How to Catch Unicorns (and Other Fairytales)

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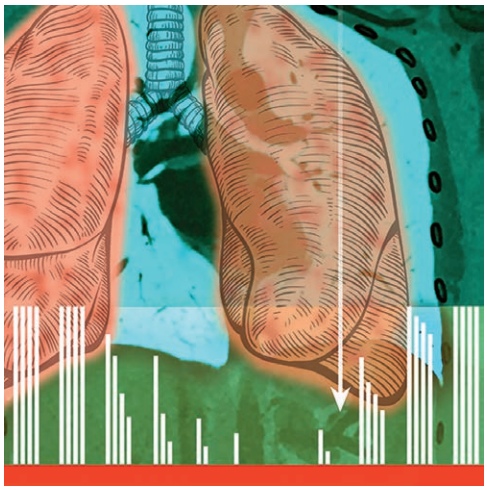
IN this issue of the journal, Murphy *et al.*[1] review previous studies on the practice of antagonism of neuromuscular block and build a strong case refuting several misunderstandings in anesthesia practice: the myth that neostigmine could result in clinically significant paradoxical neuromuscular weakness; the myth that clinical signs of recovery (*e.g.*, tidal volume, negative inspiratory pressure) and subjective evaluation are reliable indicators of neuromuscular recovery; and the myth that clinical neuromuscular blockade can be managed safely without a monitoring device. To shed light on these common misconceptions, the authors have administered, prospectively and in a blinded fashion, either neostigmine (40 μg/kg) or saline to patients whose neuromuscular function had spontaneously recovered to a nonnormalized train-of-four (TOF) ratio of at least 0.90 to represent standard clinical practice.



"...inadequate management of clinical neuromuscular blockade is one of the recurrent, frequent failures in many practices..."

Myth #1: Neostigmine Induces Clinically Significant Paradoxical Neuromuscular Weakness

One of the strengths of this well conducted prospective study[1] is that it establishes that neostigmine, at the dose of 40 μg/kg administered at the time when rocuronium can be considered sufficiently antagonized (TOF ratio of at least 0.90), does *not* induce signs or symptoms of decreased neuromuscular function. This finding contradicts previous reports.[2–4] In patients anesthetized with halothane who received a long-acting neuromuscular blocking drug (D-tubocurarine, dimethyltubocurarine, or gallamine), Payne *et al.*[2] administered 2.5 mg of neostigmine when recovery of the tetanic response had reached 50% (n = 3 patients/group) or when the first twitch recovery reached 50% of control tension (n = 2 patients/group), followed by a second dose of 2.5 mg of neostigmine 2 to 5 min later. They noted that the first dose of neostigmine (at this depth of block) restored the peak contraction height and abolished tetanic fade, but the second dose reestablished the fade. In contrast, recovery of first twitch under these conditions was not impaired by the two doses of neostigmine. In addition, the authors noted that in five patients who did not receive neuromuscular blocking drugs (and were apparently receiving halothane anesthesia), administration of a single dose of neostigmine of 2.5 mg resulted in partial block of the tetanic response, whereas four other patients required two doses of neostigmine (total dose of 5.0 mg) to produce a substantial reduction in the peak height of the tetanic response.

It is clear that the study design reported by Payne *et al.*[2] does not reflect current routine clinical practice. Inhaled anesthetics alone are known to induce a reduction in peak tetanic response and increase tetanic fade without affecting twitch response.[5] Caldwell[3] reported that administration of neostigmine 40 μg/kg (~3 mg of neostigmine) at 1, 2, 3, or 4 h after a single dose of vecuronium (0.1 mg/kg) in patients receiving nitrous oxide/isoflurane/fentanyl anesthesia resulted in an increase in TOF ratio in 32 patients but a decrease in 8 patients. It seems, however, that if neostigmine administration after recovery from neuromuscular blockade induces impairment of TOF ratio, this effect is short-lived.[6]

Grosse-Sundrup *et al.*[4] reported an analysis of a large database that included 18,579 patients who received intermediate acting neuromuscular blocking drugs (2,538 of whom did not receive neostigmine antagonism). Neuromuscular function monitoring was used in only 48.9% of patients, and neostigmine was administered to 63.2% of patients. Only 36.2% of the patients who

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received neostigmine also had neuromuscular monitoring. The authors commented, "reversal with neostigmine even increased the risk of severe postoperative respiratory failure" and "Use of... neostigmine was associated with desaturation less than 90%, as well as reintubation requiring unplanned admission to an intensive care unit."[4] It should be pointed out that "reintubation" was defined as, "any reintubation in the hospital... within seven days of surgery." It is unlikely that reintubations occurring 7 days postoperatively could reasonably be attributed to neostigmine administration.

The clinically relevant report by Murphy *et al.*[1] sends a clear and convincing message: administration of neostigmine at the time of neuromuscular recovery was not associated with clinically evident (or significant) neostigmine-induced muscle weakness; in fact, its administration was associated with *improvement* in several symptoms of muscle weakness. The potential benefits of neostigmine antagonism (even when the normalized TOF ratio is more than 0.90) were apparent when muscle strength was assessed 15 min after arrival in the postoperative care unit; neostigmine administration (in moderate doses of 40 μg/kg) is therefore unlikely to induce clinically significant neuromuscular weakness.

