Intraoperative neuromonitoring with MEPs and prediction of postoperative neurological deficits in patients undergoing surgery for cervical and cervicothoracic myelopathy

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Object. The use of intraoperative neurophysiological monitoring (IONM) in surgical decompression surgery for myelopathy may assist the surgeon in taking corrective measures to reduce or prevent permanent neurological deficits. We evaluated the efficacy of IONM in cervical and cervicothoracic spondylotic myelopathy (CSM) cases.

Methods. The authors retrospectively reviewed 140 cases involving patients who underwent surgery for CSM utilizing IONM during 2011 at the University of California, San Francisco. Data on preoperative clinical variables, intraoperative changes in transcranial motor evoked potentials (MEPs), and postoperative new neurological deficits were collected. Associations between categorical variables were analyzed with the Fisher exact test.

Results. Of the 140 patients, 16 (11%) had significant intraoperative decreases in MEPs. In 8 of these cases, the MEP signal did not return to baseline values by the end of the operation. There were 8 (6%) postoperative deficits, of which 6 were C-5 palsies and 2 were paraparesis. Six of the patients with postoperative deficits had demonstrated persistent MEP signal change on IONM. There was a significant association between persistent MEP changes and postoperative deficits (p < 0.001). The sensitivity of intraoperative MEP monitoring was 75%, the specificity 98%, the positive predictive value 75%, and the negative predictive value 98%. Due to higher rates of false negatives, the sensitivity decreased to 60% in the subgroup of patients with vascular disease comorbidity. The sensitivity and positive predictive value of deltoid and biceps MEP changes in predicting C-5 palsy were 67% and 67%, respectively.

Conclusions. The authors found a correlation between decreased intraoperative MEPs and postoperative new neurological deficits in patients with CSM. Sensitivity varies based on patient comorbidities, age, and preoperative neurological function. Monitoring of MEPs is a useful adjunct for CSM cases, and the authors have developed a checklist to standardize their responses to intraoperative MEP changes.

Key Words • neuromonitoring • MEP • cervical spondylotic myelopathy • patient safety

Intraoperative neurophysiological monitoring (IONM) is a rapidly advancing field, and neurophysiological monitoring is becoming prevalent in spinal surgery. Although almost universally employed during spinal deformity surgery, the indications in “lower risk” decompressive procedures are more controversial. The sensitivity of combined-modality monitoring may approach 100%, although sensitivities as low as 43% have been reported. Somatosensory evoked potentials, although advantageous because they can be monitored continuously, rely on signal averaging over time, and decreases may significantly lag behind transcranial MEP changes. Monitoring of MEPs may provide earlier detection of neurological injury and is associated with high sensitivity. However, MEPs cannot be monitored continuously, may induce patient movement, and are negatively affected by inhaled anesthetic agents. Some argue against the use of IONM in cervical decompression altogether. Few studies have focused on the use of IONM in decompressive surgery for myelopathy. In this study, we analyzed a large group of consecutive cases involving patients with CSM (including patients with cervicothoracic myelopathy in addition to those with purely...
cervical myelopathy) who underwent decompressive surgery at a single center over the course of 1 year with the use of MEP.

Methods

Data Collection

Patients were identified by first screening the IONM reports for all operations performed in the University of California, San Francisco, Department of Neurological Surgery from January 1 to December 31, 2011. Hospital records and operative reports of all patients who underwent spine procedures were examined. All patients who underwent cervical or cervicothoracic decompressive operations with IONM for myelopathy due to degenerative spondylosis during that time were included in our study. All patients consented to IONM as part of the surgical informed consent process. Patient demographic data were obtained from hospital and clinic charts. Age was dichotomized into 65 years or more and less than 65 years. Data regarding risk factors for vascular disease were also extracted from hospital charts; the risk factors included morbid obesity, coronary artery disease or history of myocardial infarction, peripheral vascular disease, history of stroke, diabetes, and tobacco use (Table 1). Data on preoperative and postoperative neurological function were extracted from chart documentation of the neurosurgeon’s objective examination, including the MRC validated motor scale, sensory disturbance, and evidence of hyperreflexia or pathological reflexes. To capture postoperative neurological deficits, the hospital chart was reviewed until the day of discharge. In addition, the outpatient clinic charts were also reviewed (mean 6 months). Postoperative neurological deficit was defined as new or worsening motor weakness after surgery. IONM alerts were extracted from the IONM report. A significant MEP alert was defined as an abrupt decrease in peak-to-peak amplitude of more than 50% for more than 3 successive trials over a 1–3 minute period.

