**TITLE:** Neuromuscular Monitoring for Patients Receiving Continuous Paralytic or Neuromuscular Blocking Agents: A Review of the Clinical Effectiveness and Guidelines

**DATE:** 10 February 2016

**CONTEXT AND POLICY ISSUES**

Neuromuscular blocking agents (NMBAs) interfere with the binding of acetylcholine to the motor endplate, which blocks the transmission of nerve impulses at the myoneural junction and results in temporary paralysis of the skeletal muscle. The NMBAs are categorized according to their mechanism of action as depolarizing NMBAs and non-depolarizing NMBAs. The depolarizing NMBAs bind to cholinergic receptors on the motor endplate, resulting in initial depolarization of the endplate membrane and then neuromuscular transmission blockade. The non-depolarizing NMBAs bind to acetylcholine receptors and either prevent conformational changes in the receptors or block the ion channels preventing generation of the endplate potential.

The introduction of NMBAs, which induce temporary paralysis, transformed the practice of anesthesia and NMBAs have become an important component of general anesthesia. However, it is essential to have successful recovery from neuromuscular blockade when it is no longer required, to avoid residual paralysis and its detrimental consequences. Recovery from neuromuscular blockade may be spontaneous or may require the use of pharmacologic reversal agents. The timing and dosing of these reversal agents are determined by the extent of spontaneous recovery.

Neuromuscular blockade can be assessed by different ways such as assessment based on clinical signs and assessments based on train of four (TOF). Clinical signs include spontaneous ventilation, eye opening and five-second head lift. TOF involves stimulation of the peripheral nerves. Using a peripheral nerve stimulator, four shocks of 2 Hz each are applied to the ulnar or facial nerves and visual observation of the muscular response is used to determine the degree of neuromuscular blockade. This enables assessment of the extent of neuromuscular transmission when NMBAs are administered to block musculoskeletal activity. Patients treated with NMBAs have progressive reduction in the magnitude of response to the TOF stimuli and TOF stimulation and monitoring may be used to assist in the titration of the NMBA dose. Appropriate titration may prevent unnecessary prolonged paralysis.

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In the intensive care unit (ICU), NMBAs may be used to facilitate short procedures under general anesthesia, to facilitate mechanical ventilation, to manage patients with increased intracranial pressure, massive hemothysis, tetanus, or neuroleptic malignant syndrome.\(^1\, 5\)

There appears to be controversy regarding the use of neuromuscular monitoring. One review\(^1\) has reported on three trials comparing neuromuscular monitoring using the peripheral nerve stimulator (TOF monitoring) versus clinical assessment and reported conflicting results, with benefit being demonstrated with TOF in one trial and not in two trials.

The purpose of this report is to review the clinical efficacy and the evidence-based guidelines regarding neuromuscular monitoring for guiding treatment and therapy for patients in the intensive care unit receiving continuous paralytic or neuromuscular blocking agents.

**RESEARCH QUESTIONS**

1. What is the clinical effectiveness of neuromuscular monitoring to guide treatment and therapy for patients in the intensive care unit receiving continuous paralytic or neuromuscular blocking agents?

2. What are the evidence-based guidelines regarding the use of neuromuscular monitoring for patients in the intensive care unit receiving continuous paralytic or neuromuscular blocking agents?

**KEY FINDINGS**

The value of the train of four (TOF) monitoring of patients in ICU receiving neuromuscular blocking agents (NMBAs) remains unclear. One systematic review, which included three trials comparing TOF monitoring with clinical assessment, reported conflicting results, with benefit being demonstrated with TOF monitoring in one trial and no benefit in two trials. Use of TOF monitoring resulted in lower dose of NMBA being used and a faster recovery of neuromuscular function in one trial but not in two trials.

**METHODS**

**Literature Search Methods**

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was limited to English language documents published between January 1, 2011 and January 19, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

**Selection Criteria and Methods**

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for
inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Selection Criteria</th>
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<tr>
<td><strong>Population</strong></td>
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<td><strong>Intervention</strong></td>
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<td><strong>Comparator</strong></td>
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<td><strong>Outcomes</strong></td>
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<tr>
<td><strong>Study Designs</strong></td>
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**Exclusion Criteria**

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Studies on intraoperative monitoring or monitoring of patients in post-anesthesia care units were excluded as these patients may not be representative of critically ill patients in intensive care.

**Critical Appraisal of Individual Studies**

The included systematic review was critically appraised using the AMSTAR checklist. Summary scores were not calculated; rather, a review of the strengths and limitations were described narratively.

