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Opinion Piece

Foundations for evidence-based intraoperative neurophysiological monitoring

Jeremy Howick[d], Bernard Allan Cohen[b], Peter McCulloch[c], Matthew Thompson[a], Stanley A. Skinner[e,*]

[a] University of Washington, Department Family Medicine, Seattle, WA 98195, USA
[b] Neurological Monitoring Associates, LLC, 333 West Brown Deer Road, MS #240, Milwaukee, WI 53217-4925, USA
[c] Nuffield Department of Surgical Science, Level 6, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom
[d] Centre for Evidence-Based Medicine, Department of Primary Care Health Sciences, New Radcliffe House, University of Oxford, Oxford OX2 6GG, United Kingdom
[e] Abbott Northwestern Hospital, 800 E. 28th Street, Minneapolis, MN 55407, USA

See Editorial, pages 3–4

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HIGHLIGHTS

- Intraoperative neurophysiological monitoring (IONM) straddles the boundary between a diagnostic test and an intervention.
- More high quality studies are required to support claims that IONM benefits patients.
- Limits of evidence collection and means to prove IONM effectiveness are reviewed.

ABSTRACT

In this review, we recommend means to enhance the evidence-base for intraoperative neurophysiological monitoring (IONM). We address two preliminary issues: (1) whether IONM should be evaluated as a diagnostic test or an intervention, and (2) the state of the evidence for IONM (as presented in systematic reviews, for example). Three reasons may be suggested to evaluate at least some IONM applications as interventions (or as part of an "interventional cascade"). First, practical barriers limit our ability to measure IONM diagnostic accuracy. Second, IONM results are designed to be correlated with interventions during surgery. Third, IONM should improve patient outcomes when IONM-directed intervention alters the course of surgery. Observational evidence for IONM is growing yet more is required to understand the conditions under which IONM, in its variety of settings, can benefit patients. A multi-center observational cohort study would represent an important initial compromise between the pragmatic difficulties with conducting controlled trials in IONM and the Evidence-Based Medicine (EBM) view that large scale randomized trials are required. Such a cohort study would improve the evidence base and (if justified) provide the rationale for controlled trials.

1. Introduction: barriers to investigation of the IONM evidence base

Intraoperative neurophysiological monitoring (IONM) measures neural function and integrity during surgical procedures. Among the primary modalities used are somatosensory evoked potentials (SSEP), transcranial motor evoked potentials (MEP), and electromyography (EMG). Alerted to the loss of a neural signal, the surgeon has the opportunity to adjust the procedure to reduce the risk of permanent damage. Since surgery affecting important neural structures (such as the spinal cord or vascular supply to the brain, for example) carries the risk of temporarily or permanently impairing neurological function, it seems reasonable to employ methods to reduce these risks (Deletis and Sala, 2008; Simon et al., 2012; Trinh et al., 2013). Likewise, surgeons and other proceduralists, reassured by negative monitoring results, may proceed more confidently with difficult maneuvers. Therefore, IONM has been used extensively in spine, brain, peripheral/cranial nerve,

* Corresponding author.

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and a variety of other potentially risky surgical procedures (Nuwer, 2008). The authors point out that, despite our use of the aggregate term "IONM" throughout the manuscript, we recognize that evidence-based examination of IONM's efficacy demands discreet, differential attention to the variety of its clinical contexts, recording techniques, and models of care delivery (Emerson and Husain, 2013; Nuwer, 2008).

Evidence supporting the effectiveness of IONM must be appropriately evaluated. This is especially important given rising healthcare costs and demands to document high quality patient care through outcomes measures.

Because IONM is broadly based on a compelling pathophysiologic and probabilistic rationale, some proponents have argued that further evidence is not required: "The absence of randomized human outcome studies is no accident; in light of overwhelming animal data, it is our opinion that human experiment would be unconscionable" (Ney et al., 2012a). Others have maintained that current evidence is "strong" enough to warrant IONM use during spine surgery but further evidence is required to prospectively "validate" IONM "changes" (and interventions) (Fehlings et al., 2010). It is true that an effect in some cases is so dramatic that a randomized trial may be deemed unnecessary and unethical. During intracranial aneurysm surgery, the sequence of aneurysm clipping, IONM signal loss, and prompt signal restoration with reposition of the clip illustrates such a dramatic effect (Wiedemayer et al., 2002). Beneficial "dramatic effects" can be presumed when (a) a high treatment effect rate ratio exists (between observed treated versus untreated groups, for example) or (b) a very high "rate of change" of context-wedded individual or a relatively few repeated events is observed (Glasziou et al., 2007; Howick et al., 2009). However, "high rate of change" events during IONM more precisely constitute a "surrogate end point" rather than a patient outcome (Aronson, 2008). Similar arguments may be mounted in the setting of context pertinent IONM signal loss and prompt recovery during spine deformity correction, for example (Fig. 1) (Skinner et al., 2009). Causality guidelines and Bayesian probability may link a residue of IONM signal changes to potentially catastrophic outcomes (Hill, 1965; Howick et al., 2009; Howick, 2011; Skinner and Holdefer, 2014). Broadened and rigorous research efforts (described herein) will be required to establish such dramatic effects of surrogate outcomes as evidence that IONM benefits patients.