Myth #2: Clinical Tests of Recovery Are Reliable Indicators of Neuromuscular Recovery

For over four decades, we have known that the TOF ratio can be used reliably to determine the minimum level of neuromuscular recovery needed to ensure safe tracheal extubation.[7,8] As our understanding of airway muscle physiology expanded, the minimum degree of recovery to assure patient safety after neuromuscular blockade was redefined as a TOF ratio of at least 0.90. We also now know that clinical signs are not predictive of adequate neuromuscular function.[9] As many as 84% of patients can sustain a 5-s head lift despite a TOF ratio less than 0.50.[10] However, these failure-prone assessments of recovery continue to be used, and clinical decisions are still made based on the presence of respiratory attempts, tidal volume adequacy, and ability to sustain a 5-s head-lift. The present study[1] dispels the fallacy that using clinical tests to guide assessment of neuromuscular function can ensure the adequacy of neuromuscular reversal: 14% of patients in the control (saline) group and 6.5% of patients in the neostigmine group failed to demonstrate a sustained 5-s head lift despite a TOF ratio of more than 0.90. In fact, of the 11 clinical tests used by the authors to assess muscle strength 15 min before postanesthesia care unit arrival, not a single one was 100% predictive of adequate neuromuscular recovery. Clinical tests, therefore, have unacceptably high rates of false positive and false negative results, and clinicians should no longer rely on (or use) them.

Myth #3: Subjective Assessment of Recovery Is a Reliable Indicator of Neuromuscular Recovery

Subjective assessment of neuromuscular function consists of either watching (visual assessment) or feeling (tactile assessment) the responses to TOF stimulation and determining intuitively whether fade to TOF stimulation exists. Unfortunately, the reliability of subjective fade detection is extremely poor, and "it is very difficult, if not impossible, to estimate visually or manually a TOF ratio with sufficient certainty to exclude residual curarization."[11] As Murphy and colleagues reiterate in their report more than 30 yr later, the "absence of fade with subjective TOF assessment" did not prevent 21.1% of their patients from having a TOF less than 0.90.[1]

Having failed to reliably detect TOF fade subjectively, considerable amounts of energy, time, resources, and ink have been expended to define alternative measures of neuromuscular function. In search of improving the low sensitivity and specificity of subjective evaluation of TOF fade, the double burst stimulation (DBS) pattern was introduced into clinical practice. DBS consists of various combinations of minitetanic bursts (3,3; 3,2; 2,2).[12,13] Subsequent investigations have shown, however, that the subjective evaluation of neuromuscular fade was improved only slightly with DBS—and the ability to detect the threshold of recovery subjectively (TOF of at least 0.90) remained elusive. It should be obvious, then, that nothing has changed in the past 30 yr: subjective evaluation, whether visual or tactile, to TOF or DBS, cannot predict adequate neuromuscular recovery, and clinicians should not rely on such assessment to decide on the timing for tracheal extubation.

Myth #4: Antagonism Can Be Based on the Duration since the Last Administration of Neuromuscular Blocking Agent

The important study by Murphy *et al.*[1] again emphasizes that the duration of effects of neuromuscular blocking drugs is variable.[3,14,15] Many clinicians may rely on the "time elapsed" principle of reversal, in which they may choose not to administer anticholinesterases if the duration since the last dose of a neuromuscular blocking agent is greater than one or two elimination half-lives or, in the case of intermediate neuromuscular blocking agents, greater than 60 min.[16] It is evident that this practice should be discouraged; after the administration of a *single* small dose of rocuronium (~0.3 mg/kg), 21% of patients failed to spontaneously recover to a TOF ratio of 0.9 in 163 min.[1] The message is therefore clear: pharmacologic antagonism with neostigmine and decisions of readiness for tracheal extubation should never be based solely on the time since the last administration of a neuromuscular blocking drug. The decision should be based on documentation of a TOF ratio of at least 0.9 using a quantitative monitoring device—but with a caveat: when using acceleromyographic monitoring, it is important to ensure the return of TOF ratio

to 90% of the *baseline* (*i.e.*, normalized) TOF value. Murphy *et al.*[1] illustrate the limitation of acceleromyography unless normalization (correction) of evoked responses is performed, because "7 of their 90 patients had not achieved a normalized TOF of 0.90 at the time of reversal."

In light of the important lessons learned from Murphy *et al.*, the obvious question is: "how many failures are acceptable in clinical practice?" Unfortunately, inadequate management of clinical neuromuscular blockade is one of the recurrent, frequent failures in many practices, despite the clinicians' refusal to recognize such complications.[17] The initial failure to translate current knowledge into daily practice usually results in recurring failures that endanger patient safety. We therefore recommend that future efforts be directed toward education regarding the unreliability of clinical tests and subjective evaluation; development and dissemination of evidence-based guidelines for best practice; and development of easy-to-use, reliable, and affordable neuromuscular monitors that will help clinicians provide the best patient care and ensure patient safety. Only then will we be able to catch a unicorn and relegate it to the land of other fairytales.

Competing Interests

Dr. Brull is a member of the board of directors for Anesthesia Patient Safety Foundation (Rochester, Minnesota), has received research funding from Merck & Co., Inc. (Kenilworth, New Jersey; funds to Mayo Clinic), is a principal and shareholder in Senzime AB (publ; Uppsala, Sweden), and is a member of the scientific advisory boards for ClearLine MD (Woburn, Massachusetts) and the Doctors Company (Napa, California).

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