구 용 서
고려대학교 안암병원 신경과

Special Issues : Evidence-based INM

Yong Seo Koo
Department of Neurology, Korea University Medical Center, Anam Hospital

Over the past years, the role of intraoperative neurophysiologic monitoring (INM) has grown from its research purpose to a practice standard for surgery which might involve the risk of neural injury. Although INM is not widely used in South Korea as in United States, there is an exploding interest in INM currently. However, some surgeons are still reluctant to use INM. Although many experts in INM believe that the evidence of INM is sufficient enough to preclude further study, some do not agree. Therefore, current status of evidence-based INM is discussed in this lecture.

Key Words: Intraoperative neurophysiologic monitoring, Evidence-basd medicine, voked potentials

Introduction

The objective of intraoperative neurophysiologic monitoring (INM) is to prevent patients from neurological complications of various procedures including spinal surgery, surgeries of the aorta, thyroid surgery, and brain surgery. In United States, the cases of INM increased drastically over three decades[1] and there is not enough man power to cover the demand for INM.[2]

Many experts in INM believe that there is sufficient evidence that INM is both accurate in diagnosing neurological injury and effective in preventing the injury.[3-7] Having published the best evidence available on the use of evoke potentials during spinal operations,[3] most of the authors believed "clinical experience and animal experiments establish unequivocally that IOM warns of spinal cord injury, and interventions reverse impairment and prevent paraplegia."[5] They even harshly criticized those who questioned the evidence of INM's effectiveness in preventing neurological injury by considering the questioners as having "a lack of familiarity with and understanding of the full literature", precluding the need for further evidences or studies. However, one of the authors of the article agreed on the questioners' opinion and suggested that it is both "reasonable to use INM" and to perform further studies such as "a randomized trial to determine whether INM really helps patients".

INM is a rapidly growing field in South Korea. However, some surgeons are still reluctant to use INM due to its additional cost and sometimes do not respond to INM alert due to stress and time pressure.[8] Others even tried to insist that the evidence is against INM, showing high prevalence of complications in surgery with INM than in surgery without INM[9] and no significant neurologic injuries after surgery without INM.[10] However, the interpretations in these articles seems to be problematic.[2,5] As INM professionals, it is our responsibility to tell possible risks and benefits of the monitoring to the patients and to

Yong Seo Koo, MD, PhD
Department of Neurology, Korea University Medical Center, Anam Hospital, 73 Inchon-ro, Seongbuk-gu, Seoul 02841, Korea
TEL: +82-2-920-6276 FAX: +82-2-925-2472
E-mail: yo904@naver.com

respect the right of every patient to self-determination.[11]

In this lecture, the basics of evidence-based medicine (EBM) is discussed first, followed by the current status of evidence in INM and the necessity for future studies. At the end of this lecture, the audience should be able to understand INM in the context of EBM.

What is EBM?

Definition of EBM

EBM is defined as the "conscientious, explicit and judicious use of current best evidence in making decisions about individual patients", which means "integrating individual clinical expertise with the best available external clinical evidence from systematic research".[12]

The complete practice of EBM comprises five steps.[13]

Step 1: converting the need for information (about prevention, diagnosis, prognosis, therapy, causation, etc.)

Step 2: tracking down the best evidence with which to answer that question

Step 3: critically appraising that evidence for its validity (closeness to the truth), impact (size of the effect), and applicability (usefulness in our clinical practice)

Step 4: integrating the critical appraisal with our clinical expertise and with our patient's unique biology, values and circumstances

Step 5: evaluating our effectiveness and efficacy in executing steps 1-4 and seeking ways to improve them both for next time.

