Incidence of intraoperative seizures during motor evoked potential monitoring in a large cohort of patients undergoing different surgical procedures

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OBJECTIVE The purpose of this study was to investigate the incidence of seizures during the intraoperative monitoring of motor evoked potentials (MEPs) elicited by electrical brain stimulation in a wide spectrum of surgeries such as those of the orthopedic spine, spinal cord, and peripheral nerves, interventional radiology procedures, and craniotomies for supra- and infratentorial tumors and vascular lesions.

METHODS The authors retrospectively analyzed data from 4179 consecutive patients who underwent surgery or an interventional radiology procedure with MEP monitoring.

RESULTS Of 4179 patients, only 32 (0.8%) had 1 or more intraoperative seizures. The incidence of seizures in cranial procedures, including craniotomies and interventional neuroradiology, was 1.8%. In craniotomies in which transcranial electrical stimulation (TES) was applied to elicit MEPs, the incidence of seizures was 0.7% (6/850). When direct cortical stimulation was additionally applied, the incidence of seizures increased to 5.4% (23/422). Patients undergoing craniotomies for the excision of extraaxial brain tumors, particularly meningiomas (15 patients), exhibited the highest risk of developing an intraoperative seizure (16 patients). The incidence of seizures in orthopedic spine surgeries was 0.2% (3/1664). None of the patients who underwent surgery for conditions of the spinal cord, neck, or peripheral nerves or who underwent cranial or noncranial interventional radiology procedures had intraoperative seizures elicited by TES during MEP monitoring.

CONCLUSIONS In this largest such study to date, the authors report the incidence of intraoperative seizures in patients who underwent MEP monitoring during a wide spectrum of surgeries such as those of the orthopedic spine, spinal cord, and peripheral nerves, interventional radiology procedures, and craniotomies for supra- and infratentorial tumors and vascular lesions. The low incidence of seizures induced by electrical brain stimulation, particularly short-train TES, demonstrates that MEP monitoring is a safe technique that should not be avoided due to the risk of inducing seizures.

KEY WORDS seizure; MEP; surgery; intraoperative monitoring; epilepsy

The intraoperative monitoring of motor evoked potentials (MEPs) elicited by transcranial electrical stimulation (TES), direct cortical electrical stimulation (DCS), or other methodologies used for cortical mapping have shown evidence of reducing the rate of postoperative motor deficits in different types of surgeries, such as those for intramedullary spinal cord tumors, orthopedic spinal surgeries, and cerebral vascular surgeries. However, many surgeons are hesitant about employing MEP monitoring and cortical mapping due to the risk that electrical brain stimulation could elicit a seizure.

The incidence of seizures after a short train of electrical stimulation has been analyzed in craniotomies, primarily for supratentorial intraaxial tumor resection, and has been reported to be between 1% and 4%. Different techniques of electrical brain stimulation pose different risks for seizures. The incidence of seizures has been reported to be 1.6% after short-train DCS and 5%–24% after the Penfield stimulation technique.
No comprehensive data are available on the incidence of seizures after short-train TES in a wide spectrum of surgeries in which MEP monitoring is required but craniotomy is not performed. Whereas DCS and cortical mapping techniques require exposure of the cortex, TES is applied transcranially not only in craniotomies but also in other types of surgeries.

The objective of this study was to review the incidence of seizures during the intraoperative monitoring of MEP in a wide spectrum of surgeries such as those of the orthopedic spine, spinal cord, and peripheral nerves, interventional radiology procedures, and craniotomies for supratentorial and brainstem lesions, among others. Our final aim was to provide a wide scope of data about the incidence of seizures during different types of surgeries using different techniques for brain stimulation.

Methods

We retrospectively analyzed data from 4179 consecutive patients who underwent surgery or had an interventional radiology procedure with MEP monitoring during an 8-year period (2004–2012). All patients were treated at the same institution and were monitored by the same intraoperative neurophysiological team. The surgical services involved were neurosurgery, ENT, vascular surgery, orthopedic surgery, plastic surgery, general surgery and interventional radiology.

This review was approved by the Mount Sinai institutional review board.

We used an Axon Sentinel 4 EP analyzer (Axon Systems, Inc.) with modified hardware and software for electrical stimulation and MEP recording.

