A new criterion for the alarm point for compound muscle action potentials

Clinical article

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Object. The purpose of this study was to review the present criteria for the compound muscle action potential (CMAP) alert and for safe spinal surgery.

Methods. The authors conducted a retrospective study of 295 patients in whom spinal cord monitoring had been performed during spinal surgery. The waveforms observed during spinal surgery were divided into the following 4 grades: Grade 0, normal; Grade 1, amplitude decrease of 50% or more and latency delay of 10% or more; Grade 2, multiphase pattern; and Grade 3, loss of amplitude. Waveform grading, its relationship with postoperative motor deficit, and CMAP sensitivity and specificity were analyzed. Whenever any wave abnormality occurred, the surgeon was notified and the surgical procedures were temporarily suspended. If no improvements were seen, the surgery was terminated.

Results. Compound muscle action potential wave changes occurred in 38.6% of cases. With Grade 1 or 2 changes, no paresis was detected. Postoperative motor deficits were seen in 8 patients, all with Grade 3 waveform changes. Among the 287 patients without postoperative motor deficits, CMAP changes were not seen in 181, with a specificity of 63%. The false-positive rate was 37% (106 of 287). However, when a Grade 2 change was set as the alarm point, sensitivity was 100% and specificity was 79.4%. The false-positive rate was 20% (59 of 295).

Conclusions. Neither the Grade 1 nor the Grade 2 groups included patients who demonstrated a motor deficit. All pareses occurred in cases showing a Grade 3 change. Therefore, the authors propose a Grade 2 change (multiphasic waveform) as a new alarm point. With the application of this criterion, the false-positive rate can be reduced to 20%.

Key Words • compound muscle action potential • alarm point • multiphase wave pattern

Somatosensory evoked potentials came into use for monitoring during spine and spinal cord surgery in the 1980s.2,7,21,33,34 In the early 1990s, SCEPs after brain stimulation (D wave) were introduced for monitoring motor pathways.6,13,14,24,27,28 Various other methods of monitoring have been developed and include free-running electromyography,8,11 SCEPs after stimulation of the spinal cord,11 SCEPs after stimulation of the peripheral nerve, and CMAPs.1,17,18,19,22 Many authors have reported on the value of multimodality monitoring rather than single-modality monitoring, and combining CMAPs and D waves is considered more reliable, especially the use
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of CMAPs.\textsuperscript{23,27,28} Authors of one report have stated that CMAP accurately indicates injury in real time feedback, having both a sensitivity and specificity of around 100%.\textsuperscript{19} On the negative side, this high sensitivity is reportedly associated with frequent false-positive wave changes that disturb the surgeries.\textsuperscript{19,23,25,30} Most reports of MEP monitoring during surgery use amplitude drop, usually from 50% to 80% of baseline values, as the primary warning criterion for the reduction of a false-positive rate.\textsuperscript{5} Zhou et al.\textsuperscript{32} reported that persistent intraoperative MEP reductions of more than 50% are associated with postoperative motor deficits. Calancie and Molano\textsuperscript{6} concluded that the use of the Presence-or-Absence alarm criteria for interpreting MEPs during surgery is often incompatible with the requirement for accurate and early warning of impending injury to central motor pathways and thus should be avoided. The alarm point is still a matter of debate. We therefore aimed to review the conventional alarm point and establish a more accurate one to decrease the false-positive rate and prevent postoperative motor deficit.

Methods

Two hundred ninety-five consecutive patients, 104 males and 191 females, with a mean age of 41.5 years were treated for a variety of pathological conditions at our hospital during the period between July 2002 and September 2006 and underwent CMAP monitoring (Table 1).