Since the objective of this review is to review current

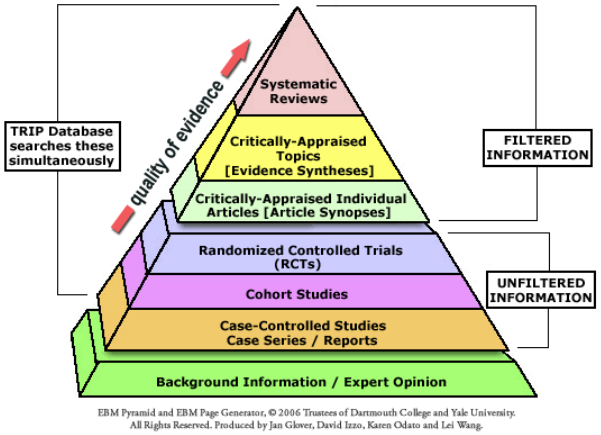

Figure 1. An example for a hierarchy of evidence[15]

Table 1. The Oxford 2011 Levels of Evidence[16]

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

evidence-based INM, we will consider only Step 1-3.

There are two fundamental principles of EBM.[14]

The first one is a hierarchy of evidence as shown in Figure 1.

This hierarchy of evidence might differ according to the types of questions as shown in Table 1.

The second one is that evidence alone is never sufficient to make a clinical decision. Decision must be based on the benefits and risks, inconvenience, and costs associated with alternative management strategies as well as the patients' values and preferences.

For details of EBM, those interested are referred to textbooks.[13,14]

Monitoring therapeutic interventions in clinical practice

Monitoring can be used in five different phases: pre-treatment, initial titration, maintenance, re-establish control, and cessation.[17] For example, monitoring is commonly used in chronic conditions such as blood pressure, Hb_{A1c}, cholesterol level, thyroid hormones, FEV1, and drug levels.

Although monitoring seems to be useful at any time, a monitoring should be accurate and simple, guide a strategy for achieving target, and improve patient outcome. Monitoring differs from both screening and intervention and can be justified by the following three criteria.[18]

1. Clinically significant changes in the condition or effect of treatment occur over time.

2. There is an available monitoring test that reliably detects clinically significant changes when they occur.

3. Cost-effective action can be taken on the basis of the test result.

Examples of other fields which considered monitoring or diagnostic testing

There are many examples of studies which changed the practice long believed to be useful by introducing evidence-based medicine.

Application of EBM in the field of INM

Step 1: Defining the questions

Since we reviewed the general principles of evidence-based medicine, we will apply these principles in the field of INM. Although the name of INM implies that it is a diagnostic test, the objective of INM seems to indicate that it is an intervention.[8] Since the hierarchy of evidence differs according to the type of question, we need to define whether INM is diagnostic test or an intervention.

INM as a diagnostic test

- If we consider INM as a diagnostic, we can ask the following question: "Does INM accurately diagnose neural injury in the patients who receive surgery or procedure?"
- According to the Oxford 2011 Levels of Evidence (Table 1), the level 1 evidence for a diagnostic test is systemic review of cross-sectional studies with consistently applied reference standard and blinding.
- There is one major problem in considering INM as a diagnostic test; there is no real time reference standard in the event of INM signal loss.[8] Since INM is only a physiologic or surrogate marker for neural injury at a specific time, the INM change during surgery without postoperative normal neurological function is not considered as "false positive". Even if we find INM change and then try wake-up tests, this still faces the same problem, which is called "treatment-paradox".[19] Therefore, we need consider whether evoked potentials, which commonly used in INM, are effective and relevant biomarkers and surrogate endpoints or not.

INM as an intervention

- Critical evaluation of INM as an intervention is strongly justified INM is only carried out when the surgery's safety can be enhanced by reports of signal loss, reassuring signal preservation, or mapping results.[8] Therefore, we can consider INM as an intervention and ask the following question: "Does

INM help to prevent neural injury in the patients who receive surgery or procedure?"

