

EDITORIALS

Neostigmine as an antagonist of residual block: best practices do not guarantee predictable results

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Recently, there has been considerable editorial opinion to affirm the position that the use of quantitative monitoring should be mandatory for all patients receiving neuromuscular blocking agents (NMBAs).^{1,2} Neostigmine has limits to its efficacy as an antagonist of non-depolarising blockade, and that qualitative or subjective monitoring with a conventional peripheral nerve stimulator can often lead the clinician astray. Thus, the current position of many experts is that it is time to retire our peripheral nerve stimulator devices in favour of objective neuromuscular monitors, and also replace neostigmine with the routine administration of sugammadex for the reversal of even modest degrees of neuromuscular block [train-of-four (TOF) counts of three or greater].

However, the general acceptance of objective or quantitative monitoring has been slow to occur, and most clinicians simply do not believe that clinically significant postoperative residual neuromuscular block is a common occurrence in their individual practices.³ Thus, the reversal of residual block with neostigmine using conventional peripheral nerve stimulator units as a guide is still widely practiced. In this issue of the *British Journal of Anaesthesia*, Thilen and colleagues⁴ set out to define the safety limits of this approach using what they propose is a 'best practice protocol'. The authors demonstrate that the use of a rigid approach to neuromuscular management, in the absence of quantitative monitoring or sugammadex,

resulted in fewer patients exhibiting severe postoperative residual neuromuscular block at the time of tracheal extubation and upon arrival in the post-anaesthesia care unit. However, the study also clearly illustrates why residual neuromuscular block still persists in many clinical practices.

There is little debate that the risk of postoperative residual neuromuscular block can be reduced with the use of quantitative monitoring and sugammadex.^{5,6} However, only two quantitative monitors are commercially available in the USA: Datex-Ohmeda NMT module, which can only be used as part of Datex anaesthesia machine (GE Healthcare, Louisville, KY, USA), and the portable STIMPOD monitor (Xavant Technology, Pretoria, South Africa), which lacks validation studies, and these are infrequently applied by clinicians. Furthermore, access to sugammadex is often limited by hospital policy because of high acquisition costs. The investigation by Thilen and colleagues⁴ attempted to determine if the risk of postoperative residual neuromuscular block could be decreased by using a simple peripheral nerve stimulator and neostigmine, which are available to most clinicians in the USA and the European Union. The authors identified several evidence-based monitoring practices [titration of NMBAs by age and gender, avoidance of deep blockade, neostigmine administration at a TOF count of four, and reversal strategies (appropriate neostigmine dosing, allowing 10 min between reversal and extubation)] documented to be effective in reducing the incidence of incomplete neuromuscular recovery.^{7,8} This study examines an important question: can these strategies reduce

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the incidence of clinically significant postoperative residual neuromuscular block?

The investigators demonstrated that the incidence of severe postoperative residual neuromuscular block at the time of post-anaesthesia care unit admission was significantly reduced in the protocol arm of the study, which suggests that careful management of neuromuscular block can improve outcomes in patients at risk for complications related to postoperative residual neuromuscular block. However, despite the optimal use of a peripheral nerve stimulator and neostigmine, 35% of subjects in the protocol cohort had a TOF ratio of <0.9 at the time of extubation. No statistically significant difference was observed in this primary outcome measure between the protocol group and a control group where clinicians were left to 'practice as usual'. On the basis of these findings, some readers may conclude that there is little value to vigilant management of neuromuscular block. However, a careful reading of the investigation also illustrates important advantages to the techniques described by the authors.

The incidence of severe postoperative residual neuromuscular block at admission to the post-anaesthesia care unit, defined as a TOF ratio <0.7 , was 0% in the protocol arm vs 21% in the control cohort. It is likely that patients with more severe levels of postoperative residual neuromuscular block are at greater risk for more significant adverse events, such as postoperative critical respiratory events and pneumonia.^{9–13} This important threshold (TOF <0.7) is not often assessed in clinical trials. The authors also observed that the incidence of the primary endpoint (TOF <0.9) was ~40% less in the protocol cohort. Although this difference appears clinically meaningful, it was not statistically significant ($P=0.068$) and likely represents a type II error. According to the sample-size calculation, 40 patients per group were needed, yet only 38 were analysed in each arm of the study, and it is probable that a larger study would have yielded statistically significant findings. In addition, the investigators also obtained baseline TOF values and calibrated the TOF-Watch SX before the NMBA administration. These practices allow for a more accurate assessment of actual neuromuscular recovery, and are often not conducted in clinical trials.^{14,15} The authors also noted a trend towards a reduction in post-anaesthesia care unit length of stay in the protocol cohort; future larger-scale studies should be conducted to examine this important economic outcome measure.

