tibialis anterior CMAP after ligation of L5 nerve root. Similarly, our data showed statistically significant amplitude reduction in absolute (1390µV) and percentage (60%) values. Furthermore, our study revealed that there was also statistically significant reduction in AUC and duration (Table 2). Percentage reduction in AUC (71.4%; range 65.6%-74.4%) was more pronounced than in amplitude (59.5%; range 55.8%-64.4%). Our data are consistent with the Mok study data cited above showing that single nerve root injury may show amplitude reduction as low as just above 50%. Such a low threshold may be prone for false positives. Indeed in our study we found that 20.6% (21/102) control patients also had 50% or more amplitude reduction with no new deficits. Alternatively, AUC showed a slightly higher degree of reduction; all three patients exhibited AUC reduction of at least 65% or more, thus allowing a slightly better sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 100%, 91.4%, 12%, and 100% vs. amplitude - 100%,
87.9%, 8.8%, and 100% (ASIA 0-2). This is consistent with the data recently published by Segura et al, who reported enhanced sensitivity by using AUC instead of amplitude\(^{23}\). The TCMEP waveform is a representation of volume of muscle fibers contracting in response to the activation of the corticospinal tract. Both waveform amplitude and duration provide information about the volume of the activated muscle fibers that is proportional to the volume of upper and lower motor neurons. Therefore amplitude alone may not fully represent the volume of activated neurons. Alternatively area under the curve combines values of both amplitude and duration and thus may better represent function of the motor pathways. Our data as well as data published by Segura support this hypothesis. Similarly Quinones-Hinojosa et al reported waveform simplification (polyphasic to biphasic morphology) as a criterion for TcMEP warning in spinal tumor surgery\(^{24}\). The limitation of this criterion is that it is subjective for interpretation. We suggest that numeric waveform parameters such as AUC that combine amplitude and duration characteristics can be utilized to better describe such a change. An example of TCMEP waveform change of a patient who suffered new postoperative foot drop with functional grade weakness 3/5 in right tibialis anterior muscle is shown in Figure 2. TCMEP amplitude on the right reduced by 55.8%, AUC - by 74.4%; duration – by 30.4%.

One of the limitations of our study is that it was a retrospective study and there was no pre-planned focus on controlling waveform variability. A recent publication points out that stimulus intensity should be set in the no-gain zone (i.e. supramaximal stimulation) in order to limit the amplitude variation\(^{25}\). One has to keep in mind that increasing stimulus intensity does improve the waveform amplitude and complexity as shown in Figure 1 and may yield false negative results\(^{26}\). Furthermore inhalational anesthetics were routinely used during the surgeries in our study, which also may have increased the number of false positives\(^{27}\).

Comparison of ipsilateral vs. contralateral side when suitable could also potentially limit the
number of false positives. Currently there are no studies suggesting the warning criteria based on the degree of the side-to-side difference in TCMEP change in spine surgery. Of 23 patients in the control group with >65% AUC reductions (false positives) only three demonstrated side-to-side asymmetry of >50%. This could significantly decrease the rate of false positives, but will potentially allow false negatives. One of our patients had AUC change of 74.4% on the foot drop side and 46.8% on the normal side. Further investigation would be necessary, but it is clear that such a study can only be performed when technical and anesthetic parameters discussed above are controlled since very subtle changes of potentially less than 50% must be investigated.

Another potential limitation is the use of mixed muscle recording which according to one porcine study can limit the sensitivity to detect isolated root injury\textsuperscript{28}. Combining the TA with EHL into a single recording was chosen specifically because of their importance in foot dorsiflexion and overlapping nerve root innervations.

PTN SSEP, free-run EMG and pedicle screw stimulation IONM modalities were not useful in our study to predict nerve root injury. Multiple nerve roots contribute to SSEP amplitude thus making it less sensitive\textsuperscript{12}. Free-run EMG is very useful to provide surgeon real time feedback while working close to the nerve roots. However as reported in literature\textsuperscript{11,14} and confirmed by our study free-run EMG has a low positive predictive value. Valone et al in a pig study showed that free-run EMG was appreciable as large burst activity during ligation, however tonic EMG of 5 seconds or longer was observed in only 20.6% of ligated nerve roots\textsuperscript{14}. No pedicle bone violation was reported in any of the patients with the foot drop. Therefore it is most likely that injury occurred during surgical approach or decompression rather than pedicle screw placement. Other modalities such as peroneal nerve SSEP\textsuperscript{29}, MEP to trans-abdominal spinal stimulation\textsuperscript{30} or threshold-level TCMEP monitoring\textsuperscript{31} might have been useful, but no published validation currently is available. Also it should be noted that more

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sensitive measurements such as threshold level TCMEP monitoring is only compatible with TIVA$^{31}$.