- According to the Oxford 2011 Levels of Evidence (Table 1), the level 1 evidence for an intervention (or treatment benefits) is systemic review of randomized trials or n-of-1 trials.
- Although conventional diagnostic testing may be viewed as a simple test-intervention-outcome paradigm, INM is more complicated and characterized as an interventional cascade: test-interpretation-communication- intervention-outcome. Therefore, the measure outcome is heavily depends on a coordinated team effort including technologists, neurophysiologists or neurologists, and surgeons. Among them, surgeon's response to an alert[6] and the diversity of INM care delivery models[20,21] are the mostly likely confounding factors when evaluating INM as an intervention.
- However, many INM experts consider the randomized controlled trials of INM as unethical.[5]

Step 2: Finding the best evidence

This has been performed in three previous articles and one recent article which summarized these articles to suggest current status of evidence-base intraoperative neurophysiological monitoring.[8]

INM as biomarkers and surrogate endpoints[22]

- Holdefer et al. recently proposed that evoked potentials are a useful biomarkers and surrogate endpoints.[22] Since clinical endpoints cannot be obtained during the anesthesia, evoked potentials such as somatosensory and motor evoked potentials should be used as surrogate endpoints during surgery. In order to evaluate evoked potentials as good biomarkers and surrogates, they used a three step framework, which included analytical validation, utilization, and qualification. After careful evaluation of evoked potentials as good biomarkers and surrogates using the following reasoning, they concluded that "evoked potentials biomarkers comply with some but not all of the framework" and stated that "controlled trials or non-randomized studies with controlled observations may be required for full validation of evoked potentials surrogates".

■ Analytical validation: Can the biomarker be accurately measured?

◆ Evoked potentials can be accurately measured.

- The signal to noise ratio is good or excellent.
- Evoked potentials are responsive to diverse surgical interventions during different surgical procedures.
- Amplitudes and latencies of somatosensory evoked potentials show little variability under stable surgical and anesthetic conditions.
- Although amplitudes of motor evoked potentials are more variable, it is still consistent enough to detect marked reduction or diappearnce.

◆ In conclusion, evoked potentials can be accurately measured.

■ Utilization: What is the specific context of the proposed use?

◆ Motor evoked potentials are probably less sensitive to compromise of individual nerve roots during lumbar surgeries, than to corticospinal tract or anterior horn gray matter damage during surgeries at the cervical and thoracic levels.[23]

■ Qualification: Is the biomarker associated with the clinical endpoint of concern?

◆ 1st components: causal pathway linking disease (injury) and clinical endpoints

- Mechanistic associations

■ The pathophysiologic mechanisms resulting in changes in evoked potentials are well understood and plausible.

- Causal links

■ When Hill's guideline for causality is applied to INM,[24] the following table summarizes the analysis for causality of two typical examples of surgery which can produce changes in monitored parameters during INM monitoring.

- Prognostic performance

■ Since definition of 'false positive' might differ among the studies, Holdefer et al. defined the 'false positive'

according to 'causality guidelines' and only considered those changes in INM which have strong association and rapid changes in response to surgical setting as having true neural injury. However, the opinions about this definition might differ among investigators. They also showed that calculated likelihood ratios using estimated sensitivity and specificity of the previous studies showed favorable result for INM as a diagnostic tests.

◆ 2nd components: causal relationships between the clinical endpoints and interventions targeting the biomarker.

● Surgical interventions, evoked potentials and outcomes

■ Since there are reversible signal changes, the surrogate markers cannot be 2 by 2 contingency table. INM change might be classified as 'None', 'Quickly reversible', 'Protracted reversible', and 'Irreversible' and clinical outcome also can be classified as more than two such as 'no deficit', 'temporary deficit', and 'permanent deficit'.

■ In the absence of controlled observations, these contingency analyses may indicate that the effects of interventions on EPs correspond to the effects on postoperative outcomes. Like estimates of EP diagnostic accuracy, they can benefit from judicious application of Hill's guidelines to evaluate causality. They may also be useful in teasing out details of intraoperative management in response to EP changes.

● Controlled observation

■ Although controlled research design may be necessary, these kinds of studies are unlikely to be available in the near future. Possible topics for the controlled research design might be anterior cervical procedures in non-myelopathic patients, decompressive surgeries at lumbar levels below the spinal cord, and pedicle screw stimulation.

