Transcranial motor-evoked potentials for prediction of postoperative neurologic and motor deficit following surgery for thoracolumbar scoliosis

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Abstract
Transcranial motor-evoked potentials (TcMEPs) are used to monitor the descending motor pathway during scoliosis surgery. By comparing potentials before and after correction, surgeons may prevent postoperative functional loss in distal muscles. There is currently no consensus as to which muscles should be monitored. The purpose of this study is to determine the least invasive monitoring protocol with the best localization of potential neurologic deficit. A retrospective review of 125 patients with TcMEP monitoring during surgery for thoracolumbar scoliosis between 2008 and 2015 was conducted. 18 patients had postoperative neurologic deficit due to surgery. The remaining 107 patients were a consecutive cohort without postoperative neurologic consult. TcMEPs were recorded from vastus lateralis (VL), tibialis anterior (TA), peroneus longus (PL), adductor hallucis (AH) and abductor pollicis brevis (APB) bilaterally. The effectiveness of each muscle combination was evaluated independently and then compared to other combinations using Akaike Information Criterion (AIC). Monitoring of VL, TA, PL, and AH yielded sensitivity of 77.8% and specificity of 94.4% (AIC=62.4). Monitoring of VL, TA and PL yielded sensitivity of 72.2% and specificity of 93.5% (AIC=70.1). Monitoring of TA and PL yielded sensitivity of 72.2% and specificity of 96.3% (AIC=63.9). TcMEP monitoring of TA, PL, and AH provided the highest sensitivity and specificity and best predictive power for postoperative lower extremity weakness.

Introduction
Intraoperative neurophysiological monitoring is used to identify acute footdrop and other neurologic deficits during spine surgery. The field of intraoperative neurophysiological monitoring has altered the management of spine surgery by providing real-time data on perioperative neurologic function to spinal surgeons.1 As the field of intraoperative neurologic monitoring has evolved, the use of transcranial motor-evoked potentials (TcMEPs) to monitor the functionality of the descending motor pathway has become more common during these spinal procedures.1 By analyzing the morphological changes of motor-evoked potentials (MEPs) following electric stimulation, it is possible to assess the ability of the spinal cord and corresponding nerve roots to carry an electrical impulse from the brain to the muscle in question.2 TcMEPs demonstrate a decrease in amplitude if the spinal cord is injured or altered in the thoracic spine, and will also reflect compression or stretching of nerve roots in the lumbar spine.3 This technique is used during the correction of thoracolumbar deformities,4 as well as other procedures involving spinal instrumentation.2 At present, there is not a consensus as to which muscles should be monitored during surgical correction of spinal deformity. In the vast majority of cases, muscles are chosen based on the spinal levels of operation. However, in thoracolumbar scoliosis cases, correction can involve the majority of the spine, making the collection of MEPs from all corresponding levels cumbersome as well as redundant. With this in mind, different groups are proposed to monitor different combinations of muscles in the lower extremities.4,5,6 Ultimately, the most effective combination of muscles would allow for accurate identification of spinal cord injury while limiting false positives.6,7 Further, it would do so using the fewest possible muscles to limit setup time as well as the cost of materials needed for intraoperative TcMEP analysis.8

Materials and Methods
A retrospective cohort study was designed to evaluate the efficacy of various muscle combinations in predicting postoperative neurologic deficit in patients receiving surgery for thoracolumbar scoliosis.

Patient demographics
127 patients undergoing a thoracolumbar spinal fusion procedure with MEP monitoring at a single institution were retrospectively selected for this study in accordance with IRB approval. Patients ranged in age from five to 79 years old. Eighteen patients were selected based on their presentation with a postoperative neurologic deficit that was not present prior to surgery. Fifteen of these patients were found to have specifically motor deficits that presented as focal lower extremity weakness (Table 1). Separate analyses were performed for the entire neurologic deficit cohort and for the subset of those with motor deficits.

