In Reply:

We thank Drs. Phillips and Stewart for their interest in the work by Murphy *et al.*[1] and our accompanying editorial.[2] They "respectfully questioned five areas of the study" by Murphy *et al.*, and we are delighted to respond; we feel this topic has significant implications on clinical care and that a thorough understanding of the effects of neostigmine on neuromuscular transmission is paramount for optimal anesthetic care and patient safety.

Neostigmine Does *Not* Cause Muscle Weakness if Administered after a Nondepolarizing Neuromuscular Blocking Drug

Drs. Phillips and Stewart are absolutely correct about the potential for neostigmine to induce a depolarizing block, and thus, neuromuscular weakness. However, neostigmine may cause a depolarizing block (and clinical weakness) if it is *not* preceded by a nondepolarizing neuromuscular blocking drug. In most clinical settings, neostigmine is administered during periods of neuromuscular recovery, when a significant proportion of postsynaptic acetylcholine receptors are still occupied (blocked) by the neuromuscular blocking drug; in fact, it has been estimated that up to 70 to 75% of the receptors may be blocked by a neuromuscular blocking drug before fade to repetitive stimulation becomes apparent.[3] This partial nondepolarizing block appears to be protective of the depolarizing actions of excess acetylcholine produced by neostigmine. Published data confirm Murphy *et al.*'s observation[1] that neostigmine administration at neuromuscular recovery was not associated with evidence of muscle weakness. For instance, Caldwell[4] studied the effect of neostigmine 40 μg/kg administered at 1, 2, 3, and 4 h after a single dose of vecuronium (0.10 mg/kg) to groups of 10 patients each during nitrous oxide/oxygen/isoflurane anesthesia. At 1, 2, or 3 h after vecuronium administration, neostigmine was always followed by an increase in the train-of-four ratio. At 4 h, a slight transient decrease in the mean train-of-four ratio (from 0.91 to 0.83) was noted 10 min later, followed by return to a train-of-four ratio value of 0.95 at the end of the surgical procedure. In an additional 10 patients antagonized with only 20 μg/kg at 4 h, no decrease in the train-of-four ratio was observed. It must also be noted that in eight patients in whom the train-of-four ratio decreased after neostigmine, the amplitudes of both the first twitch and the fourth twitch increased after neostigmine administration, but the magnitude of the first twitch increase was proportionately greater than that of fourth twitch, resulting in a lower train-of-four ratio.[4]

Drs. Phillips and Stewart also stated that, "Neostigmine induced *depolarizing* neuromuscular blockade was not excluded in this study because twitch height was not recorded." In fact, single twitch depression *cannot* differentiate between a depolarizing and a nondepolarizing block. Lack of fade to train-of-four stimulation and absence of posttetanic potentiation are the characteristics of depolarizing block that can be used to differentiate it from a nondepolarizing block.[5]

Clinical Tests for Weakness Are Unreliable

We have no argument with this statement, and in fact much has been written about the lack of sensitivity and specificity of clinical tests in identifying residual neuromuscular paralysis[5]; however, we believe that Drs. Phillips and Stewart's statement should be placed in the context of Murphy *et al.*'s report. Clinical tests were performed "by a research assistant on a data collection sheet immediately before administration of neostigmine or saline and then every 12 s thereafter until tracheal extubation was performed."[1] Moreover, Murphy *et al.* stated, "On arrival to the [postanesthesia care unit], [train-of-four] ratios were again assessed. Two consecutive [train-of-four] measurements were obtained."[1] It is therefore clear that objective (quantitative) data were obtained, and that these data were used for correlating with the "11 signs and 16 symptoms of muscle weakness" that were collected from patients after postanesthesia care unit admission.[1]

Timing Is of the Essence

Here again, we agree with Drs. Phillips and Stewart: "Neostigmine-induced clinical weakness is expected to peak at 5 to 10 min after IV administration." However, given the well-known, wide variability in the response time to neostigmine (and most other drugs), it is highly unlikely that neuromuscular weakness would have been absent (or missed) in 100% of the patients because of a 5-min delay.