TES was performed by placing stimulating corkscrew electrodes (Viasys Healthcare or CareFusion) on the scalp over the motor cortex. Common TES montages were interhemispheric C1/C2 or C3/C4 and hemispheric C3/Cz or C4/Cz according to the International 10–20 EEG system. DCS was performed by stimulation via an 8-contact strip electrode (Ad-Tech Medical Instrument Corp. or Medtronic, Inc.) placed directly over the motor cortex. Motor cortex mapping was performed by applying and stimulating the monopolar probe (Medtronic Xomed, Inc.) directly over the motor cortex. For both DCS and motor cortex mapping, a corkscrew or subdermal needle electrode was placed at Fpz as a reference.

The maximum intensity applied was 200 mA for TES and 30 mA for DCS and cortical mapping. Electrical stimulation was performed with a short train of 5 to 7 anodal stimuli, with 0.5-msec pulse duration, 4.0-msec interstimulus interval, and a train repetition rate of 2 Hz. In cases in which the patient had of a history of seizures, the train repetition rate was decreased and could be as low as 0.4 Hz.

To record MEP responses, a pair of disposable subdermal needle electrodes (Viasys Healthcare) were inserted into the monitored muscles. Muscles that were typically monitored included the following: abductor pollicis brevis, adductor digiti minimi, tibialis anterior, and abductor hallucis brevis. Additional muscles were included according to the type of surgery. The detailed methods and parameters have been described previously. Over the 8-year period of the study the above-described protocol was never changed, and we meticulously followed conventional MEP guidelines. Seizures were detected through clinical observation of movement.

Descriptive statistical analysis was performed for the selected parameters, including patient characteristics and seizure frequencies.

The anesthetic regimen that was required to facilitate TES was total intravenous anesthesia (TIVA), which avoided the use of inhalation anesthetics. The choice of anesthetic depended solely on MEP monitoring and was independent of the type of surgery. The agents used for TIVA were an infusion of propofol and remifentanil, an ultra–short-acting opioid that helps to facilitate quick awakening and neurological testing after surgery. An infusion of phenylephrine was sometimes necessary to maintain blood pressure. In young children, an intravenous induction was usually not possible, and these children were initially anesthetized with inhalational agents such as sevoflurane. The inhalation agent was discontinued once the patient was started on TIVA.

Results

Patients included 2049 males and 2130 females, with a mean age of 49 ± 20 years (mean ± SD) and a range of ages from 1 month to 92 years. Patients were grouped according to the type of surgery. The operations included 1272 craniotomies, 322 spinal cord surgeries, 1664 orthopedic spine surgeries, 322 neck surgeries, 28 peripheral nerve surgeries and 571 interventional radiology procedures. The diagnosis and/or tumor histology and location for each group are detailed in Table 1. The type of brain stimulation technique for each group is also shown in Table 1. During craniotomies, MEP was elicited by short-train TES alone, TES plus DCS, or TES plus DCS and cortical mapping. In surgical procedures in which the motor cortex was not exposed, MEP was only elicited by short-train TES.

The number of patients with seizures in each diagnostic and/or tumor histology group and the location and type of brain stimulation are presented in Table 1. Overall, in the entire group of 4179 patients, only 32 patients (0.8%) had 1 or more intraoperative seizures. All 32 patients belonged to the craniotomy and orthopedic spine groups. None of the patients who underwent surgery for conditions of the spinal cord, neck, or peripheral nerve or who underwent an interventional radiology procedure had intraoperative seizures during MEP monitoring. The overall incidence of seizures in craniotomies was 2.3% (29/1272). The incidence of seizures in craniotomies was 0.7% (6/850) when only TES was used and 5.4% (23/422) when TES and DCS were used (including 3 cases in which cortex mapping with a monopolar probe was performed in addition to TES and DCS). The average intensity of DCS in the group with seizures was 22.6 mA (minimum 15 mA, maximum 30 mA). The incidence of seizures after TES in orthopedic spine surgeries was 0.2% (3/1664). Table 2 summarizes the incidence of seizures in the entire group.

Patients who had intraoperative seizures included 12
men and 20 women with a mean age of 50 ± 13 years (mean ± SD). As shown in Table 3, 3 patients had orthopedic spine surgery (involving the cervical spine in 2 cases and the lumbar spine in 1 case); 23 had craniotomy for tumor resection (supratentorial in 20 cases and infratentorial in 3), and 6 had craniotomy for vascular lesion removal. Craniotomies for tumors and vascular lesions included 10 frontal, 10 temporal, 3 parietal, 2 occipital, and 4 sphenoorbital procedures. The highest incidence of seizures was found in patients undergoing craniotomies for extraxial brain tumors, particularly meningiomas. Of 23 patients with cranial tumors and intraoperative seizures, the tumor was extraaxial in 16 patients (14 meningiomas) and intraaxial in 7 patients (including 5 with gliomas).