Inclusion criteria for patients with neurologic deficit included their having undergone a postoperative neurologic consultation from an attending neurologist who confirmed their deficit through physical exam. MEP attenuation, although noted and evaluated by the monitoring physician, did not meet criteria for inclusion in the study. The
eighteen patients mentioned previously represent the entire cohort satisfying the above conditions between 2008 and 2015. The intraoperative monitoring records were obtained for each, and the MEPs were analyzed. The remaining 107 patients did not present with postoperative neurologic deficit and were included as a control group. These control patients represent a consecutive cohort of patients receiving thoracolumbar scoliosis surgery at this single institution in 2015. Their MEP data were analyzed in the same manner.

Patient selection
Patients were evaluated prior to surgery to ensure that transcranial electric stimulation was appropriate. Exclusionary criteria included the presence of cochlear implants, intracranial implants or electrodes and aneurysm clips. Additionally, patients with histories of brain surgery, skull fracture or seizures were carefully evaluated and screened prior to stimulation.

Cranial stimulation
MEPs were obtained utilizing Transcranial Electric Stimulation. Needle electrodes were placed above the motor cortex at locations approximately 2 cm anterior to C3 (anode) and C4 (cathode). Needles measured 13 mm long and 0.4 mm in diameter. A constant voltage of between 300 and 500 volts was applied across these needles using Transcranial Electrical Stimulators (TCS-4) (Cadwell: Kenwick, WA).

Stimulation parameters
Pulses were run in two trains of four pulses each and measured in duration from 50 to 75 microseconds. Inter-train intervals measure 20 milliseconds and inter-stimulus intervals measured 2.5 milliseconds. MEPs were acquired every 10-15 minutes during critical parts of the surgery, including decompression, instrumentation and correction. During less critical periods (as judged by the neuromonitoring technician), MEPs were acquired less frequently and at the discretion of the surgeon and neuromonitoring technician.

MEP Acquisition
Measures of motor evoked potentials were obtained from four different muscles in the legs and feet including vastus lateralis (VL), tibialis anterior (TA), peroneus longus (PL), and abductor hallucis (AH). As a control to identify systemic changes due to anesthesia, motor evoked potentials were also recorded at abductor pollicis brevis (APB)\(^\text{11}\) for a total of five muscles monitored. Two needle electrodes identical to those used in the transcranial stimulation were placed at each muscle location at a distance of no more than 3cm apart. Needles were inserted at angles of 45° to the horizontal and secured using medical tape (3M: St. Paul, MN).

**MEP Interpretation**
Interpretation of motor evoked potentials was performed by the attending neurologists at this single institution. Baseline measures were obtained prior to incision at which time appropriate stimulation parameters were determined. The “train of four” response\(^\text{12}\) was monitored to assess the effect of neuromuscular blockade given at intubation on the generation of MEPs. Patients included in this study were those whose baseline MEPs were polyphasic in appearance and sufficient in amplitude to confirm their presence and gauge intraoperative changes.

MEP loss was classified as a decrease in complexity and amplitude of a given signal when compared to these baseline measures.\(^\text{4}\) Episodes were deemed to be “MEP losses” only if signals did not return to baseline levels by the end of the case. Constant contact was maintained with the attending anesthesiologists to record and incorporate the doses of anesthetic and neuromuscular blocking agents into analysis. The effects of anesthesia and of fluctuating blood pressure were therefore taken into account when interpreting MEP losses. Each episode was analyzed individually.

APB was used as a control muscle to identify MEP changes due to the systemic effects of anesthesia.\(^\text{11}\) It was assumed that if evoked potentials were seen to decrease in amplitude in APB, that the losses in APB as well as any other lower extremity muscles were likely due to the systemic effects of anesthesia. This was based on the fact that the cervical spinal cord was not manipulated in any of the procedures included in this study, and that therefore none of the surgeries would implicate a mechanism by which the neural pathway from the motor cortex to APB could have been physically compromised. With this in mind, the use of MEPs to assess spinal cord function in the instances in which APB signals were lost was deemed inappropriate. Thus, the two patients in whom APB signals were lost were eliminated from our analyses, leaving us with 125 patients.

