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Clinical Investigation

CLINICAL INVESTIGATION

Management of rocuronium neuromuscular block using a protocol for qualitative monitoring and reversal with neostigmine

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Abstract

Background: Neuromuscular block using subjective monitoring and neostigmine reversal is commonly associated with postoperative residual neuromuscular block. We tested whether a protocol for the management of neuromuscular block that specified appropriate dosing and optimal neostigmine reversal was associated with a reduction in PRNB.
Methods: Rocuronium administration was guided by surgical requirements and based on the ideal body weight, with dose reductions for female sex and age >55 yr. Neostigmine was administered in adjusted doses after a train-of-four count of four was confirmed at the thumb. The protocol ensured a minimum of 10 min between neostigmine administration and tracheal extubation. We measured the PRNB in patients undergoing abdominal surgery before and after the introduction of the protocol. Pre-specified primary and secondary endpoints were incidence of postoperative residual neuromuscular block and severe postoperative residual neuromuscular block at the time of tracheal extubation, defined as normalised train-of-four ratios <0.9 and <0.7, respectively.
Results: The incidence of postoperative residual neuromuscular block at tracheal extubation was 14/40 (35%) for patients managed according to the protocol compared with 22/38 (58%) for patients in the control group, odds ratio of 0.39, and 95% confidence interval of 0.14–1.07; $P=0.068$. The incidence of severe postoperative residual neuromuscular block at tracheal extubation showed a highly significant difference, odds ratio=0.06, and confidence interval of 0.00–0.43; $P=0.001$.
Conclusions: The incidence of severe postoperative residual neuromuscular block was significantly reduced after the protocol was introduced. Given the limitations inherent in this before-and-after study, further research is needed to confirm these results.
Clinical trial registration: NCT02660398.

Keywords: muscle weakness/chemically induced; neostigmine; neuromuscular blocking agents; rocuronium

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Editor's key points

- Whilst quantitation neuromuscular function monitoring is recommended, subjective qualitative monitoring is more commonly practiced.
- A protocol for management of neuromuscular block with specified appropriate rocuronium dosing and optimal neostigmine reversal was tested in a small pragmatic before/after study at a single centre.
- Use of the protocol was associated with a reduction in severe postoperative residual neuromuscular block as assessed by several secondary endpoints.
- Further studies are needed to test whether rates of residual neuromuscular block can be lowered by implementing such a protocol with specific strategies to maximise adherence.

The majority of anaesthesia providers worldwide manage intraoperative muscle relaxation without the use of quantitative neuromuscular monitoring.[1] Rather, they practice within the limitations of clinical observations that include the subjective evaluation of the twitch response evoked by peripheral-nerve stimulators. With regard to reversal, the use of sugammadex is often limited or restricted, and cholinesterase inhibitors are frequently used. Multiple studies of the use of conventional peripheral-nerve stimulators and neostigmine reversal of intermediate-acting neuromuscular blocking drugs (NMBDs) have documented a high incidence of postoperative residual neuromuscular block (PRNB).[2,3] A recent multicentre study reported an incidence of PRNB of 64% at the time of tracheal extubation and 57% at arrival to the post-anaesthesia care unit (PACU).[4] In this observational study, anaesthetic management was left at the discretion of the individual anaesthesiologist, and specific practice details were not reported.

A previous study demonstrated the benefit of using a protocol for muscle relaxant and subsequent neostigmine administration.[5] The protocol was based on the subjective evaluation of the evoked response of peripheral-nerve stimulation and neostigmine administration at an *adductor pollicis* train-of-four (TOF) count of 2. Ten minutes after the neostigmine administration, the incidence of TOF ratio <0.7 was 30%. Since the publication of this report, several experts have recommended that neostigmine administration be deferred until a TOF count of 4.[6–9] Moreover, recent reports have highlighted common risk factors for PRNB, notably obesity, sex, and age.[10–16]

We designed a prospective cohort study to evaluate an updated protocol for the management of neuromuscular block and reversal, enrolling participants before and after the introduction of the protocol. We hypothesised that implementing this protocol for the management of muscle relaxation and reversal with neostigmine would be associated with a lower risk of PRNB defined as normalised TOF (nTOF) ratio <0.9 at the time of tracheal extubation and of severe residual paralysis, defined as nTOF ratio <0.7 at tracheal extubation.

Methods

The study was approved by the Human Subjects Division of the University of Washington (Seattle, WA, USA) and registered at ClinicalTrials.gov (NCT02660398). Written informed consent was obtained from all participants. This before-and-after study was conducted at two teaching hospitals: Harborview Medical Center and University of Washington Medical Center from January to June 2016. We prospectively enrolled participants with ASA Physical status 1–4 who were free from underlying neuromuscular disorders and scheduled to undergo elective abdominal surgery expected to last <4 h and with anticipated use of NMBDs. The exclusion criteria included age <18 yr, pregnant or lactating women, and non-English-speaking patients.

The initial control period consisted of an observational cohort that was managed at the discretion of the anaesthesia providers. The protocol period consisted of a cohort of patients that was managed according to a standardised protocol for the management of rocuronium and subsequent reversal with neostigmine. The primary providers of anaesthesia for all patients in both periods of the study were certified registered nurse anaesthetists and residents, practising with attending staff supervision. No attempt was made to standardise other aspects of care, such as airway management or general anaesthesia induction and maintenance. All patients received usual anaesthesia care, including standard monitoring with electrocardiography, pulse oximetry, end-tidal carbon dioxide concentration, and non-invasive blood-pressure monitoring.

Control period

Each operating room was equipped with a conventional peripheral-nerve stimulator for TOF monitoring (DigiStim II Nerve Stimulator; Neuro Technology, CCR Medical, Inc., St Petersburg, FL, USA) also capable of delivering 50 and 100 Hz tetanic stimulation. Although no written policy was in place, the use of these conventional nerve stimulators was part of routine practice. Documentation of neuromuscular monitoring data in the electronic anaesthesia record requires manual entry, which was not consistently performed. Quantitative monitoring was not routine and was not used by the anaesthesia providers in this study. During the control period, the frequency of neuromuscular monitoring, the choice and administration of NMBD, and the timing and dose of neostigmine for reversal were at the discretion of the provider.

Protocol for neuromuscular monitoring, and rocuronium and neostigmine use

The protocol recommended the manual assessment of the *adductor pollicis* TOF count, if feasible, and intraoperative muscle relaxation according to surgical requirement (Table 1). All rocuronium and neostigmine doses were calculated using the ideal body weight (IBW). Previous studies indicate that NMBDs are more appropriately dosed based on IBW than on total body weight,[10,11] and high BMI has been identified as a risk factor for PRNB.[12] IBW was defined as $50.0+2.3\ kg\ in^{-1}$ over 5 ft for males and $45.5+2.3\ kg\ in^{-1}$ over 5 ft for females, with intubation dose calculated as $0.6\ mg\ kg^{-1}$ (IBW). Doses for females were reduced by 15%, as the ED_{95} is lower for females, and females given the same dose as males have a prolonged effect.[13–15] We calculated an additional 1% dose reduction per year over 55 yr of patient age because of previous studies indicating a prolonged effect in the elderly,[14] and age reported as a risk factor for PRNB.[16] The protocol recommended avoiding deep block (complete depression of the TOF response) because there is conflicting evidence that deep block