A history of seizures, the use of antiepileptic drugs (AEDs) at admission, the use of AEDs for prophylaxis in the operating room, and the number of intraoperative seizures for the group of 32 patients are detailed in Table 3. In this table, patients are grouped according to the type of surgery and brain stimulation technique used to evoke MEP. From this group, 15 patients (46.9%) had a history of previous seizures. At admission, 9 of these 15 patients were on AED medication (levetiracetam or phenytoin), and in the operating room, 12 of these 15 patients were on AED medication (levetiracetam, phenytoin, or fosphenytoin). Three patients (Table 3: ID 5, ID 20, and ID 21) were not on AED in the operating room despite a history of seizures. Of the 32 patients, 17 patients (53.1%) had no history of seizures. Among these 17 patients, only one patient was on AED medication (phenytoin) at admission, and 10 patients were on AED (levetiracetam, phenytoin, or fosphenytoin) in the operating room. Overall, 22 of the 32 patients (68.7%) were on AED in the operating room. Twenty-five patients (78.1%) experienced 1 single intraoperative seizure and 4 patients (12.5%) experienced a second seizure.

In 29 patients, irrigation with ice-cold Ringer lactate solution was employed to quickly stop the seizure. In orthopedic spine surgeries, anesthesia was deepened to burst suppression to stop the seizure.

After the occurrence of the first seizure, MEP monitoring was abandoned in 22 (69%) of 32 patients. From this group, 2 patients presented a second seizure (9%) and 1 patient presented a third seizure (4.5%). In 10 patients (31%), MEP monitoring was continued even after the occurrence of the first intraoperative seizure. From this group, 3 patients presented a second seizure (30%) and 1 patient presented a fourth seizure (10%).

The 2 patients with multiple intraoperative seizures are identified in Table 3 by Case 18 and 19, respectively.
Incidence of intraoperative seizures during MEP monitoring

MEP monitoring may be especially advisable for patients undergoing surgery for tumors that involve the cortex, such as meningiomas. Nevertheless, it was beyond our proposed goal to study in detail preoperative factors such as edema in the MRI that could have predicted this higher risk of seizures.

In a total of 1664 orthopedic spine surgeries, 3 patients (0.18%) exhibited seizures induced during MEP monitoring. Schwartz et al. reported no intraoperative seizures in a very large group of spine surgeries, but seizures may very well occur in spine surgeries. We recommend maintaining awareness of the risk of induced seizures during orthopedic spine procedures and treating with midazolam and propofol if an intraoperative seizure occurs.

The decision to administer seizure prophylaxis was made in consultation with the surgeon. In our study, most patients who underwent TES for supratentorial surgery received seizure prophylaxis, whether or not they had a prior history of seizures. Patients who underwent DCS always received seizure prophylaxis. The 2 most commonly used seizure prophylaxis medications at our institution were fosphenytoin and levetiracetam, with the latter given more frequently due to its better side effect profile.

For extracranial surgery with TES in patients without a history of seizures, prophylaxis was not given. In patients with a history of seizures, an intraoperative dose of levetiracetam was usually given.

Despite prophylaxis, some patients still experienced seizures during TES or DCS. Our protocol for treating intraoperative seizures during craniotomies included irrigation of the surgical field with ice-cold Ringer lactate solution. In addition, medications such as midazolam and propofol were given to help induce burst suppression.

Whether a preoperative history of seizures is a contraindication for eliciting MEPs by electrical brain stimulation has been long debated. Most groups agree that electrical brain stimulation can also be performed in patients with symptomatic seizures due to structural lesions. Furthermore, DCS or cortical mapping is required in epileptic surgery if the resection of epileptogenic tissue is close to motor areas.

The reported incidence of intraoperative seizures induced by the short-train technique ranged from 0.7% to 4.4%. The published reports were all based on small numbers of patients (45–200), most of whom underwent craniotomy for tumor resection. We monitored 1633 cranial surgeries and interventional procedures. No single induced seizure occurred in the 361 cranial interventional radiology procedures, including angiography and coil or glue embolization. Intraoperative seizures occurred in 29 of 1272 procedures involving craniotomies, for an incidence rate of 2.3%; when craniotomies were stratified by the condition treated, the rates for patients treated for tumors and vascular lesions were 2.8% and 2.1%, respectively. The highest incidence of seizure was found in patients undergoing craniotomy for extracerebral brain tumors, particularly meningioma. In several published studies, meningioma tumors had a high incidence of intraoperative seizures, even in patients who did not undergo MEP monitoring. The low threshold for seizures may be cortical edema and cortex compression, especially if cortex invasion occurs in these tumors. Therefore, a sufficient antiepileptic prophylaxis during MEP monitoring may be especially advisable for patients undergoing surgery for tumors that involve the cortex, such as meningiomas.