Neostigmine May Have Been Administered before Full Recovery from Blockade

Drs. Phillips and Stewart hypothesize that neostigmine may have been administered to some patients in Murphy *et al.*'s report when the train-of-four ratio was less than 0.9. This is certainly possible, although Murphy *et al.* "followed the good clinical research practice guidelines in pharmacodynamic studies of NMBAs [neuromuscular blocking agents]," which included delivery of a 5-s, 50-Hz tetanic stimulation for baseline stabilization, followed by calibration (CAL 2 mode).[1] So, even if "some of Murphy's patients may have received the dose of neostigmine while still partially paralyzed," the muscle weakness would have been mitigated only in some, but not *all* patients. We feel that Murphy *et al.*'s message is clear: neostigmine does not cause clinically significant muscle weakness if it is preceded by a nondepolarizing neuromuscular blocking drug.

What Use Is Acceleromyography in Awake Patients?

Drs. Phillips and Stewart reasonably question the validity of using acceleromyography in awake patients, and cite the

work by Baillard *et al.*[6] In fact, later work by Dubois *et al.*[7] has evaluated the repeatability of paired train-of-four ratio determinations, and their results showed much less variability of acceleromyography measurements. Most investigators agree that if high stimulating currents (50 to 60 mA) are used, best practice may be to test patients in the operating room during anesthesia and to check for adequate recovery before emergence from anesthesia, assuring patient comfort.

Residual Neuromuscular Blockade and Quantitative Monitoring

We wholeheartedly agree with Drs. Phillips and Stewart that the proper use of quantitative monitoring will help improve the quality of patient care by decreasing the incidence of postoperative residual blockade. In a recent article, we clearly stated our position and addressed the current challenges facing the implementation of routine objective monitoring.[8]

We do, however, disagree with Drs. Phillips and Stewart in their statement that the results of Murphy *et al.*'s study do not support the conclusion; we believe the results are clear. We have attempted to point out that neostigmine, administered during near-complete recovery from nondepolarizing neuromuscular block (not in the absence of a neuromuscular blocking drug), will *not* induce paradoxical neuromuscular weakness. Murphy *et al.* have settled this controversy, and clinicians owe them a debt of gratitude. We would be remiss, however, if we did not reiterate our warnings and recommendations that we have made for the past three decades—and that are identical to those of Drs. Phillips and Stewart: "To improve the safety of reversal, routine use of quantitative monitoring of neuromuscular function to guide the selection of most appropriate reversal agent and to confirm adequacy of reversal should be mandatory."

Competing Interests

Dr. Brull has intellectual property assigned to Mayo Clinic (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), The Doctors Company (Napa, California), and NMD Pharma (Aarhus, Denmark). Dr. Naguib has served as a consultant for GE Healthcare (Chicago, Illinois) in 2018.

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In Reply:

We thank Drs. Phillips and Stewart for their interest in our article.[1] The effect of neostigmine when given at the time neuromuscular recovery remains controversial, and Drs. Phillips and Stewart raise some important questions. We welcome the opportunity to respond to their queries.

We agree that we did not determine whether neostigmine induced depolarizing neuromuscular blockade. In order to assess this outcome measure, single twitch height must be recorded before and after muscle relaxant administration. In our clinical trial, we objectively evaluated muscle strength recovery by determining train-of-four ratios.[1] No patient exhibited evidence of neostigmine-induced muscle weakness, as train-of-four ratios did not decrease in any subject. Both quantitative techniques (single twitch height and train-of-four ratios) are effective in objectively measuring muscle strength, and further studies are needed to assess the effect of neostigmine on single twitch height.

We also agree that standard clinical tests of *signs* of muscle weakness (5-s head lift) are unreliable in determining the presence of full neuromuscular recovery.[2] However, we have previously determined that *symptoms* of muscle weakness (subjective feeling of difficulty performing the 5-s head lift) may be present when all clinical signs suggest full neuromuscular recovery has occurred, and may be more predictive of incomplete recovery.[3,4] In our investigation, more symptoms of muscle weakness were present in the group randomized to receive saline, compared to neostigmine, which suggests that neostigmine did not produce clinical evidence of muscle weakness. We hypothesize that the reason that all patients were able to perform the 5-s head lift before extubation, and nine patients were unable to complete the test after