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(Accepted for publication February 21, 2012.)

A Train-of-Four Count Should Be a Train-of-Four Count, Independently of the Method It Was Determined With

To the Editor:

We read with interest the article from Murphy *et al.* entitled "Intraoperative Acceleromyography Monitoring Reduces Symptoms of Muscle Weakness and Improves Quality of Recovery in the Early Postoperative Period."[1]

Indeed, the authors confirmed previous findings that objective acceleromyographic neuromuscular monitoring may improve perioperative neuromuscular management.[2] In the current study this improved perioperative management led to a better spontaneous recovery at the time of neostigmine administration: 61 of 76 patients in the acceleromyographic group compared with 41 of 74 patients in the control group had a train-of-four (TOF) count of 4 when neostigmine was given: $P = 0.014$. However, it is well known that the degree of spontaneous recovery at the time of neostigmine administration may have a major effect on neostigmine's efficacy. In this context Kirkegaard *et al.*[3] reported that 20 min after the administration of neostigmine 70 $\mu g/kg^{-1}$ at a TOF count of 4 the incidence of residual paralysis (defined as a TOF ratio less than 0.9) was 25%. This incidence increased to 56% when neostigmine was given at a TOF count of 2 instead of 4 without changing any of the other parameters.[3] Unfortunately, the timing of neostigmine administration was hardly controlled in the trial by Murphy *et al.*[2] and therefore some points seem quite unclear to us: first, according to the Methods section neostigmine should be given when a TOF count of at least 3 was present. In the Results section, however, the TOF count at the time of neostigmine administration ranged from a TOFcount between 0 and 4. Second, and as mentioned previously, the number of patients who had a TOF count of 4 at this time was increased by 30% in the acceleromyographic group *versus* control. Murphy et al. found a significant difference in repeat doses of rocuronium between the two groups during the last 45 min of the surgical procedure, a finding that is supposed to explain the effect in the acceleromyographic group. As stated in the Methods section, participating anesthesiologists were allowed to use "TOF ratio data to guide neuromuscular blocking agents dosing when surgical relaxation was not longer required." The authors are requested to provide some information about the management of neuromuscular blocking agents dosing in the control group during this period. Third, most patients (102 of 150) had 4 TOF responses at the moment of neostigmine administration. It is not obvious whether these patients all had a simple TOF count of 4 (4 responses present with the first response less than 20%; the TOF-Watch SX® [Bluestar Enterprises, Omaha, NE] display shows the TOF count) or whether recovery was even more advanced in some patients (still 4 responses present but the first response more than 20%; the TOF-Watch SX® calculates and shows the TOF ratio). Further, it should be reported if and how this distinction was made in the control group. Finally, it would be interesting to know if all patients received a standard dose of 50 $\mu g/kg^{-1}$ neostigmine, even in case of a deeper residual block with less than three twitch responses. Some information about the real doses of neostigmine that have been used could be helpful in this context.

Based on the information provided, we must conclude that the difference in symptoms of muscle weakness and improved quality of recovery observed in this study could simply be the consequence of the dose or the timing of the administration of neostigmine rather than the direct consequences of intraoperative acceleromyographic monitoring as supposed by Murphy *et al.*

We suggest that the authors should complete the missing information and report the incidence of residual blockade and associated unpleasant symptoms of muscle weakness separately according to the patients' individual TOF count at the time of neostigmine administration to clarify this key issue. In our opinion, these data are essential for the reader to allow a correct interpretation of the results and, thus, to improve patient's safety. Moreover, it would be very instructive to see whether there were any significant differences in unpleasant symptoms if neostigmine was given at TOF count of 4 independently from the technique of determination (acceleromyographic or conventional qualitative monitoring, respectively), as supposed by Murphy *et al.* Currently, we are in doubt about this issue.

In addition, the number of included patients reported in the "What This Article Tells Us That Is New" section is probably incorrect and should be 155 instead of 115.