- Since INM can be used as biomarkers and surrogate endpoints, Howick et al. tried to find the evidences for INM as a diagnostic test as well as an intervention.

INM as a diagnostic test

- Howick et al.[8] identified two reviews which investigated diagnostic accuracy[7,25] and clinical effectiveness and one review which investigated whether INM predicted adverse outcomes.[3]
- Nuwer et al. evaluated whether spinal cord INM with somatosensory and transcranial electrical motor evoked potentials predict adverse surgical outcomes.[3] They identified 4 Class I[26-29] and 8 Class II studies.[30-37]

INM as an intervention

- Howick et al. found 6 articles which studied INM[38-43] as an intervention four[38-41] studies on spinal surgery from one previous systematic review[7] and they found two more studies on thyroid surgery.
- Two other systematic reviews did not found any studies in humans which directly measured the efficacy of intervention.[3,25]

Step 3: what is the current status of EBM in the field of intraoperative neurophysiologic monitoring?

Systematic reviews on diagnostic value of INM

- Howick et al.[8] combined evidence from two reviews.[7,25]

■ Most of the studies were case-comparison or

	Clipping during aneurysm surgery	Spinal correction during deformity surgery
Strength of association	Very strong	Strong
Consistency across settings	Very strong	Strong
Specificity	No	No
Temporality (does treatment precede effect)	Yes	Yes
Biological gradient (dose response)	Yes	Yes
Biological plausibility (mechanistic reasoning)	Very strong	Strong
Coherence with existing data	Yes	Yes
Experiment	No	No
Analogy	NA	NA

historically controlled studies without blinding, which rank as level 3 or 4 according to the Oxford center for Evidence-Based Medicine Levels of Evidence Table.[16] Two studies had higher quality evidence (level 2) because they were cross-sectional and involved blinded outcome assessors.[30,36] The high quality studies indicate the potential for INM to provide patient benefit by showing the sensitivity ranging from 77-99% and specificity ranging from 27-100%. However, their heterogeneous results suggest further research is warranted to corroborate the findings. All accuracy studies cited here have problems with reference standards and complicated role of the surgeon's response to alerts as mentioned above.

- Articles[26-37] found by Nuwer et al. showed significant association between INM or evoked potentials change and clinical outcome except for one Class II study.[33] In 4 Class I studies, patients who had evoked potentials change had bad clinical outcome in 16-40%.
- According to the evidence, INM is considered to be accurate in diagnosing neural injury during surgery.

Systematic reviews on therapeutic value of INM

- Nuwer et al. rejected the possibility of future studies for controlled human studies designed to determine the efficacy of post-INM alert intervention and considered it as unethical because of multiple controlled studies in animals[44-49] which demonstrated that intervening after INM alerts reduces the risk of permanent neurologic injury.
- All the studies[38-43] of INM effectiveness found by Howick et al. used historical controls or were retrospective cohort studies, which provide only low quality evidence.[16] The summary rate for neurological deficits in monitored patients was 2.1% and 3.6% in unmonitored patients, which equates to a test-benefit rate ratio of 1.7. There was high heterogeneity (I^2=75%), reducing the strength of conclusion. Therefore, dramatic effects were not seen in INM.

Do we need more studies to improve the evidence?

Not all treatments need double-blind randomized clinical trials.[50] However, evidences of INM as an intervention is not complete and some do not agree with its efficacy in preventing neural injury during surgery. In line with this, Eccher et al. suggested that it would not be impossible to do such a prospective trials with careful choice of surgical population and randomization design.[51] Clinical trials might be done in the surgery of scoliosis, anterior cervical discectomy and fusion, kyphotic deformity correction, intrinsic cord tumor, cerebral hemispheric tumor, pedicle screw INM, and alert criteria for motor evoked potentials.[8,51] However, there are many problems with such trials such as absence of regulatory to prove its effectiveness, cost, and unwillingness to do such a trial for a surgeon.[51] Therefore, Howick et al. also suggested to perform a large collaborative prospective observational cohort study.