### Table 2. Incidence of seizures according to type of surgery

<table>
<thead>
<tr>
<th>Procedure</th>
<th>No. of Cases</th>
<th>No. of Sz</th>
<th>Incidence of Sz (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranial</td>
<td>1633</td>
<td>29</td>
<td>1.2</td>
</tr>
<tr>
<td>Craniotomy</td>
<td>1272</td>
<td>29</td>
<td>2.3</td>
</tr>
<tr>
<td>w TES</td>
<td>850</td>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>w TES + DCS</td>
<td>422</td>
<td>23</td>
<td>5.4</td>
</tr>
<tr>
<td>Interventional neuroradiology</td>
<td>361</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Spine arthrodesis</td>
<td>1664</td>
<td>3</td>
<td>0.2</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>322</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Noncranial interventional radiology</td>
<td>210</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CEA</td>
<td>292</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>4179</td>
<td>32</td>
<td>0.8</td>
</tr>
</tbody>
</table>

It is important to note that in our large series none of the patients displayed noticeable brain swelling after seizure; even in cases of multiple seizures we did not record any adverse brain reaction that required a change in the surgical plan.

### Discussion

MEP monitoring reduces the rate of postoperative motor deficits in spine and brain surgeries by assessing the functional integrity of the motor pathway throughout surgery. Short-train electrical brain stimulation (TES and DCS) is a safe method for evoking MEPs, although induced seizures have been reported.

Legitimate concerns exist about inducing seizures with MEP monitoring, particularly if the patient has had preoperative seizures (related or unrelated to his or her illness), if the seizure is induced by brain stimulation, or if seizures repeatedly occur while MEP monitoring continues. In this review, we address these concerns and provide recommendations for how MEP monitoring should proceed.

To date, the reported incidence of induced seizures after eliciting MEPs by short-train electrical brain stimulation ranges from 0.7% to 4.4%. The published reports were all based on small numbers of patients (45–200), most of whom underwent craniotomy for tumor resection. We monitored 1633 cranial surgeries and interventional procedures. No single induced seizure occurred in the 361 cranial interventional radiology procedures, including angiography and coil or glue embolization. Intraoperative seizures occurred in 29 of 1272 procedures involving craniotomies, for an incidence rate of 2.3%; when craniotomies were stratified by the condition treated, the rates for patients treated for tumors and vascular lesions were 2.8% and 2.1%, respectively. The highest incidence of seizure was found in patients undergoing craniotomy for extracerebral brain tumors, particularly meningioma. In several published studies, meningioma tumors had a high incidence of intraoperative seizures, even in patients who did not undergo MEP monitoring. The low threshold for seizures may be cortical edema and cortex compression, especially if cortex invasion occurs in these tumors.

Therefore, a sufficient antiepileptic prophylaxis during MEP monitoring may be especially advisable for patients undergoing surgery for tumors that involve the cortex, such as meningiomas. Nevertheless, it was beyond our proposed goal to study in detail preoperative factors such as edema in the MRI that could have predicted this higher risk of seizures.

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The reported incidence of intraoperative seizures induced by the short-train technique ranged from 0.7% to 1.5% in patients without a history of preoperative seizures and increased to 1.1%—4.4% in patients with preoperative seizures.

In a recent study, the incidence of intraoperative seizures was compared between a group of 63 patients with a tumor and symptomatic epilepsy and a group of 66 patients with a tumor and without a preoperative history of seizures. Both groups underwent intraoperative electrical brain stimulation using short-train TES for eliciting MEPs. The incidence of stimulation-associated seizures was 1.6% in the group with symptomatic epilepsy versus 1.5% in the group without a preoperative history of seizures. In our study, half of the patients with an intraoperative seizure had a history of preoperative seizures. However, the history of preoperative seizure in the whole group of 4179 patients undergoing MEP monitoring in our study is unknown. Therefore, although calculating the true incidence is impossible, these data still show that the
occurrence of induced seizures in patients with a preoperative history of seizure is very low. Therefore, electrical stimulation can be considered a safe technique, even in patients with preoperative seizures.