Very practically, surgeons have very strong preferences about which procedures they take to be the best because they believe the procedures they use to be effective. Potential surgical patients often share these preferences. This creates a barrier to conducting randomized trials in surgery (or IONM) because surgeons are unlikely to enroll patients in a trial that might involve *not* offering the preferred procedure (McCulloch et al., 2009).

At the other end of the spectrum, some fervent supporters of Evidence-Based Medicine (EBM) might refuse to accept any evidence about IONM benefits other than randomized trials (McCulloch et al., 2002). Much can be said practically and philosophically in support of randomized trials (including in the field of IONM) (Howick, 2011). Many apparently beneficial treatments (and diagnostic/monitoring techniques) have proved useless or harmful when subjected to unconfounded trials (Alfirevic et al., 2006; Evans et al., 2011; Lacchetti et al., 2008; Sandham et al., 2003). Moreover, immediately apparent neurological deficits can resolve spontaneously (Kelleher et al., 2008; Resnick et al., 2009). In addition, all interventions (including some diagnostic testing regimes) carry risks. IONM has been associated with many minor adverse effects, mostly dental or lingual injuries during MEP. Potentially more serious risks include: stimulation induced seizures, cautery related burns due to capacitive coupling to monitoring electrodes, cardiac arrhythmia, and movement related injury after MEP (so far unreported) (MacDonald, 2002, 2006). Indirect risks may include interruptions of the start or progress of surgery (Chu et al., 2008; Wimmer et al., 1998; Wolters et al., 1996) or altered surgery due to false reporting (Resnick et al., 2009).

In this paper we argue for a middle ground. While we acknowledge that the evidence-base for IONM is insufficient to preclude the need for further evidence, we also appreciate that practical and ethical barriers to evidence gathering need to be addressed. Uniquely, evidence-based IONM evaluation faces an additional challenge: namely, IONM straddles the boundary between a diagnostic test and an intervention. Whether IONM is considered a therapeutic intervention or a diagnostic test will determine the type of evidence we should seek and require. The debate over the nature and value of IONM continues to rankle its adherents and critics (Sala and Di Rocco, 2015; Vadivelu et al., 2014). Therefore, we first discuss whether IONM should be assessed as a diagnostic test versus a therapeutic intervention. We will then summarize the current evidence for IONM and make recommendations for future research.

2. IONM: diagnostic test or intervention?

2.1. IONM as a diagnostic test (the 'treatment paradox')

One way to evaluate a new diagnostic test is to measure its diagnostic *accuracy*. This is achieved by comparing the accuracy of a new test with a "gold" or "reference" standard (Ferrant e di Ruffano et al., 2012; Lijmer et al., 1999). A new test that meets a threshold for accuracy (specificity, sensitivity, positive predictive value, negative predictive value) will be considered acceptable. However, no test is perfectly accurate. No matter how good, tests will sometimes either reveal an abnormality when the condition of the patient is unchanged (false positive) or fail to reveal abnormality when, in fact, the patient's clinical status has deteriorated (false negative). For IONM, especially MEP deployed to monitor spinal cord function, very sensitive alert criteria tend to preclude false negative but favor false positive reporting (Langeloo et al., 2003; Skinner and Holdefer, 2014). False positive results can lead to unnecessary treatment (and associated harms and costs). The evaluation of IONM's diagnostic accuracy is further confounded by the inability to implement a real time reference standard in the event of IONM signal loss. The most common reference test is a measure of post-operative neurological deficits. However this method does not permit distinction between false positive and true positive alerts during surgery. Other reference standards, such as wake-up tests, face similar problems. As a result of this "treatment paradox," reported measures of IONM sensitivity and positive predictive value are likely inflated (Resnick et al., 2009; Skinner and Holdefer, 2014). Given the lack of a suitable reference standard, therefore, it is problematic to simply rely on evaluations of IONM diagnostic accuracy. The use of causality criteria within a likelihood framework may point to a smaller subset of "truer" positive results when evaluating intraoperative recovered signal loss (Skinner and Holdefer, 2014). A "dose response" relationship between IONM testing results and outcomes (negative versus reversed signal change versus unreversed signal loss) has also been recently proposed (Holdefer et al., 2015). Nevertheless, the inability to deploy an effective real time reference standard inevitably confounds the analysis of IONM as a diagnostic test.

2.2. IONM as an intervention (complexities of the interventional cascade)

Evidence scholars increasingly demand proof of test effectiveness beyond diagnostic test accuracy alone. They demand evidence that the *consequences* of accurate testing benefit patients (Ferrant e