**MEPs as predictors of postoperative neurologic deficit and postoperative motor deficit**
Patients with postoperative neurologic deficit were identified by the request for a postoperative neurologic consult. Neurologic consult documentation was reviewed by the neurologist to confirm that the observed intraoperative MEP losses reflected the specific postoperative neurologic deficits seen in the patients. Our final sample consisted of 125 patients, eighteen of whom presented with postoperative neurologic deficit and 107 of whom did not. Of the eighteen patients with postoperative neurologic deficit, fifteen were found to have a motor deficit. This yielded an alternative breakdown of the 125 patients cohort – fifteen patients with postoperative motor deficit and 110 patients without.

Four different muscle combinations were analyzed in each of these patients. The combinations were as follows:
- VL, TA, PL, AH
- VL, TA, PL
- TA, PL, AH
- TA, PL

These combinations were determined based on common practice and the anatomical contribution of each muscle to lower extremity motor function.\(^\text{4,6,7}\) MEPs were considered successful predictors of postoperative neurologic deficit when there was either neither an intraoperative loss nor a postoperative consult, as well as when an intraoperative loss was followed by a postoperative consult. MEPs were considered unsuccessful when a patient with an observed loss did not receive a postoperative consult and when an intraoperative loss was not observed prior to a postoperative consult. These same criteria applied to determining the success of MEPs in predicting postoperative motor deficit, except that the patients with motor deficits were considered to be those sixteen patients who pre-

| Neuro deficit | Postop Deficit (N=18) | No Deficit (N=107) | P-value |
|---------------|-----------------------|-------------------|---------|
| Age (years)   | 41.4                  | 43.5              | 0.74    |
| Gender (% female) | 83.3              | 65.4              | 0.18    |
| Levels instrumented | 13.8              | 11.9              | 0.06    |

| Motor deficit | Postop Deficit (N=18) | No Deficit (N=107) | P-value |
|---------------|-----------------------|-------------------|---------|
| Age (years)   | 40.7                  | 43.6              | 0.64    |
| Gender (% female) | 86.7              | 65.4              | 0.14    |
| Levels instrumented | 14.4              | 11.9              | <0.05   |

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sented with postoperative lower extremity weakness specifically.

Statistical methods
Differences in demographics between patients with and without postoperative deficit were tested using chi-square test for categorical variables, and Student’s t-test for continuous variables. Sensitivity and specificity were calculated to determine the efficiency of each individual muscle combination. The Akaike Information Criterion (AIC) was then calculated to compare the different muscle combinations. Lower AIC values were indicative of more effective muscle combinations. Analysis was conducted for patients with postoperative neurologic deficit and then separately for the more specific subset of patients with postoperative motor deficit. Statistical significance was set at P<0.05. All statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC).

Results
Postoperative neurologic deficit
Of the eighteen patients who received a postoperative neurologic consult for lower extremity weakness, fifteen showed an attenuation or complete loss of lower extremity MEPs that did not resolve by the end of their procedures (sensitivity = 15/18 = 83.3%). Additionally, 99 of the 107 patients with intact neurologic function showed no change in MEPs from their measured baselines (specificity = 99/107 = 92.5%).

Descriptive analysis
There was no observed difference in age between those with deficit and those without deficit (41.4 years vs. 43.5 years, P=0.74). Additionally, our data revealed no difference in gender between those with and without deficit (83.3% female vs. 65.4%, P=0.18) and the number of levels that were instrumented (13.8 vs. 11.9, P=0.06) (Table 1).

Diagnostic analysis
Monitoring of VL, TA, PL, and AH for patients with postoperative neurologic deficit yielded a sensitivity of 77.8% and specificity of 92.5% for postoperative neurologic deficit. Monitoring of VL, TA, and PL yielded a sensitivity of 72.2% and specificity of 93.5%. TA, PL and AH yielded a sensitivity of 77.8% and specificity of 94.4%. Monitoring of TA and PL yielded a sensitivity of 72.2% and specificity of 96.3% (Table 2).

The Akaike Information Criterion (AIC) was then used to further evaluate the effectiveness of each muscle combination. Monitoring of VL, TA, PL, and AH yielded an AIC of 66.7. VL, TA, and PL yielded an AIC of 69.1. TA, PL and AH yielded an AIC of 62.4. Monitoring of TA and PL yielded an AIC of 63.9 (Table 2).