IONM MEP Recording

Transcranial MEPs were generated by multipulse transcranial electrical stimulation (0–800 V, 50–75 μsec pulse duration, 0–9 pulses at 1–3 msec) delivered to electrodes placed over motor cortical regions at C3 and C4 using a Cadwell TCS-4 constant voltage transcranial stimulator. Electromyographic responses were recorded from needle electrodes placed bilaterally in the deltoid (axillary nerve, C5–6), biceps (musculocutaneous nerve, C5–7), triceps (radial nerve, C6–8), and thenar and hypothenar eminences of the hand (C8–TI). Waveforms were recorded on a commercially available Cadwell neurophysiology workstation (model Elite or Cascade).

Statistical Analysis

A true positive was defined as presence of an IONM MEP alert during surgery followed by a neurological deficit in the postoperative period. Conversely, a true negative was defined as absence of IONM MEP alerts during surgery and lack of a new neurological deficit after surgery. A false positive was defined as presence of an IONM MEP alert during surgery that was not followed by a neurological deficit. A false negative was defined as absence of IONM MEP alerts during an operation followed by a new neurological deficit. Sensitivity was calculated as true positives/(true positives + false negatives). Specificity was calculated as true negatives/(true negatives + false positives). Positive predictive value was calculated as true positives/(true positives + false positives). Negative predictive value was calculated as true negatives/(true negatives + false negatives). Associations between IONM MEP changes and postoperative new neurological deficits were analyzed with the Fisher exact test. All analyses were performed using PASW Statistics 18.0 software (SPSS, Inc.); p values less than 0.05 were considered statistically significant.

Results

Patient Demographics

During the 1-year study period, 140 patients underwent decompressive surgery with IONM for myelopathy. Their median age was 63 years, and 71% of the patients were
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male. In 54% of cases, T2 signal abnormality was noted on preoperative MR images. All patients had evidence of spinal cord compression on MRI, and 58% had a preoperative motor deficit, defined as less than 5/5 motor function in any single muscle group on the MRC scale. Anterior fusion was performed in 34% of cases, posterior fusion in 34%, laminoplasty in 29%, and laminectomy in 3%.

**Intraoperative MEP Changes and Outcome**

Major IONM MEP alerts were recorded in 16 operations (11%). In 8 cases, the MEP signal did not return to baseline. Overall, 8 patients (6%) experienced new postoperative neurological deficits. Six patients had a C-5 palsy, one had bilateral arm weakness, and one had bilateral leg weakness. In those with postoperative deficits, the median MRC strength was 3/5 (range 1–4). There was a significant association between IONM MEP alerts and the presence of a new postoperative deficit (Table 2, p < 0.001). This corresponds to a sensitivity of 75% and a specificity of 92%. The positive predictive value of IONM MEP alerts was 38%, and the negative predictive value was 98%. Specificity (98%) and positive predictive value (75%) were higher for MEP changes that were not followed by return to baseline (Table 3).

**Vascular Disease Risk Factors, MEP Changes, and Outcome**

We were interested in identifying specific groups of patients who might have higher associations between MEP changes and postoperative deficits. Fifty-five patients (39%) had risk factors for vascular disease. Of these, 17 had coronary artery disease, 19 had diabetes mellitus, 17 used tobacco products, 12 were morbidly obese, and 6 had peripheral vascular disease. Many patients had more than one risk factor. Within this subgroup of patients, there was a higher rate of neuromonitoring changes in those with a postoperative deficit compared with those without one (Table 4, p = 0.001). However, this corresponds to a lower sensitivity (60%) than in the overall patient group. In the remaining patients with no vascular risk factors, the sensitivity was higher (100%).

**Preoperative Motor Deficit, MEP Changes, and Outcome**

Eighty-one patients (58%) presented with a preexisting motor deficit. In this subgroup, MEP changes were significantly associated with new or worsening postoperative motor deficits (Table 4, p < 0.001). The sensitivity was 100% and the specificity was 99%. The positive predictive value was 80%, and the negative predictive value was 100%. In patients who did not have motor deficits before surgery, the sensitivity was lower (50%).