Stimulating and Recording Methods

Transcranial stimulation was performed using a D185 MultiPulse stimulator (Digitimer, Ltd.). The stimulation parameters were 4–5 stimuli in a row with 2-msec interstimulus intervals, 300- to 600-V stimulus voltage, 50- to 1000-Hz filter, and 100-msec epoch time, with ≤ 20 individual recorded responses. The stimulated point was 2 cm anterior and 3 cm lateral from the Cz location (International 10-20 System) over the cerebral cortex motor area (left: anode, right: cathode). Using Neuropack MEB-2200 version 04.02 (Nihon Kohden), which is expandable to 16 channels, muscle action potentials were recorded from the upper and lower extremities via needle electrodes and from the anus via plug-type electrodes. Motor evoked potentials were recorded from deltoid, biceps, triceps, hypothenar, quadriceps femoris, hamstring, tibialis anterior, gastrocnemius, and anal sphincter muscles, depending on the spinal cord level at which surgery was performed. And, when possible, we performed multimodality monitoring in all cases. More particularly, we combined SCEPs after brain stimulation (D wave) and SSEPs. A single transcranial electrical stimulus was applied using the same montage as for the MEPs to elicit a D wave that was recorded by an electrode placed in the epic- or subdural space of the spinal cord caudal to the tumor. Signals were amplified 10,000 times, and the 1.5- to 1700-Hz bandwidth baseline D waves were recorded after exposing the spinal cord. We elicited cortical and subcortical SSEPs by stimulation of the median nerve at the wrist and the posterior tibial nerve at the ankle (intensity 40 mA, duration 0.2 msec, and repetition rate 4.3 Hz). Recordings were performed via corkscrew-like electrodes inserted in the scalp (CS electrode, Nicolet Biomedical, Inc.) at Cz–Fz (legs) and C3/C4–Fz (arms), according to the International 10-20 System.

The D wave was used in 62 of the 295 cases, including the 44 cases of intramedullary spinal cord tumor surgery.

Anesthesia Protocol

Because benzodiazepine as a preanesthetic medication suppresses latency and amplitude, it was used minimally if at all. The drugs initially administered were propofol (3–4 μg/ml), fentanyl (2 μg/kg), and vecuronium (0.12–0.16 mg/kg). Anesthesia was maintained using propofol (3 μg/ml), fentanyl (1–2.5 μg/kg/hr), and vecuronium (0.01–0.04 mg/kg/hr). To monitor the muscle relaxation level, a train-of-four monitor was also used, setting the train-of-four count to 2–3 times. Concomitant hypotensive anesthesia was given, as appropriate, by continuously administering prostaglandin E1 and a short-acting β1-blocker (landiolol). Our patients are always kept normothermic. Should intraoperative spinal damage occur, the patient’s temperature is raised. The anesthetist endeavors to maintain end-tidal CO\textsubscript{2} in the normal range throughout the surgery.

Waveform Change Grading and Alarm

We used 4 grades to describe the CMAP waveform. Our experience revealed that the waveform changed from Grade 1 to 3 corresponding to the severity of injury. Each grade was defined as follows: Grade 0, normal waveform; Grade 1, an amplitude decline of 50% or more and a latency delay of 10% or more; Grade 2, multiphase waveform whose number of wave peaks increased and dispersed without amplitude loss, through either prolonged duration or a shift in peak latency; Grade 3, loss of amplitude (no response), that is, an amplitude < 1 μV, for which the shape of the waveform cannot be captured (Fig. 1). When any of the waveforms changed during the surgery, we ordered the anesthetist to raise the systolic blood pressure or reverse hypotensive anesthesia and to warm the core temperature. When the waveform still did not recover, such cases were considered to have a waveform change, and the surgeon was alerted to suspend the surgery. For example, when the wave showed Grade 2 in one muscle, even if another muscle showed Grade 1 in the same patient, the waveform change in the patient was defined as Grade 2. When the wave showed Grade 3 in one muscle, even if another muscle showed Grade 1 or 2 in the same patient, the waveform change in the patient was defined as Grade 3. Thereafter, waveform was frequently monitored. Surgery was resumed if the waveform improved (Grade 0). The surgery was terminated if no improvement was seen. We suspended the surgery at the current site of operation to work at a different site until the waveform recovered.

Waveform grading, its relationship with postoperative motor deficit, and CMAP sensitivity and specificity were analyzed. Simultaneously, an amplitude loss of 50% or more and a latency delay of 10% or more for D wave and SSEPs were used as the alarm points.
Results

Waveform Change

Wave change in at least one muscle could be detected in 114 (38.6%) of the 295 patients (Table 1). One hundred eighty-one patients (61.4%) were classified as having Grade 0 waveforms, showing no wave change; 47 patients (15.9%), Grade 1 waveforms; 28 patients (9.5%), Grade 2; and 39 patients (13.2%), Grade 3 (Table 2). Refer to Figs. 2 and 3 for representative cases of Grade 2 and 3 waveforms. An amplitude reduction of 50% or more was noted in 6 of the 62 cases in which a D wave was used, and postoperative motor deficits were observed in all 6 of these cases.

Relation Between Waveform Changes and Postoperative Motor Deficits

No motor deficit was seen for Grade 1 or 2 waveform groups. The 8 patients who suffered from postoperative motor deficits were all in the Grade 3 waveform group (Table 3). In all 39 cases with Grade 3 waveforms, surgery was temporarily discontinued until the waveform recovered; however, the waveform in 24 of the 39 cases did not improve. There were postoperative motor deficits in 5 cases of intramedullary tumor, 2 cases of thoracic OPLL, and 1 case of cervical myelopathy with cerebral palsy. In all of these cases except for Case 4, the postoperative motor deficit was transient.