The authors' protocol involved a bundled intervention of evidence-based strategies identified to reduce the risk of postoperative residual neuromuscular block. They suggest that delaying neostigmine administration until the reappearance of the fourth response to TOF stimulation and further postponing tracheal extubation for at least 10 min are the critical components of the protocol. There are only a few investigations that have previously examined this important strategy. Kim and colleagues¹⁶ observed that the median time required to achieve a TOF ratio of 0.9 (from the reappearance of the fourth twitch) after $70 \mu\text{g kg}^{-1}$ of neostigmine was 9.7 min. However, both shorter (3.3 min) and longer (16.5 min) median time intervals have been reported.^{17,18} Additionally, it is important to note that a wide range of recovery times, from 19 to 143 min, was also observed in these investigations.^{16–18} Thus, the finding that 35% of the subjects in the study by Thilen and colleagues⁴ had not achieved full neuromuscular recovery, despite reversal at a TOF count of four and waiting at least 10 min before performing extubation, is not surprising.

There are some limitations to the study that were not addressed by the authors. Although the incidence of severe

postoperative residual neuromuscular block was reduced in protocol subjects, the reasons for this beneficial effect are not clear. No differences in total rocuronium dose, time from the last doses of NMBA to extubation, or time from the neostigmine dose to extubation were noted. However, the last dose of rocuronium was smaller and neostigmine doses were lower in the protocol groups, which may have contributed to the reduction in severe postoperative residual neuromuscular block. Appropriate dosing of neostigmine, based on ideal body weight and the presence or absence of fade, likely reduced the risk of potential neostigmine-induced muscle weakness. In addition, the generalisability of these findings into different clinical practices may be difficult. Frequently, a standard dose of rocuronium (for induction and maintenance) and neostigmine is administered, and many practitioners may be reluctant to perform the more complex dosage calculations suggested by the authors. Routinely achieving a TOF count of four at *adductor pollicis* at the end of surgery can be difficult, and many clinicians will be unwilling to wait an additional 10–15 min before performing extubation because of time pressures in the operating room.³

The authors correctly observe: 'Since this protocol involved a bundled intervention, we do not know which of the several components of the protocol contributed most to the improved outcome'. Does limiting the administered dose of relaxant matter? Perhaps.¹⁹ After a dose $\leq 2 \times$ the ED₉₅, plasma concentrations of the drug are reduced by both elimination/metabolism and by redistribution away from the effect site. With larger doses, redistribution plays an increasingly smaller role in the recovery process. Thus, it is possible that rocuronium reversal with neostigmine at a threshold TOF count of four will be more successful if the total administered dose is limited. Nevertheless, it is not clear that the authors' dose manipulations really mattered. We suspect that the key element of the authors' protocol was delaying neostigmine administration until the TOF count had returned to four palpable responses at the thumb.

What should the reader conclude from these findings? We believe that the study demonstrates that the risk of postoperative residual neuromuscular block can be reduced, but not eliminated, through the routine use of a peripheral nerve stimulator and neostigmine. Despite clinicians achieving a TOF count of four at the time of reversal, and then delaying extubation for an additional 10–15 min, a high percentage of patients continued to exhibit postoperative residual neuromuscular block at the time of extubation. However, the risk of severe postoperative residual neuromuscular block, which is likely associated with more significant postoperative complications, was reduced to 0% at admission to the post-anaesthesia care unit using this protocol. We believe that the investigation by Thilen and colleagues⁴ provides clear support for the concept that careful neuromuscular block management, when quantitative monitoring and sugammadex are unavailable, can reduce the risk of postoperative residual neuromuscular block. There are surprisingly few published studies of the efficacy of neostigmine when administered at a threshold TOF count of four. This investigation is a worthwhile addition to this small list of studies.

Authors' contributions

Both authors contributed to the preparation of this manuscript.

Declaration of interest

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A poisoned chalice: the heritage of parental anaesthesia exposure

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