**Changes in Deltoid/Biceps MEP and Postoperative C-5 Palsy**

Changes in deltoid or biceps MEPs were observed in 8 cases. In 6 cases (4%) the MEP signal did not return to baseline by the completion of the operation. There was a significant association between MEP changes without return to baseline and postoperative C-5 palsy (Fig. 1, Table 5, p < 0.001). The sensitivity was 67%, the specificity was 99%, the positive predictive value was 67%, and the negative predictive value was 99%. We also compared the rate of postoperative C-5 palsy in patients who underwent only posterior approaches and those who underwent only anterior approaches. Although there was a trend toward an increased rate of C-5 palsy after posterior-only operations (5.7% vs 2.1% for anterior), it was not statistically significant (p = 0.67).

**Discussion**

Intraoperative neurophysiological monitoring is routinely employed in spine surgery, particularly for procedures involving spinal neoplasms, spinal vascular lesions, and scoliosis correction. Over the past decade, IONM has also been incorporated into surgical procedures involving the cervical spine with increasing frequency. However, there continues to be significant debate regarding its utility in predicting and mitigating postoperative neurological deficits in cervical spine surgery. Considerations against the use of IONM for cervical spine surgery include the additional cost and difficulty interpreting marginal

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**TABLE 2: Contingency table describing the association between IONM MEP alerts at any time during the operation and new postoperative neurological deficits**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MEP Alert</th>
<th>No Alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>16</td>
<td>124</td>
</tr>
<tr>
<td>new motor deficit</td>
<td>6 (38)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>yes (%)</td>
<td>10 (62)</td>
<td>122 (98)</td>
</tr>
</tbody>
</table>

* There was a significant association between MEP alert and new deficit (p < 0.001). Maneuvers were done based on the IONM checklist described by Ziewacz et al. that may have resulted in resolution of some of the alerts.

**TABLE 3: Contingency table describing the association between IONM MEP alerts that persisted until completion of the operation and new postoperative neurological deficits**

<table>
<thead>
<tr>
<th>Variable</th>
<th>MEP Alert</th>
<th>No Alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>8</td>
<td>132</td>
</tr>
<tr>
<td>new motor deficit</td>
<td>6 (75)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>yes (%)</td>
<td>2 (25)</td>
<td>130 (98.5)</td>
</tr>
</tbody>
</table>

* Significant association between MEP alert and new deficit (p < 0.001).
waveform changes.\textsuperscript{12,20} As rising health care costs become a greater focus, minimizing cost while not compromising patient care is critical. Traynelis et al.\textsuperscript{20} performed a retrospective cost analysis of 720 cases in which patients underwent anterior, posterior, or combined anterior-posterior cervical spine surgery without IONM. They concluded that decompression and reconstruction/fusion for symptomatic cervical spine disease without IONM may reduce the cost of treatment without adversely impacting patient safety. Their rationale stemmed from low rates of postoperative deficits (0.4\%) and an estimated additional cost of more than a million dollars in their series of patients who had undergone IONM. A major limitation to their cost analysis was estimating that each procedure required an IONM average of 4 hours; this may be an overestimate for common procedures such as single-level anterior cervical discectomy and fusion, anterior cervical corpectomy and fusion, and laminectomy. In addition, the comparative costs of mitigating future events versus managing postoperative neurological deficits that may have been prevented with IONM are unknown. Based on the study by Traynelis et al.\textsuperscript{20}, the cost of IONM in 2011 based on Medicare billing is $158.33/hour with an additional flat fee of $233.26 and $247.69 for upper- and lower-extremity MEPs, respectively. The cost of neurological injury, particularly spinal cord injury, is extremely high. Ney et al.\textsuperscript{16} recently reported cost-effectiveness data with respect to all spinal surgery and demonstrated a savings of $63,387 per neurological injury averted. However, it has not yet been definitively proven that IONM can help prevent neurological injury during surgery.