Conclusion

INM should be used in patients who receive surgery which might result in neural injury due to the operation. However, the evidence of the role of INM in preventing patients from any neural injury is not complete. Therefore, further studies are needed to validate the role of INM. Until the full validation of INM, the practice of INM is recommended to follow the published guidelines[3,11,52] whenever it's possible.

References

1. Nuwer MR, Cohen BH, Shepard KM. Practice patterns for intraoperative neurophysiologic monitoring. *Neurology* 2013; 80:1156-1160.
2. Sala F, Di Rocco C. Intraoperative neurophysiological monitoring in neurosurgery: moving the debate from evidence and cost-effectiveness to education and training. *World neurosurgery* 2015;83:32-34.
3. Nuwer MR, Emerson RG, Galloway G, et al. Evidence-based guideline update: intraoperative spinal monitoring with somatosensory and transcranial electrical motor evoked poten-

tials: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Clinical Neurophysiology Society. *Neurology* 2012;78:585-589.
4. Nuwer MR, Emerson RG, Galloway G, et al. Evidence-based guideline update: intraoperative spinal monitoring with somatosensory and transcranial electrical motor evoked potentials*. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society* 2012;29:101-108.
5. Ney JP, van der Goes DN. Evidence-based guideline update: Intraoperative spinal monitoring with somatosensory and transcranial electrical motor evoked potentials. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the American Clinical Neurophysiology Society. *Neurology* 2012; 79:292; author replies 292-294.
6. Wiedemayer H, Fauser B, Sandalcioglu IE, Schafer H, Stolke D. The impact of neurophysiological intraoperative monitoring on surgical decisions: a critical analysis of 423 cases. *Journal of neurosurgery* 2002;96:255-262.
7. Fehlings MG, Brodke DS, Norvell DC, Dettori JR. The evidence for intraoperative neurophysiological monitoring in spine surgery: does it make a difference? *Spine* 2010;35: S37-46.
8. Howick J, Cohen BA, McCulloch P, Thompson M, Skinner SA. Foundations for evidence-based intraoperative neurophysiological monitoring. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 2015.
9. Vadivelu S, Sivaganesan A, Patel AJ, et al. Practice trends in the utilization of intraoperative neurophysiological monitoring in pediatric neurosurgery as a function of complication rate, and patient-, surgeon-, and procedure-related factors. *World neurosurgery* 2014;81:617-623.
10. Traynelis VC, Abode-Iyamah KO, Leick KM, Bender SM, Greenlee JD. Cervical decompression and reconstruction without intraoperative neurophysiological monitoring. *Journal of neurosurgery Spine* 2012;16:107-113.
11. Skinner SA, Cohen BA, Morledge DE, et al. Practice guidelines for the supervising professional: intraoperative neurophysiological monitoring. *Journal of clinical monitoring and computing* 2014;28:103-111.
12. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ (Clinical research ed)* 1996;312:71-72.
13. Straus SE, Glasziou P, Richardson WS, Haynes RB. Evidence-Based Medicine: How to Practice and Teach It, 4 ed: Churchill Livingstone, 2010.
14. Guyatt G. Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice. New York: McGraw-Hill Professiona, 2008.
15. Glover J, Izzo D, Odato K, Wang L. EBM Pyramid and EBM Page Generator [online]. Available at: http://hsls.pitt.edu/resources/ebm.
16. OCEBM Levels of Evidence Working Group. The Oxford Levels of Evidence 2. 2011. Available at: http://www.cebm.net/index.aspx?o=5653.
17. Glasziou PP, Aronson JK. An introduction to monitoring therapeutic interventions in clinical practice. In: Glasziou PP, Irwig L, Aronson JK, eds. Evidence-based medical monitoring : from principles to practice: Blackwell Publishing Ltd, 2008: 3-14.
18. Mant D. A framework for developing and evaluating a monitoring strategy. In: Glasziou PP, Irwig L, Aronson JK, eds. *Evidence-based medical monitoring : from principles to practice*: Blackwell Publishing Ltd, 2008: 15-30.
19. Skinner SA, Holdefer RN. Intraoperative neuromonitoring alerts that reverse with intervention: treatment paradox and what to do about it. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society* 2014;31:118-126.
20. Nuwer MR. A new multicenter survey of neurologic deficits after spinal deformity surgery: are new models of intraoperative neurophysiologic monitoring less accurate? *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society* 2011;28: 602-604.
21. Skinner S. Patient-centered care model in IONM: a review and commentary. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society* 2013;30:204-209.
22. Holdefer RN, MacDonald DB, Skinner SA. Somatosensory and motor evoked potentials as biomarkers for post-operative neurological status. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 2015;126:857-865.
23. MacDonald DB, Stigsby B, Al Homoud I, Abalkhail T, Mokeem A. Utility of motor evoked potentials for intraoperative nerve root monitoring. *Journal of Clinical Neurophysiology* 2012;29: 118-125.
24. Hill AB. THE ENVIRONMENT AND DISEASE: ASSOCIATION OR CAUSATION? *Proceedings of the Royal Society of Medicine* 1965;58:295-300.
25. Resnick DK, Anderson PA, Kaiser MG, et al. Electrophysiological monitoring during surgery for cervical degenerative myelopathy and radiculopathy. *Journal of neurosurgery Spine* 2009; 11:245-252.
26. Cunningham JN, Jr., Laschinger JC, Spencer FC. Monitoring of somatosensory evoked potentials during surgical procedures on the thoracoabdominal aorta. IV. Clinical observations and results. *J Thorac Cardiovasc Surg* 1987;94: 275-285.
27. Costa P, Bruno A, Bonzanino M, et al. Somatosensory- and motor-evoked potential monitoring during spine and spinal cord surgery. *Spinal cord* 2007;45:86-91.
28. Sutter M, Eggspuehler A, Grob D, et al. The validity of multimodal intraoperative monitoring (MIOM) in surgery of 109