Recovery Rate

Waveform recovery during surgery was noted in 39 (83%) of 47 cases with Grade 1 waveforms, 10 (36%) of 28 cases with Grade 2 waveforms, and 15 (38%) of 39 cases with Grade 3 waveforms (Table 4). Grade 1 showed a significantly higher recovery rate compared with other grades (p < 0.05).

Surgery was resumed when waveform recovery was observed. When there was no waveform recovery, the surgery was completed by performing an alternative procedure at an unaffected site. Of the 39 cases that exhibited Grade 3 waveforms, 24 showed no wave recovery, and in 8 of these 24 cases, motor deficit was observed. Therefore, a Grade 3 waveform is thought to be predictive of paresis.

Compound Muscle Action Potential Sensitivity, Specificity, and False-Positive Rates

When Grade 1 was set as the alarm point, sensitivity was 100%, given that CMAPs declined in all 8 motor deficit cases (Table 5). As regards the 287 cases without paresis, 181 were free from CMAP decline, and specificity was 63%. The false-positive rate was 37% (106 of 287 cases). The PPV was 7.0%, and the NPV was 100%.

However, when Grade 2 was used as the alarm point, sensitivity was 100% and specificity was 79.4%. The false-positive rate was 20.6% (59 of 287 cases). The PPV was 11.9%, and the NPV was 100%. That is, the false-positive rate could be reduced by 16.4% when the alarm point was set to Grade 2 instead of Grade 1.

Furthermore, when Grade 3 was used as the alarm point, sensitivity was 100% and specificity was 89.2%. The false-positive rate was 10.8% (31 of 287 cases). The PPV was 20.5%, and the NPV was 100%. But postoperative motor deficits were seen in 8 of 39 patients. The PPV has also been calculated as the rate of cases in which no motor deficit occurred despite changed waveforms (100 – PPV, expressed in %). When Grade 1 was used as the alarm point, the rate was 93%; with Grade 2, 88.1%; and with Grade 3, 79.5%.

Table 1: Diseases and waveform change rates in 295 patients who underwent CMAP

<table>
<thead>
<tr>
<th>Disease</th>
<th>No. of Cases</th>
<th>Waveform Change (% of total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>extramedullary spinal cord tumor</td>
<td>63</td>
<td>12 (19)</td>
</tr>
<tr>
<td>intramedullary spinal cord tumor</td>
<td>44</td>
<td>32 (73)</td>
</tr>
<tr>
<td>scoliosis</td>
<td>42</td>
<td>20 (48)</td>
</tr>
<tr>
<td>cervical myelopathy*</td>
<td>35</td>
<td>1 (3)</td>
</tr>
<tr>
<td>OPLL (thoracic)</td>
<td>17</td>
<td>15 (88)</td>
</tr>
<tr>
<td>spinal tumor</td>
<td>15</td>
<td>7 (47)</td>
</tr>
<tr>
<td>other</td>
<td>69</td>
<td>27 (39)</td>
</tr>
<tr>
<td>total</td>
<td>295</td>
<td>114 (38.6)</td>
</tr>
</tbody>
</table>

* Including CP kyphosis.

Table 2: Relationship between waveform changes and postoperative motor deficits

<table>
<thead>
<tr>
<th>Grade</th>
<th>No. of Cases (%)</th>
<th>Postop Motor Deficit (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>181 (61.4)</td>
<td>0/181</td>
</tr>
<tr>
<td>1</td>
<td>47 (15.9)</td>
<td>0/47</td>
</tr>
<tr>
<td>2</td>
<td>28 (9.5)</td>
<td>0/28</td>
</tr>
<tr>
<td>3</td>
<td>39 (13.2)</td>
<td>8/39 (20.5)</td>
</tr>
<tr>
<td>total</td>
<td>295</td>
<td>8/295 (2.7)</td>
</tr>
</tbody>
</table>
Nevertheless, considering that the false-negative rate is 0% and the NPV is 100%, CMAP is a reliable monitoring method regardless of the alarm point setting.