There are known limitations to IONM when using SSEPs or MEPs. Multiple nonneurological related factors can affect the waveforms for both of these modalities; among these are blood pressure (mean and diastolic), heart rate, temperature, partial pressure of alveolar carbon dioxide, and anesthetic drugs.\textsuperscript{20} In addition, challenging clinical conditions, such as severe myelopathy, spinal cord tumor,
TABLE 5: Association between IONM MEP alerts in the deltoid and/or biceps without return to baseline and new or worsened C-5 palsy postoperatively*

<table>
<thead>
<tr>
<th>Variable</th>
<th>MEP Alert</th>
<th>No Alert</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>6</td>
<td>134</td>
</tr>
<tr>
<td>new C-5 palsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes (%)</td>
<td>4 (67%)</td>
<td>2 (1.5%)</td>
</tr>
<tr>
<td>no (%)</td>
<td>2 (33%)</td>
<td>132 (98.5%)</td>
</tr>
</tbody>
</table>

* Significant association between MEP alert and new deficit (p < 0.001).

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- Obesity, or peripheral neuropathy, can make interpretation difficult or even impossible. An example presented by Bose et al. involved a patient with preexisting upper-extremity weakness who subsequently developed quadriparesis postoperatively. MEP monitoring was precluded by the use of excessive neuromuscular blockade during the procedure, and the patient’s baseline posterior tibial nerve SSEPs were severely attenuated, precluding reliable monitoring. Additionally, despite relatively high reported rates of sensitivity and specificity for IONM, postoperative neurological deficits may also arise in cases without significant changes in monitoring signals.

- Despite concerns regarding the cost and functionality of IONM, the preponderance of the current literature concentrating on this topic supports the use of IONM, and some authors demonstrated significant benefits in being able to prevent spinal cord injury and/or postoperative neurological deficits. As we have shown in this study, intraoperative decreases in MEPs were significantly associated with new postoperative deficits following cervical decompression for myelopathy. Other studies have also found similar results. Bose et al. and Xu et al. both demonstrated that intraoperative SSEPs and MEP monitoring are useful and correlative techniques for identifying changes in spinal cord function and preventing neurological deficits, respectively. Bose et al. performed a retrospective review of 119 cases involving patients who underwent instrumented anterior cervical spine surgery (the majority of patients had only radiculopathy) and found that neurophysiological alerts were present more often during multilevel decompression. In addition, they noted that certain physiological changes and maneuvers resulted in alerts as well: sudden decreases in blood pressure (detecting hypotensive effects on the spinal cord), unusual arm positioning, and hyperextension of the neck. Xu et al. retrospectively reviewed 57 cases involving patients who underwent anterior cervical discectomy and fusion with SSEP and MEP monitoring. In their series, they emphasized that intraoperative SSEP and MEP monitoring allowed them to immediately make changes in the operative procedure and implement measures that protect the spinal cord (such as maintaining adequate blood pressure and intravenous administration of steroid agents). This occurred in 5% of their patients. Permanent neurological deficits did not develop in any of these patients; however, there was no control group for comparison. The authors suggested that MEP monitoring is an effective modality in anterior cervical spine surgery given the anterior location of the corticospinal tracts and the fact that MEP monitoring relies on these tracts.

- Whereas Bose et al. and Xu et al. concentrated on patients who underwent anterior cervical spine surgery, most of the patients in our cohort underwent posterior decompression. Prior studies suggested that IONM offers significant benefits to patients undergoing posterior cervical spine surgery as well, especially when utilizing MEPS. In our study we found that MEP alerts in the biceps and deltoid distribution were associated with postoperative C-5 palsies. A similar observation was reported in a study by Fan et al. In patients undergoing cervical laminectomy, C-5 palsy is not uncommon given the horizontal exit of the C-5 spinal nerve from the vertebral column and its relatively short length compared with other spinal nerves, both of which make it more susceptible to stretch injuries. Therefore utilization of MEPS in posterior cervical decompression may be beneficial in preventing postoperative deficits, especially C-5 palsies. Our study also included corpectomy and nonfusion (laminoplasty) procedures, which we have previously reported have similar risks of C-5 palsy.

- Overall, significant abnormal alerts occur in 3% to 12% of patients undergoing cervical spine surgery with IONM. This range is likely due to differences in study definitions of an abnormal signal or waveform, which in turn also affect the performance (including sensitivity and specificity) of IONM as a diagnostic test. In addition, the ability to interpret indistinguishable waveforms can be limited because of small amplitudes and poor waveform morphology. This factor also influences the test performance of IONM. Nonetheless, the performance measures for MEP monitoring in conjunction with SSEP monitoring have been reported as high—sensitivity (100.0%), specificity (95.6%), positive predictive value (75.0%), and negative predictive value (100%)—and superior to SSEP monitoring alone.