**SUMMARY OF EVIDENCE**

**Quantity of Research Available**

A total of 238 citations were identified in the literature search. Following screening of titles and abstracts, 219 citations were excluded and 19 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 18 publications were excluded for various reasons, while one publication (a systematic review) met the inclusion criteria and was included in this report. No HTAs, RCTs, non-randomized studies or evidence-based guidelines were identified. Appendix 1 describes the PRISMA flowchart of the study selection.

An additional reference of potential interest is provided in Appendix 5.

**Summary of Study Characteristics**

Characteristics of the included systematic review are summarized below and details are available in Appendix 2, Table A1.
One relevant systematic review\(^7\) was identified. It was published in 2011 from Canada. It had a broad objective and reported on the therapeutic uses, pharmacology, and clinical considerations of NMBAs for critical care of adults. It included a section on comparison of neuromuscular monitoring using a peripheral nerve stimulator (TOF monitoring) with clinical assessment and reported on three clinical trials. Two of the trials were published in 1997 and one study was published in 2004. The NMBAs used were vecuronium in one trial, atracurium in one trial, and cisatracurium in one trial. Findings were stated qualitatively as benefits with respect to reduction in occurrence of prolonged paralysis.

**Summary of Critical Appraisal**

Critical appraisal of the included systematic review is summarized below and details are available in Appendix 3, Tables A2.

In the included systematic review\(^7\) the objective was clearly stated, multiple databases were searched, and the inclusion and exclusion criteria were stated. The authors mentioned that there were no conflicts of interest. However, it has a number of limitations. The article selection process was not described. A list of excluded articles was not provided. It was unclear as to how article selection and data extraction had been performed. Characteristics of the individual studies were not described. It appears that quality assessment of the studies was not conducted. Details of the findings of the individual studies were not provided. It appears that publication bias was not explored.

**Summary of Findings**

*What is the clinical effectiveness of neuromuscular monitoring to guide treatment and therapy for patients in the intensive care unit receiving continuous paralytic or neuromuscular blocking agents?*

Findings are summarized below and details are provided in Appendix 4, Tables A3.

The included systematic review\(^7\) reported on the comparison of TOF monitoring with clinical assessment for assessing neuromuscular blockade with NMBAs and found conflicting findings. One included trial in the systematic review reported benefits with TOF monitoring with respect to reduction in occurrence of prolonged paralysis whereas the other two included trials reported no benefit. In the trial demonstrating benefit, use of TOF monitoring resulted in lower dose of NMBAs being used and a faster recovery of neuromuscular function. The two trials not demonstrating benefit, found no differences in NMBAs doses used or recovery times when either TOF monitoring or clinical assessments were used. The trial reporting benefit had used vecuronium as the NMBAs and the two trials not reporting benefit had used atracurium and cisatracurium.

*What are the evidence-based guidelines regarding the use of neuromuscular monitoring for patients in the intensive care unit receiving continuous paralytic or neuromuscular blocking agents?*

No relevant evidence-based guidelines, regarding the use of neuromuscular monitoring for patients in the intensive care unit receiving continuous paralytic or neuromuscular blocking agents, were identified.
Limitations

There appears to be limited evidence regarding the comparison between neuromuscular monitoring with TOF and no monitoring, i.e. assessment based on clinical signs. One relevant systematic review, which included a section on neuromuscular monitoring, was identified. However, this systematic review had a broad objective and the main focus was on NMBAs, hence the information reported for the studies on neuromuscular monitoring was not detailed.

No definitive conclusions are possible as results were conflicting.

No HTAs, RCTs, non-randomized studies or evidence-based guidelines were identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

One relevant systematic review was included in this review. It included three trials comparing TOF monitoring with clinical assessment for patients in ICU receiving NMBAs; however, results were conflicting. Benefit was demonstrated for TOF monitoring in one trial but not in the other two trials. Use of TOF monitoring resulted in lower dose of NMBAs being used and a faster recovery of neuromuscular function in one trial but not in two trials. These same three trials were also mentioned in an existing narrative review.