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(Accepted for publication February 21, 2012.)

In Reply:

The authors thank Drs. Fuchs-Buder and Schreiber for their interest in our clinical investigation,[1] and we welcome the opportunity to respond to the questions raised in their Letter to the Editor. We agree that the degree of spontaneous neuromuscular recovery at the time of neostigmine administration has an important effect on the incidence of residual paresis in the postanesthesia care unit. As demonstrated in the investigation of Kim *et al.*, the median (range) times required to achieve a train-of-four (TOF) ratio of 0.9 after reversal with neostigmine (0.07 mg/kg) were 22.6 (8.3–57.4) min at a TOF count of 2 and 9.7 (5.1–26.4) min at a TOF count of 4.[2] The relatively common practice of administering an anticholinesterase agent only a few minutes before tracheal extubation, regardless of the TOF count, likely explains the high incidence of residual neuromuscular blockade reported in numerous clinical investigations.[3]

However, our data do not support the conclusion by Drs. Fuchs-Buder and Schreiber "that the difference in symptoms of muscle weakness and improved quality of recovery observed in this study could simply be the consequence of the dose or the timing of the administration of neostigmine." In fact, no differences in management of reversal of neuromuscular blockade (time or dose) were observed between the acceleromyography and control groups. All patients in the study received a standard dose of neostigmine (50 μg/kg) "at the conclusion of the surgical closure." The study protocol specifically defined the timing of neostigmine administration to standardize management in both groups and to account for the relatively long time required to achieve adequate recovery of neuromuscular function, even at a TOF count of 4 (10 min).[3] The protocol also stated that neostigmine should be given at a TOF count of 3–4 and this was achieved in the majority of patients because the median TOF count in both groups was 4 at reversal (only 1 patient of 150 had a TOF count of 0 at this time). Nonetheless, a higher percentage of patients in the acceleromyography group achieved spontaneous recovery to a TOF count of 4 at the time of reversal compared with our control group (80.3% *vs.* 55.4%, respectively). We believe this was due to more careful management of neuromuscular blockade at the end of surgery in the patients monitored with acceleromyography. In both study groups, dosing of neuromuscular blocking agents was carefully standardized; however, administration of additional neuromuscular blocking agents during the times of the operation not requiring neuromuscular blockade was at the discretion of the anesthesia care team. We hypothesized that acceleromyography monitoring would allow for more accurate titration of neuromuscular blocking agents during this important time period, and our findings supported this hypothesis (*i.e.*, fewer patients in the acceleromyography group received neuromuscular blocking agents during the last 45 min of the surgical procedure). Thus, our findings suggest that improved spontaneous recovery of neuromuscular function at the time of neostigmine administration in the acceleromyography group resulted in fewer patients with residual muscle weakness in the postanesthesia care unit.

It should be noted that the protocol used a simple definition of the TOF count at the time of reversal. As indicated, neostigmine was administered when at least three to four visual responses ("twitches") to TOF stimulation were observed. Data from the TOF-Watch SX® (Bluestar Enterprises, Omaha, NE) display were not used in the decision process at the time of reversal. We did not attempt to differentiate between a "strong fourth twitch" and a "weak fourth twitch."

In conclusion, we agree that improved spontaneous recovery at the time of reversal resulted in fewer symptoms of muscle weakness in the postanesthesia care unit. Our data suggest that acceleromyography monitoring, by allowing for more rational and accurate management of neuromuscular blockade, resulted in more patients with a TOF count of 4 at the time of reversal and fewer patients with residual paresis after tracheal extubation. Although additional analysis of our data could reveal that patients with higher TOF counts at the time of reversal have fewer symptoms of muscle weakness and improved quality of recovery, such an analysis is beyond the scope of a Letter to the Editor. Additional studies are needed to identify the mechanisms by which acceleromyography monitoring decreases the incidence of residual neuromuscular blockade.

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