Another hypothesis we tested in our study was whether TCMEP waveform parameters will be reduced in patients with known preoperative foot drop. These patients indeed had lower amplitude and AUC than the control group; however statistical significance was not reached. Our data correlate with the similar findings reported by Rajshekhar et al, who showed that likelihood of obtaining lower-limb MEPs is significantly greater in patients with better function grades$^{32}$. In their study the success rate of obtaining muscle responses from lower extremities after transcranial stimulation was overall 68.2% (75/110) patients; muscle MEPs could be obtained from 91.4% with muscle power of 4/5 or more, but 0% in patients with 2/5 or less. Significant interpatient variability makes this parameter not useful for diagnostic purposes, but serves as a clinical correlation with the patient status only.

Conclusions

Reduction of TCMEP waveform associated with postoperative severe foot drop can be detected during lumbar surgery. Other waveform parameters such as area under the curve may carry additional information about the function of the motor pathways and may predict foot drop better than the amplitude. Factors that decrease waveform variability (standardized stimulation protocol and TIVA) should be considered to limit the rate of false positives. Additional examinations in larger samples of foot drops are needed to validate these alert threshold findings.

Acknowledgement

Authors thank Kyle Malone, Director of Clinical Resources, Biostatistics and Research Output, Nuvasive, Inc. who provided statistical analysis.
References


Figure Captions

Figure 1. A 42 year-old female undergoing lumbar decompression and fusion with TLIF L5-S1 who preoperatively presented with left 3/5 tibialis anterior and extensor hallucis longus weakness. TCMEP response is increased in amplitude (A) 120%, area under the curve (AUC) 185%, and duration (D) 205% as stimulation intensity is increased from 125mA to 185mA: Set 2 (125mA): AUC – 220.3 μVms; A – 9.8 μV; D – 10.4 mS; L – 41.1 ms; Set 37 (185mA): AUC – 628.2; A – 21.6; D – 31.7; L – 41.1ms.
Figure 2. 79 year-old female undergoing decompression and fusion T12-S2 who developed foot drop (3/5 tibialis anterior) on the right. Area under the curve (AUC) decreased by 74.4%, duration decreased by 30.4%, amplitude decreased by 55.8% and latency decreased by 8.6%. Anesthetic fade was observed as well since there was amplitude, AUC and duration reduction on the left; however these changes were insignificant. TCMEP stimulus parameters: Baseline - intensity 150mA, pulse width 0.5ms, 250Hz, 9 pulses; Closing - stimulus intensity 200mA, pulse width - 0.5ms, 350Hz, 9 pulses. Anesthesia: Desflurane 3.3-3.5%, propofol 55 µg/kg/min, remifentanil 0.15 µg/kg/min, Train-of-four - 4/4 twitches.
Table 1. Patient characteristics. BMI – body mass index.

<table>
<thead>
<tr>
<th></th>
<th># of patients</th>
<th>Gender M/F</th>
<th>Age Mean (range)</th>
<th>BMI Mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>102</td>
<td>49/53</td>
<td>58.8 (13-91)</td>
<td>32.2 (19.7-53.8)</td>
</tr>
<tr>
<td>Preoperative foot drop</td>
<td>23</td>
<td>10/13</td>
<td>61.0 (34-75)</td>
<td>33.3 (20.9-46.2)</td>
</tr>
<tr>
<td>Postoperative foot drop</td>
<td>5</td>
<td>1/4</td>
<td>63.6 (49-79)</td>
<td>35.6 (27.1-53.5)</td>
</tr>
<tr>
<td>Total</td>
<td>130</td>
<td>60/70</td>
<td>59.4 (13-91)</td>
<td>32.5 (19.7-53.8)</td>
</tr>
</tbody>
</table>
Table 2. Change from the baseline in L5 myotome TCMEP parameters calculated as absolute value and percentage for the patients with new postoperative foot drop (severe and mild) and unchanged neurological status (Control).