Postoperative motor deficit
Fourteen of the fifteen patients with postoperative motor deficits showed a loss of MEPs (sensitivity = 14/15 = 93.3%) while 102 of the 110 patients with intact motor function showed no change in their MEPs (specificity = 102/110 = 92.7%).

Descriptive analysis
There was no observed difference in age between those with deficit and those without deficit (40.7 years vs. 43.6 years, P=0.64). Again, there was no observed difference in gender (86.7% female vs. 65.4%, P=0.14). In this cohort, there was a significant difference between the number of instrumented spinal levels (14.4 vs. 11.9, P<0.05) (Table 1).

Diagnostic analysis
Monitoring of VL, TA, PL, and AH for postoperative motor deficit yielded a sensitivity of 93.3% and specificity of 92.7%. Monitoring of VL, TA, and PL yielded a sensitivity of 86.7% and specificity of 93.6%. TA, PL and AH yielded a sensitivity of 93.3% and specificity of 94.5%. Monitoring of TA and PL yielded a sensitivity of 86.7% and specificity of 96.4% (Table 2).

The Akaike Information Criterion (AIC) was then used to further evaluate the effectiveness of each muscle combination. Monitoring of VL, TA, PL, and AH yielded an AIC of 44.1. VL, TA, and PL yielded an AIC of 49.7. TA, PL and AH yielded an AIC of 39.7. Monitoring of TA and PL yielded an AIC of 42.5 (Table 2).

Table 2. Motor-Evoked Potentials analysis for postoperative deficit cohort.

| Patient Code | Levels | Reason for consult request | Postop Neuro Deficit (Y/N) | Postop Motor Deficit (Y/N) | MEP Loss (Y/N) |
|--------------|--------|----------------------------|-----------------------------|-----------------------------|----------------|
| 1            | 13     | B LE weakness              | Y                           | Y                           | Y              |
| 2            | 15     | B LE weakness              | Y                           | Y                           | Y              |
| 3            | 7      | B LE weakness              | Y                           | N**                         | N              |
| 4            | 7      | L LE weakness              | Y                           | Y                           | Y              |
| 5            | 16     | R LE weakness              | Y                           | Y                           | Y              |
| 6            | 9      | R LE weakness              | Y                           | N**                         | N              |
| 7            | 15     | R distal LE weakness       | Y                           | Y                           | Y              |
| 8            | 18     | L LE weakness              | Y                           | Y                           | Y              |
| 9            | 15     | L LE weakness              | Y                           | Y                           | Y              |
| 10           | 15     | B LE weakness              | Y                           | Y                           | Y              |
| 11           | 17     | B LE weakness              | Y                           | N***                        | N              |
| 12           | 8      | B LE weakness              | Y                           | Y                           | Y              |
| 13           | 14     | R LE weakness              | Y                           | Y                           | Y              |
| 14           | 17     | B LE weakness              | Y                           | Y                           | Y              |
| 15           | 18     | B LE weakness              | Y                           | Y                           | Y              |
| 16           | 18     | B LE weakness              | Y                           | Y                           | Y              |
| 17           | 7      | B LE weakness              | Y                           | Y                           | Y              |
| 18           | 18     | B LE weakness              | Y                           | Y                           | Y              |
Discussion and Conclusions

The results of this investigation support the use of intraoperative transcranial motor-evoked potentials to predict postoperative neurologic deficit as well as postoperative motor deficit. With evaluation of APB used to discern systemic effects of anesthesia from those related to surgical manipulation, the monitoring of tibialis anterior, peroneus longus and abductor hallucis was determined to be the most effective group of muscles in predicting these deficits. This combination yielded the highest combined sensitivity and specificity scores as well as the lowest AIC in both the neurologic deficit and motor deficit cohorts.

The addition of vastus lateralis to the previously mentioned muscle combination improved sensitivity while lowering specificity. The increased specificity is explained simply by the fact that the addition of any muscle in the lower extremity would likely improve the ability of TcMEP monitoring to detect lower extremity weakness. However, the decline in specificity makes this combination less effective. TcMEP monitoring of vastus lateralis is difficult based on the length of the needle electrodes and the subcutaneous fat present superficial to the muscle tissue. The needles used in this study were 13 mm in length and thus were likely not long enough to pierce through the adipose tissue and implant within the vastus lateralis of overweight patients. Potentials observed in vastus lateralis are therefore less consistent and ultimately less reliable.