The technique used for electrical brain stimulation has the highest impact on the risk of inducing seizures during MEP monitoring. During intraoperative neurophysiological monitoring, the 2 most widespread techniques are Penfield stimulation (50–60 Hz continuous stimulation for 1–4 seconds) and the short-train technique (train of 5 stimuli with an interstimulus interval of 2–4 msec). Penfield stimulation has been shown to have a higher risk for seizure induction. A recent review of both techniques showed that up to 24% of seizures were associated with Penfield stimulation and 1.2% were associated with the short-train technique.25,28,32

In our group of patients undergoing craniotomies, the incidence of seizures was much higher when TES was combined with intermittent DCS (5.4%) than when TES was applied alone (0.7%). In cases in which DCS is combined with TES, it is advisable to reduce the repetition rate of short-train stimuli to 0.4 Hz,33 and the MEPs can be assessed less frequently if the surgery is at a less critical step. When cortical mapping is critical, the repetition rate should be kept at at least 1 Hz despite the risk of seizure.

Most of the patients with an intraoperative seizure in our study experienced 1 (78%) or 2 (16%) seizures. Multiple intraoperative seizures are rare (6.2%). In our group, 2 patients, in Cases 18 and 19, presented 3 and 4 seizures, respectively. They were the youngest of the patients with intraoperative seizures, and they both had a previous history of seizures. Neither of them was being treated with...
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an AED at admission, but both received AED prophylaxis (levetiracetam) in the operating room. The patient in Case 18 was undergoing resection of a frontotemporal recurrent low-grade glioma, and the patient in Case 19 was undergoing resection of a parietal meningioma.

Interestingly, multiple seizures occurred either if electrical brain stimulation was stopped, as in Case 18, or if electrical brain stimulation was not stopped due to surgical need, as in the Case 19. Therefore, based on our data, we are not able to recommend the discontinuation of electrical brain stimulation after the occurrence of the first seizure, and whether stimulation should be discontinued should be determined in consideration of the surgical need for monitoring MEP in each case. However, neither of these 2 patients demonstrated postoperative neurological deficits.

Conclusions

In the present study, we report the incidence of intraoperative seizures in patients who underwent MEP monitoring during different surgical procedures. Our study shows that TES and DCS have a low risk for inducing intraoperative seizures. Patients undergoing craniotomy for extraxial brain tumor resection had the highest risk for developing an intraoperative seizure. Nevertheless, the low incidence of seizures in craniotomies (2.3%) and in spine procedures (0.2%) shows that MEP stimulation is a safe technique with respect to intraoperative seizures and that a concern of seizure induction should not lead to the avoidance of MEP monitoring.

A limitation of the study might be its retrospective nature. It is evident that this study includes a nonselected heterogeneous patient population undergoing different types of surgical procedures. Therefore, our findings demonstrate the safety related to MEP monitoring in general. Even more, information of seizure incidence in certain subgroups like extraxial brain tumors is provided but studies of larger case series related to certain high-risk groups might be necessary to make a definitive statement.

Both TES and DCS stimulation techniques for evoking MEPs have been included in our analysis to provide a general overview of the risk of seizures during electrical brain stimulation. The significant difference of seizure induction between TES used alone and the 2 techniques used in combination is highlighted in Table 2 and is in accordance with previous reports.23 Our study provides the largest overview of nonselected data concerning seizure induction during electrical brain stimulation. It is beyond our goal to make general recommendations on what type of surgery requires MEP monitoring or what type of stimulation should be applied for each surgery. Nevertheless we believe this data may help individual surgeon to make a preoperative risk assessment in every single case.

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

Supplemental Information
Previous Presentations
This study was partially presented as an abstract at the Annual Meeting of the American Association of Neurology (AAN) in San Diego, CA, USA (2013), and at the Meeting of the International Society of Intraoperative Neurophysiology (ISIN) in Cape Town, South Africa (2013).

Author Contributions
Conception and design: Ulkatan, Téllez, Deletis. Acquisition of data: Ulkatan, Jaramillo, Téllez, Seidel. Analysis and interpretation of data: Ulkatan, Jaramillo, Téllez, Seidel. Critically revising the article: Ulkatan, Téllez, Kim, Deletis, Seidel. Drafting the article: Ulkatan, Téllez, Kim, Deletis, Seidel. Approved the final version of the manuscript: Ulkatan, Deletis. Approved the final version of the manuscript on behalf of all authors: Ulkatan.

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