spine and spinal cord tumors. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2007;16 Suppl 2:S197-208.
29. Weinzierl MR, Reinacher P, Gilsbach JM, Rohde V. Combined motor and somatosensory evoked potentials for intraoperative monitoring: intra- and postoperative data in a series of 69 operations. *Neurosurgical review* 2007;30:109-116; discussion 116.
30. May DM, Jones SJ, Crockard HA. Somatosensory evoked potential monitoring in cervical surgery: identification of pre- and intraoperative risk factors associated with neurological deterioration. *Journal of neurosurgery* 1996;85:566-573.
31. Jacobs MJ, Elenbaas TW, Schurink GW, Mess WH, Mochtar B. Assessment of spinal cord integrity during thoracoabdominal aortic aneurysm repair. *The Annals of thoracic surgery* 2002;74:S1864-1866; discussion S1892-1868.
32. Pelosi L, Lamb J, Grevitt M, Mehdian SM, Webb JK, Blumhardt LD. Combined monitoring of motor and somatosensory evoked potentials in orthopaedic spinal surgery. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology* 2002;113:1082-1091.
33. Langeloo DD, Lelivelt A, Louis Journee H, Slappendel R, de Kleuver M. Transcranial electrical motor-evoked potential monitoring during surgery for spinal deformity: a study of 145 patients. *Spine* 2003;28:1043-1050.
34. Hilibrand AS, Schwartz DM, Sethuraman V, Vaccaro AR, Albert TJ. Comparison of transcranial electric motor and somatosensory evoked potential monitoring during cervical spine surgery. *The Journal of bone and joint surgery American volume* 2004;86-A:1248-1253.
35. Etz CD, Halstead JC, Spielvogel D, et al. Thoracic and thoracoabdominal aneurysm repair: is reimplantation of spinal cord arteries a waste of time? The Annals of thoracic surgery 2006;82:1670-1677.
36. Khan MH, Smith PN, Balzer JR, et al. Intraoperative somatosensory evoked potential monitoring during cervical spine corpectomy surgery: experience with 508 cases. *Spine* 2006; 31:E105-113.
37. Lee JY, Hilibrand AS, Lim MR, et al. Characterization of neurophysiologic alerts during anterior cervical spine surgery. *Spine* 2006;31:1916-1922.
38. Smith PN, Balzer JR, Khan MH, et al. Intraoperative somatosensory evoked potential monitoring during anterior cervical discectomy and fusion in nonmyelopathic patients--a review of 1,039 cases. *The spine journal : official journal of the North American Spine Society* 2007;7:83-87.
39. Sala F, Palandri G, Basso E, et al. Motor evoked potential monitoring improves outcome after surgery for intramedullary spinal cord tumors: a historical control study. *Neurosurgery* 2006;58:1129-1143; discussion 1129-1143.
40. Meyer PR Jr, Cotler HB, Gireesan GT. Operative neurological complications resulting from thoracic and lumbar spine internal fixation. *Clinical orthopaedics and related research* 1988:125-131.
41. Epstein NE, Danto J, Nardi D. Evaluation of intraoperative somatosensory-evoked potential monitoring during 100 cervical operations. *Spine* 1993;18:737-747.
42. Barczynski M, Konturek A, Stopa M, Hubalewska- Dydejczyk A, Richter P, Nowak W. Clinical value of intraoperative neuromonitoring of the recurrent laryngeal nerves in improving outcomes of surgery for well-differentiated thyroid cancer. *Polski przeglad chirurgiczny* 2011;83:196- 203.
43. Alesina PF, Rolfs T, Hommeltenberg S, et al. Intraoperative neuromonitoring does not reduce the incidence of recurrent laryngeal nerve palsy in thyroid reoperations: results of a retrospective comparative analysis. *World journal of surgery* 2012;36:1348-1353.
44. Coles JG, Wilson GJ, Sima AF, Klement P, Tait GA. Intraoperative detection of spinal cord ischemia using somatosensory cortical evoked potentials during thoracic aortic occlusion. *The Annals of thoracic surgery* 1982;34:299-306.
45. Kojima Y, Yamamoto T, Ogino H, Okada K, Ono K. Evoked spinal potentials as a monitor of spinal cord viability. *Spine* 1979;4:471-477.
46. Laschinger JC, Cunningham JN, Jr., Catinella FP, Nathan IM, Knopp EA, Spencer FC. Detection and prevention of intraoperative spinal cord ischemia after cross-clamping of the thoracic aorta: use of somatosensory evoked potentials. *Surgery* 1982;92:1109-1117.
47. Cheng MK, Robertson C, Grossman RG, Foltz R, Williams V. Neurological outcome correlated with spinal evoked potentials in a spinal cord ischemia model. *Journal of neurosurgery* 1984;60:786-795.
48. Nordwall A, Axelgaard J, Harada Y, Valencia P, McNeal DR, Brown JC. Spinal cord monitoring using evoked potentials recorded from feline vertebral bone. *Spine* 1979;4:486-494.
49. Bennett MH. Effects of compression and ischemia on spinal cord evoked potentials. *Exp Neurol* 1983;80:508-519.
50. Glasziou P, Chalmers I, Rawlins M, McCulloch P. When are randomised trials unnecessary? Picking signal from noise. *BMJ (Clinical research ed)* 2007;334:349-351.
51. Eccher MA, Ghogawala Z, Steinmetz MP. The possibility of clinical trials in neurophysiologic intraoperative monitoring: a review. *Journal of clinical neurophysiology : official publication of the American Electroencephalographic Society* 2014;31:106-111.
52. Isley MR, Edmonds HL, Jr., Stecker M. Guidelines for intraoperative neuromonitoring using raw (analog or digital waveforms) and quantitative electroencephalography: a position statement by the American Society of Neurophysiological Monitoring. *Journal of clinical monitoring and computing* 2009;23:369-390.