- While we assessed the utility of using MEPS alone, our results demonstrated a high specificity (92%) and negative predictive value (98%), with 75% sensitivity and a low positive predictive value (38%). Although SSEP monitoring and MEP monitoring are different modalities of IONM, they are commonly used in conjunction with one another. One possibility for the low positive predictive value in our study is that in our institution many steps are undertaken to mitigate possible spinal cord injury following a significant MEP alert, which might possibly have prevented neurological injury. However, there is no control group available for comparison. Studies comparing MEP and SSEP monitoring directly have suggested that MEP monitoring is superior to SSEP monitoring. A study of 427 patients who underwent cervical spine surgery demonstrated that MEP monitoring was able to identify all patients who experienced new postoperative deficit (100% sensitivity) with no false positives (100% specificity). In the same study, the sensitivity for SSEP monitoring was only 25%. Kim et al. reported similar rates of sensitivity and specificity with MEPS among their cohort as well (100% and 90%, respectively). In addition, MEP monitoring may lead to earlier detection of changes than SSEP monitoring, possibly allowing earlier interventions to be implemented.
While there is evidence to suggest that MEP monitoring is superior to SSEP monitoring, other studies have emphasized the importance of utilizing both SSEPs and MEPs in detecting neurological compromise, spinal cord injury, and potential postoperative deficits. In a partially retrospective, partially prospective study of 200 patients who underwent cervical laminectomy and laminoplasty, the authors demonstrated that, with SSEP moni-

Checklist for Neuromonitoring (MEP) Alert in Patients with Myelopathy or Deformity

**Spine Surgeon:**
- Stop current manipulation
- Assess field for structural cord compression (misplaced hardware or bone graft, osteophytes, or hematoma)
- Perform further decompression if stenosis is present
- Consider reversing correction of a spinal deformity

**Neurophysiologist:**
- Repeat trials of MEPs and SSEPs to rule out potential false positive
- Check all leads to make sure no pull-out, may add leads in proximal muscle groups if possible
- Assess the pattern of changes
  - Asymmetric changes (associated with cord or nerve root injury)
  - Symmetric changes (associated with anesthetic or hypotension issues)
- Quantify improvement and communicate to the surgical team

**Anesthesiologist:**
- Check if neuromuscular blockade (muscle relaxant) given
  - If yes, check train of four (TOF)
- Verify that no change in anesthetic administration occurred
- Assess anesthetic depth
  - Blood pressure (BP), heart rate (HR), bispectral index (BIS), mean arterial pressure (MAP)
- Restore or maintain blood pressure (goal mean arterial pressure of 90-100)
- Check Hemoglobin/Hematocrit (goal hemoglobin >9-10)
- Check temperature and I/O’s for adequate resuscitation
- Check extremity position in case of plexus palsy
- Lighten depth of anesthesia
  - Reduce to 1/3 MAC or temporarily eliminate inhaled agents (i.e. desflurane)
  - Reduce intravenous anesthetics such as propofol (which may accumulate systemically during the case and blunt MEPs)
  - Add adjuvant agents such as Ketamine to permit reduction of MEP suppressive agents (i.e. propofol and inhalational anesthetics)

**IF No Change:**
- Increase MAP >100
- Consider Steroid Administration
- Consider Wake-up test
- Consider Aborting surgery
- Consider Calcium Channel Blocker (topical to cord or iv)

*The checklist assumes baseline anesthetic regimen is 1/3-1/2 MAC of halogenated anesthetic (desflurane) and TIVA (total intravenous anesthesia) with propofol +/- ketamine.