As for the SSEPs, of the 8 cases in which paralysis occurred, only 4 (Cases 1, 3, 4, and 7) exhibited an increased amplitude of 50% or less and a prolonged latency of 10% or more, whereas the remaining 4 cases did not reach the SSEP alarm point. This translated into a sensitivity of 50%, a specificity of 90%, a PPV of 12%, and an NPV of 98%. As for the D wave, among the aforementioned 8 cases in which paralysis occurred, 6 (Cases 1–4, 6, and 7) exhibited amplitudes of 50% or less, and the remaining 2 cases did not reach the D wave alarm point. This translated into a sensitivity of 75%, a specificity of 94%, a PPV of 67%, and an NPV of 96%.

**Discussion**

Spinal surgeries, especially intramedullary tumor excision, decompression of OPLL, and correction of scoliosis, occasionally encounter critical phases and require safe procedures to minimize postoperative motor and sensory deficits. Many authors have reported on the importance of spinal cord monitoring, emphasizing the necessity of multimodality monitoring rather than single-modality monitoring. Among other measures, CMAP monitoring is considered the most sensitive and effective. We conduct 16-channel motor pathway monitoring (CMAP) through high-frequency transcranial electrical stimulation at our hospital. Besides its advantages, CMAP has several disadvantages such as 1) wave pattern susceptibility to false changes with anesthesia (inhalation anesthesia and muscle relaxants) and 2) an inability to detect posterior column impairments. As many authors have pointed out, the high false-positive rate resulting from its high sensitivity is the most serious disadvantage. Kim et al. reviewed 1445 cases of anterior cervical spine surgery monitored via CMAPs and found a false-positive rate of approximately 80%. Since a high false-positive rate can impede progress in surgery, the rate should be lowered as much as possible. Furthermore, as regards the alarm point for CMAP, most reports of MEP monitoring during surgery use amplitude drop, usually from 50% to 80% of baseline values, as the primary warning criterion. Langeloo et al. assumed that surgeons should be alerted when an amplitude decrease of 80% or more...
occurred in any of the monitored muscles, while Sala and colleagues\textsuperscript{27,28} considered the alarm point as complete disappearance of the waveform. According to Quiñones-Hinojosa et al.,\textsuperscript{26} the alarm point is when the waveform changes from biphasic to monophasic. Kothbauer et al.\textsuperscript{14} reported that in surgery for intramedullary tumors, if the D wave amplitudes remained 50\% or more, resulting paralysis, if any, was temporary even in the event of total loss of the MEP. In this report, Kothbauer and colleagues presented detailed and specific waveform data about each case, classifying the waveform changes as unchanged, decreased, and lost. Hilibrand et al.\textsuperscript{9} regarded an amplitude reduction of 60\% or more in the MEP waveform that was sustained for at least 10 minutes as a significant deterioration. Hsu et al.\textsuperscript{10} regarded an amplitude reduction of 50\% or more in the MEP waveform that was sustained for at least 1 minute as a significant change in monitoring and reported significant MEP deteriorations in 15 of 172 cases of spinal deformity surgery, with a complete loss of the waveform in 7 cases. In a study comparing 50 cases of intramedullary spinal cord tumor surgery with intraoperative monitoring and 50 cases of the same surgery without intraoperative monitoring, Sala et al.\textsuperscript{28} defined absent waveform as no indication of waveform even when the MEP scale was reduced to as low as 30 μV. As seen above, the optimal alarm point is still controversial.\textsuperscript{5,8,16,30} Thus, it is beneficial to establish a new alarm point with the lowest possible false-positive rate. In the present study, 28 cases (9.5\%) exhibited Grade 2 waveforms before Grade 3 waveforms during the surgery. With the application of our criterion of Grade 2 waveforms, the false-positive rate can be reduced to 20\%.

Lee et al.\textsuperscript{20} reported that it was unclear whether amplitude decreases resulted merely from false-positive measurements or from subclinical spinal cord irritations; however, we consider Grade 1 amplitude decreases as false-positives and Grade 2 as subclinical spinal cord irritations. That assumption was based on Burke and colleagues\textsuperscript{3,31} report that amplitude and latency can fluctuate 13\%–50\% and 2\%–3\%, respectively, within the same anesthesia conditions when monitoring via complex D wave. Compound muscle action potential recording, which is more sensitive, is considered more susceptible to anesthesia-related wave changes. As shown in Table 4, quick waveform recovery occurred in 39 (83\%) of 47 cases. As seen in Fig. 4, since the conduction times from anterior horn cells to muscles are the same in Grade 0, the timing of the waveform obtained from each neurofiber is the same, resulting in a total waveform of high amplitude. In Grade 1, amplitude is easily influenced by environmental factors such as anesthesia and noise. If some of the anterior horn cells are not excited due to anesthesia or other environmental factors, partial stimulus conduction results and the total waveform exhibits a lower am-