MEPs are better suited to predict postoperative motor deficit than postoperative neurologic deficit. This can be explained anatomically by the fact that MEPs monitor the function of the corticospinal tract and resultant motor function. Neurologic injury can also be the result of an intervention in the communication of afferent sensory information along the posterior columns. With this in mind, intraoperative neurophysiological monitoring should include somatosensory-evoked potential monitoring (SSEPs) as well as MEP monitoring.15,14

The use of APB to assess the intraoperative validity of lower extremity MEP monitoring has become common practice and is outlined in the current guidelines published by the American Clinical Neurophysiology Society.11 The two cases that were excluded from these analyses based on the bilateral loss of MEPS in APB each showed multiple MEP losses in lower extremity muscles as well. Thus, without APB monitoring, these losses of lower extremity MEPs would have been identified as the result of surgical manipulation. However, neither of these two patients showed a postoperative neurologic deficit. As such, the loss of APB successfully indicated that the use of lower extremity MEPs to assess spinal cord function was invalid and helped us to exclude two cases that would have otherwise been considered false positives.

The descriptive analyses revealed a number of interesting trends and findings that deserve further investigation in the future. First, there was a trend toward more women than men experiencing both postoperative neurologic deficit as well as the more specific postoperative motor deficit. Prior research has shown that women are more likely than men to experience complications after spinal deformity surgery.13 However, there has not been research done into the impact of gender on neurologic complications following surgery for spinal deformity. We also observed a trend toward significance in the difference in number of levels receiving instrumentation between the patients who experienced postoperative neurologic deficit and those who did not. This difference became statistically significant when comparing those patients with and without postoperative motor deficit. In both cases, patients with postoperative deficits had more levels of instrumentation. More complex spine surgeries have been shown to result in higher rates of complication.14 It stands to reason that placing instrumentation in more spinal levels provides more opportunity for injury to the spinal cord and thus, would result in higher rates of postoperative neurologic and motor injury. This finding would benefit from future investigation as well.

This study is not without its limitations. We elected to include only cases in which persistent MEP losses were observed that did not resolve by the conclusion of surgery. In many cases, MEPs from lower extremity muscles were temporarily lost or physiologically attenuated but ultimately returned. These losses and resolutions can be due to spontaneous recovery or come as a result of a surgical intervention after communication between the surgeon and neurophysiology technician.17 As it was not possible to intraoperatively corroborate MEP losses with clinical evidence, these instances were not included in our analyses. While these losses may not be clinically significant, they are often tangible examples of the utility of neurophysiologic monitoring – a MEP loss is identified, the surgeon is informed, and an intervention is made that restores the previously compromised neurologic pathway. With this in mind, the utility of MEP monitoring to identify and help correct intraoperative spinal cord injury is likely better than is suggested by these data. We propose that more widespread use of MEP monitoring is highly relevant to incidence of perioperative motor deficit. The alternative, a Stagnara wake-up test, requires waking a patient during surgery and asking him or her to move his or her feet on command.14 This test does not have the benefit of continual assessment of neural function and prolongs the time of surgery. In addition, the timing of the test is less likely to allow for intervention as close as possible to the time of injury.

We conclude that MEP monitoring is an essential tool in intraoperative neurophysiologic monitoring to influence the outcome of postoperative neurologic and motor deficits. The technique used in this research to evaluate and identify the muscle combinations is most useful to a number of different spine surgeries, including those performed on pediatric patients, as well as deformities specific to the cervical, thoracic or lumbar spines. We hope that through further refinement and careful localization of these chosen muscles, the ability of the monitoring physician to identify a neurologic deficit with a timing that may influence the outcome may ultimately improve preservation of neurologic function.