FIG. 2. Checklist for the response to an IONM alert. BIS = bispectral index; BP = blood pressure; HR = heart rate; I/O = input/output; iv = intravenous; MAC = minimum alveolar concentration; MAP = mean arterial pressure; RR = respiration rate. Reproduced with permission from Ziewacz et al: Neurosurg Focus 33(5):E11, 2012.
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nting alone, 6 of 6 patients who developed C-5 palsy experienced this complication despite unremarkable SSEP monitoring.\textsuperscript{11} However, when they prospectively added in MEP monitoring with SSEP monitoring, 2 of 2 cases of postoperative C-5 palsy were accurately predicted. In addition, a prospective study of 1055 patients who underwent cervical spine surgery of any type with SSEP (± MEP) monitoring concluded not only that IONM is helpful in predicting and preventing neurological deficit, but also that utilizing combined IONM methods can increase sensitivity significantly.\textsuperscript{13} Although our study focused on MEPs alone, the best modality, or combination of modalities remains to be determined.

A principal finding from this study was that diagnostic performance of MEP monitoring depended on certain risk factors among patients. Patients with vascular risk factors had low MEP sensitivity (60%), but in patients without vascular disease the sensitivity was 100%. In addition, MEP monitoring in patients older than 65 years had a sensitivity of 100%, specificity of 98%, positive predictive value of 80%, and negative predictive value of 100%. Other reported risk factors that influence MEP monitoring performance, including obesity and increased length of surgery, may result in false positives.\textsuperscript{12} Therefore, selecting patients who may benefit most from MEP monitoring will likely result in higher sensitivity and specificity, while partly mitigating the increase in cost.

A potential advantage of utilizing IONM—based on SSEPs, MEPs, or both—is to adequately implement immediate actions to prevent spinal cord injury and postoperative neurological deficits in the event of a significant monitoring change. In this light, based on a large retrospective study of 1445 cases, Lee et al.\textsuperscript{14} recommended the following when an IONM alert is encountered: reverse any antecedent surgical event (for example, distraction or neck extension), maintain mean arterial blood pressure between 85 and 95 mm Hg, and if there is a partial or complete return of IONM signal within 20 minutes to continue on with surgery. If the waveform does not return to baseline in the setting of an unstable spine, then continue with surgery, or if the spine is deemed stable, perform an awake clinical examination to determine whether to continue surgery. Ziewacz et al.\textsuperscript{22} recently proposed an evidence-based checklist (Fig. 2) for the response to significant IONM alerts in spine surgery. The effect of checklist usage during cervical spine surgery is currently being evaluated at our institution. First, however, the utility of IONM in cervical spine surgery must be established, ideally in the setting of a prospective randomized controlled clinical trial.

Conclusions

The use of IONM is increasing in cervical spine surgery. The findings from this study demonstrated a correlation between a decrease in intraoperative MEPs and new postoperative neurological deficits in cervical or cervicothoracic myelopathy cases. The performance of MEP monitoring as a diagnostic test varies based on risk factors such as patient comorbidities, age, and preoperative neurological function. We found that the sensitivity of MEP monitoring is higher in certain subgroups. Specifically, the sensitivity is increased in patients without vascular risk factors. Sensitivity is also increased in those aged 65 years and older as well as those with preoperative neurological deficits.

Disclosure

Dr. Chou reports being a consultant for Globus, DePuy, Medtronic, and Orthofix. Dr. Ames reports being a consultant for DePuy, Medtronic, and Stryker; holding a patent with Fish & Richardson, P.C.; grants/pending grants from and stock/stock options in Trans1; receiving royalties from LANX and Aesculap; and having stock/stock options in Visualase and Doctors Research Group. Dr. Mummaneni reports honoraria and royalties from DePuy Spine, honoraria from Globus, and royalties from Thieme Medical Publishers and Quality Medical Publishing.

Author contributions to the study and manuscript preparation include the following. Conception and design: Mummaneni, Clark, Lyon. Acquisition of data: Mummaneni, Clark, Safaee, Lyon, Chou, Weinstein, Ames, Clark. Analysis and interpretation of data: Mummaneni, Clark, Ziewacz, Safaee, Lyon, Chou, Clark. Drafting the article: Mummaneni, Clark, Ziewacz, Clark. Critically revising the article: Mummaneni, Clark, Ziewacz, Safaee, Lau, Chou, Weinstein, Ames. Reviewed submitted version of manuscript: all authors. Statistical analysis: Mummaneni, Clark, Ziewacz. Administrative/technical/material support: Mummaneni, Chou, Weinstein, Ames, Clark. Study supervision: Mummaneni.

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