One study, which did not meet our inclusion criteria but may provide some insights with respect to neuromuscular monitoring with TOF, was identified. The study by Dieye et al. compared the dose of cisatracurium required for complete paralysis (no response to TOF) of patients after induction of anesthesia in patients in ICU with the doses used in patients undergoing elective surgery. Neuromuscular monitoring was conducted by observing the TOF response using a peripheral nerve stimulator. They found that time to achieve complete neuromuscular blockade and the doses of cisatracurium required were higher for ICU patients compared to those for elective surgery patients. Considering their findings, they suggested that neuromuscular monitoring should be used to ensure adequate neuromuscular blockade in ICU patients requiring deep neuromuscular relaxation (TOF = 0) for surgical procedures.

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REFERENCES


APPENDIX 1: Selection of Included Studies

238 citations identified from electronic literature search and screened

219 citations excluded

19 potentially relevant articles retrieved for scrutiny (full text, if available)

No potentially relevant reports retrieved from other sources (grey literature, hand search)

19 potentially relevant reports

18 reports excluded:
- irrelevant population (4)
- irrelevant comparison (4)
- irrelevant design (1)
- other (review articles, editorials, correspondences, survey) (9)

1 report included in review
## APPENDIX 2: Characteristics of Included Publications

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Types and numbers of primary studies included</th>
<th>Population Characteristics</th>
<th>Comparisons</th>
<th>Clinical Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Warr, 2011, Canada</td>
<td>3 prospective clinical trials (Rudis et al., 1997; Strange et al., 1997; and Baumann et al. 2004)</td>
<td>Critically ill adults.</td>
<td>TOF monitoring versus clinical assessment</td>
<td>Reduction in occurrence of prolonged paralysis (defined as recovery that is 50% to 100% longer than predicted by the pharmacological parameters)</td>
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</table>

RCT = randomized controlled trial, TOF = train of four
APPENDIX 3: Critical Appraisal of Included Publications

| Table A2: Strengths and Limitations of Systematic Review using AMSTAR checklist® |
|--------------------------------------------------|--------------------------------------------------|
| **Strengths** | **Limitations** |
| Warr, 2011, Canada | |
| • The objective was clearly stated. | • The study selection process was not provided |
| • The inclusion and exclusion criteria were stated. | • List of excluded studies was not provided |
| • Multiple databases (Medline, Embase, and Cumulative Index to Nursing and Allied Health Literature. Also eligible articles were manually searched. | • Unclear how article selection or data extraction was performed |
| • Included studies were listed in some case | • Characteristics of the individual studies were not provided |
| • Authors mentioned that there were no conflicts of interest | • Details of the findings of the individual studies, which were relevant for this Rapid Response report were not provided. |
| | • Quality assessment of the studies does not appear to have been undertaken |
| | • Publication bias does not appear to have been explored |
APPENDIX 4: Main Study Findings and Author’s Conclusions

Table A3: Summary of Findings of the Systematic Review

<table>
<thead>
<tr>
<th>Warr,† 2011, Canada</th>
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<tr>
<td><strong>Main Study Findings:</strong></td>
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<td>Evidence regarding the neuromuscular monitoring with TOF compared to clinical assessment were obtained from three prospective clinical trials (Rudis et al., 1997; Strange et al., 1997; and Baumann et al. 2004). The NMBA used in each trial was different (vecuronium, cisatracurium or atracurium). TOF monitoring showed benefits with respect to reducing the occurrence of prolonged paralysis (defined as recovery that is 50% to 100% longer than predicted by the pharmacological parameters), in the trial where vecuronium was used. This was not observed in the two trials where cisatracurium and atracurium were used and the authors suggested that this may be due to the more predictable elimination of these agents.</td>
</tr>
<tr>
<td><strong>Authors’ Conclusions:</strong></td>
</tr>
<tr>
<td>“NMBAs are high-alert agents used to manage critically ill patients for compromised gas exchange and ventilation, control of life-threatening intracranial hypertension, and reduction of cerebral metabolism due to shivering during therapeutic hypothermia. To promote patient safety and inform clinical decision making when applying these agents to practice, multidisciplinary ICU team members should be familiar with efficacy data, as well as pharmacology, pharmacokinetics, dosing, drug interactions, required monitoring, and adverse effects. Crucial considerations for optimization of treatment with NMBAs include patient-based selection of the drug, identification and frequent reassessment of treatment goals, titration of the agents to objective parameters (using clinical assessment and TOF monitoring), use of intermittent therapy when possible, implementation of interruption strategies, and daily assessment for the need of continuous therapy.”</td>
</tr>
</tbody>
</table>

ICU = intensive care unit, NMBA = neuromuscular blocking agent, TOF = train of four
APPENDIX 5: Additional References of Potential Interest

Guideline (prior to literature search date, and unclear method)