<table>
<thead>
<tr>
<th></th>
<th>Amplitude</th>
<th>AUC</th>
<th>Latency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute</td>
<td>Absolute</td>
<td>Absolute</td>
<td>Absolute</td>
</tr>
<tr>
<td></td>
<td>µV</td>
<td>µV·ms</td>
<td>ms</td>
<td>ms</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>Severe foot drop (3 limbs)</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (stdev), significance:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 1</td>
<td>-1390 (853), p=0.005</td>
<td>-7900 (4304), p=0.005</td>
<td>0 (4), p=0.606</td>
<td>-10 (2), p=0.013</td>
</tr>
<tr>
<td></td>
<td>-60 (5), p&lt;0.001</td>
<td>-71 (5), p&lt;0.001</td>
<td>1 (6), p=0.510</td>
<td>-26 (7), p=0.016</td>
</tr>
<tr>
<td></td>
<td>-5800</td>
<td>-74.4</td>
<td>-8.6</td>
<td>-10.6</td>
</tr>
<tr>
<td></td>
<td>-5800</td>
<td>-74.4</td>
<td>-8.6</td>
<td>-10.6</td>
</tr>
<tr>
<td></td>
<td>-9500</td>
<td>-74.2</td>
<td>3.4</td>
<td>11.4</td>
</tr>
<tr>
<td>Patient 2</td>
<td>-1800</td>
<td>-58.1</td>
<td>-65.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Patient 3</td>
<td>-1421</td>
<td>-64.6</td>
<td>-9500</td>
<td>3.4</td>
</tr>
<tr>
<td><strong>Mild foot drop (2 limbs)</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (stdev), significance:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>83 (127), p=0.321</td>
<td>38 (653), p=0.068</td>
<td>11 (11), p=0.345</td>
<td>11 (11), p=0.358</td>
</tr>
<tr>
<td></td>
<td>54 (78), p=0.592</td>
<td>-14 (31), p=0.015</td>
<td>-3 (14), p=0.308</td>
<td>-13 (11), p=0.358</td>
</tr>
<tr>
<td></td>
<td>38 (653), p=0.068</td>
<td>-14 (31), p=0.015</td>
<td>-3 (14), p=0.308</td>
<td>-13 (11), p=0.358</td>
</tr>
<tr>
<td></td>
<td>38 (653), p=0.068</td>
<td>-14 (31), p=0.015</td>
<td>-3 (14), p=0.308</td>
<td>-13 (11), p=0.358</td>
</tr>
<tr>
<td>Patient 5</td>
<td>172</td>
<td>109</td>
<td>-35</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>-7</td>
<td>-1</td>
<td>500</td>
<td>3</td>
</tr>
<tr>
<td><strong>Control, mean (stdev):</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(255 limbs)</td>
<td>223 (853)</td>
<td>1657 (7481)</td>
<td>-1.7 (5.9)</td>
<td>-0.7 (8.2)</td>
</tr>
<tr>
<td></td>
<td>94.5 (245)</td>
<td>114 (335)</td>
<td>-3.2 (14)</td>
<td>0.7 (22)</td>
</tr>
</tbody>
</table>

*mean values per cohort compared individually against the control group using an independent-samples T-test.
Table 3. Comparison of TCMEP waveform parameters for patients with no preoperative deficits (Control) versus patients with known preoperative weakness. Each parameter is given as a mean value with a range.

<table>
<thead>
<tr>
<th></th>
<th># of limbs</th>
<th>Intensity (mA)</th>
<th>Amplitude (µV)</th>
<th>AUC (µV·ms)</th>
<th>Latency (ms)</th>
<th>Duration (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>204</td>
<td>158.2 (100-200)</td>
<td>923.1 (28-6,300)</td>
<td>8,573.7 (152-78,200)</td>
<td>40.1 (23-70)</td>
<td>39.5 (20-55)</td>
</tr>
<tr>
<td>Preoperative weakness 4/5</td>
<td>16</td>
<td>160.8 (125-200)</td>
<td>969.5 (60-3,600)</td>
<td>10,454.0 (329-51,100)</td>
<td>39.6 (31-53)</td>
<td>41.4 (36-54)</td>
</tr>
<tr>
<td>Preoperative weakness 3/5</td>
<td>6</td>
<td>171.7 (125-200)</td>
<td>832.0 (104-2,500)</td>
<td>6167.8 (703-18,300)</td>
<td>41.7 (34-52)</td>
<td>38.0 (29-45)</td>
</tr>
<tr>
<td>Preoperative weakness 0-2/5</td>
<td>4</td>
<td>167.5 (135-200)</td>
<td>211.5 (262-484)</td>
<td>1296.0 (884-2,300)</td>
<td>44.3 (39-54)</td>
<td>41.3 (32-59)</td>
</tr>
<tr>
<td>Significance (p-value)</td>
<td></td>
<td>0.6098</td>
<td>0.4921</td>
<td>0.4490</td>
<td>0.2118</td>
<td>0.0999</td>
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