References

1. Péréon Y, Bernard J-M, Fayet G, et al. Usefulness of neurogenic motor evoked potentials for spinal cord monitoring findings in 112 consecutive patients undergoing surgery for spinal deformity. Electroencephalogr Clin Neurophysiol 1998;108:17-23.
2. Calancie B, Harris W, Broton JG, et al. “Threshold-level” multipulse transcranial electrical stimulation of motor cortex for intraoperative monitoring of spinal motor tracts: description of method and comparison to somatosensory evoked potential monitoring. J Neurosurg 1998;88:457-70.
3. Lieberman JA, Lyon R, Feiner J, et al. The efficacy of motor evoked potentials in fixed sagittal imbalance deformity correction surgery. Spine (Phila Pa 1976) 2008;33:E414-24.
4. Langelo DD, Lelivelt A, Journée HL, et al. Transcranial electrical motor-evoked potential monitoring during surgery for spinal deformity: a study of 145 patients. Spine (Phila Pa 1976) 2003;28:1043-50.
5. MacDonald DB, Al Zayed Z, Al Saddigi A. Four-limb muscle motor evoked potential and optimized somatosensory evoked potential monitoring with
decussation assessment: results in 206 thoracolumbar spine surgeries. Eur Spine J 2007;16:171-87.
6. Novak K, Widhalm G, de Camargo AB, et al. The value of intraoperative motor evoked potential monitoring during surgical intervention for thoracic idiopathic spinal cord herniation. J Neurosurg Spine 2012;16:114-26.
7. Valone F, Lyon R, Lieberman J, Burch S. Efficacy of transcranial motor evoked potentials, mechanically elicited electromyography, and evoked electromyography to assess nerve root function during sustained compression in a porcine model. Spine (Phila Pa 1976) 2014;39:E989-93.
8. Ito Z, Matsuyama Y, Ando M, et al. What Is the Best Multimodality Combination for Intraoperative Spinal Cord Monitoring of Motor Function? A Multicenter Study by the Monitoring Committee of the Japanese Society for Spine Surgery and Related Research. Glob Spine J 2016;6:234-41.
9. Kim DH, Zaremski J, Kwon B, et al. Risk factors for false positive transcranial motor evoked potential monitoring alerts during surgical treatment of cervical myelopathy. Spine (Phila Pa 1976) 2007;32:3041-6.
10. Lall RR, Lall RR, Hauptman JS, et al. Intraoperative neurophysiological monitoring in spine surgery: indications, efficacy, and role of the preoperative checklist. Neurosurg Focus 2012;33:E10.
11. Legatt AD, Emerson RG, Epstein CM, et al. ACNS Guideline: Transcranial Electrical Stimulation Motor Evoked Potential Monitoring. J Clin Neurophysiol 2016;33:42-50.
12. Gavranč B, Lolis A, Beric A. Train-of-Four Test in Intraoperative Neurophysiologic Monitoring. J Clin Neurophysiol 2014;31:575-9.
13. Nuwer MR, Dawson EG, Carlson LG, et al. Somatosensory evoked potential spinal cord monitoring reduces neurologic deficits after scoliosis surgery: results of a large multicenter survey. Electroencephalogr Clin Neurophysiol 1995;96:6-11.
14. Nuwer MR, Emerson RG, Galloway G, et al. Evidence-based guideline update: intraoperative spinal monitoring with somatosensory and transcranial electrical motor evoked potentials. J Clin Neurophysiol 2012;29:101-8.
15. Kothari P, Lee NJ, Leven DM, et al. Impact of Gender on 30-Day Complications After Adult Spinal Deformity Surgery. Spine (Phila Pa 1976) 2016;41:1133-8.
16. Bekelis K, Desai A, Bakhoum SF, Missios S. A predictive model of complications after spine surgery: the National Surgical Quality Improvement Program (NSQIP) 2005-2010. Spine J 2014;14:1247-55.
17. Pelosi L, Lamb J, Grevitt M, et al. Combined monitoring of motor and somatosensory evoked potentials in orthopaedic spinal surgery. Clin Neurophysiol 2002;113:1082-91.
18. Vauzelle C, Stagnara P, Jouvinroux P. Functional monitoring of spinal cord activity during spinal surgery. Clin Orthop Relat Res 1973:173-8.