\textbf{Fig. 3.} Tracings obtained in a 44-year-old woman with cervical ependymoma. Grade 3 changes were seen in bilateral gastrocnemius (GC) and sphincter muscles during resection of the tumor. The surgical procedure was discontinued, but even after 15 minutes no waveform recovery was seen, and the surgery was terminated. The tumor could only be partially resected. Transient motor deficit occurred postoperatively in this patient. TA = tibialis anterior.
New criterion for CMAP alarm point

In Grade 2, if injuries exist in the neurofibers, the conduction velocity slows at the injured sites, resulting in different timings of the arrival of waveforms from the neurofibers to the muscles. The total waveform will be multiphase. In more advanced states of injury, conduction from neurofibers is blocked, as was the case in Grade 3. In the Grade 3 group, postoperative motor deficits occurred in 8 (20.5%) of 39 patients. It is too late to alert after complete wave pattern loss is detected, as paresis may have already occurred at this stage, thus rendering Grade 3 inappropriate for use as the alarm point. Therefore, we consider it appropriate to alert when Grade 2 waveforms are seen. Applying this new criterion reduces the false-positive rate by 16.4% (from 37.0% to 20.6%)

A limitation in this study is still the high false-positive rate of 20.6%, which results from our multichannel (maximum 16) monitoring in which even wave changes in one muscle are considered as an alarm. We included all transient pareses in our analysis; however, analysis of only permanent pareses should also be performed to avoid the high false-positive rate.

Another limitation is the use of hypotensive anesthesia that may cause waveform changes. Spinal surgery is often performed with the patient prone. As this position leads to increased abdominal pressure, hypotensive anesthesia is recommended for hemorrhage control. While lowered blood pressure decreases the spinal blood flow, the waveform amplitude is likely to decrease as well. Moreover, based on our experience, intramedullary tumor surgery, in particular, can cause waveform changes if the patient is under hypotensive anesthesia. In addition to the decreased spinal blood flow, tumor extraction involves the risk of directly damaging the blood vessels, which will further reduce blood flow. As such, intramedullary tumors are more likely to involve changes in waveform. Nevertheless, we use hypotensive anesthesia at all times to maintain blood pressure at about 90–100 mm Hg because it makes hemorrhage control easier.

A final limitation is the inclusion of all diseases in our analysis. The waveform in cases of intramedullary spinal cord tumor would be especially more changeable than in other diseases. Intramedullary spinal cord tumor should be analyzed separately, and one should consider the possibility that it would have another alarm point. Thus, the Grade 2 multiphase wave pattern can be recommended as a new alarm point.

**Conclusions**

To ensure the safety of spinal surgery without impeding its progress, new alarm point criteria should be
Fig. 4. Schematics showing mechanisms of wave change.

TABLE 5: Compound muscle action potential sensitivity and specificity and the false positive rate*

<table>
<thead>
<tr>
<th>Alarm Point</th>
<th>Motor Deficit</th>
<th>No Motor Deficit</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>False-Positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
<td>7</td>
<td>100</td>
<td>100</td>
<td>63</td>
<td>37.0</td>
</tr>
<tr>
<td>change</td>
<td>8</td>
<td>106</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no change</td>
<td>0</td>
<td>181</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>8</td>
<td>59</td>
<td>11.9</td>
<td>100</td>
<td>100</td>
<td>79.4</td>
<td>20.6</td>
</tr>
<tr>
<td>no change</td>
<td>0</td>
<td>228</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>8</td>
<td>31</td>
<td>20.5</td>
<td>100</td>
<td>100</td>
<td>89.2</td>
<td>10.8</td>
</tr>
<tr>
<td>no change</td>
<td>0</td>
<td>256</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

* Grade 1 means Grade 1 or higher, indicating a figure covering Grades 1–3; analogously, Grade 2 means Grade 2 or higher, indicating a figure covering Grades 2–3.
New criterion for CMAP alarm point

established. Grade 1 is not a reliable criterion for determining the alarm point because the amplitude is changeable. Grade 3 (loss of amplitude) is also unsuitable as a criterion because it includes cases in which there is postoperative paresis. We propose a multiphasic waveform of Grade 2 as a new alarm point. With the application of this criterion, the false-negative rate can be reduced to 20.6%.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Ito. Acquisition of data: Ito. Analysis and interpretation of data: Ito. Drafting the article: Ito. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript: all authors. Statistical analysis: Ito. Study supervision: Imagama, Sakai, Katayama, Wakao, Ando, Hirano, Tauchi, Muramoto, El Zahlawy, Matsuyama, Ishiguro.

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