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Postoperative impairment of motor function at train-of-four ratio ≥0.9 cannot be improved by sugammadex (1 mg kg^{-1})

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Editor's key points

- Recovery of neuromuscular block to a train-of-four ratio ≥0.9 is deemed sufficient for extubation.
- At this ratio, many postsynaptic receptors are still occupied by the neuromuscular blocking agent.
- The authors thus studied the effect of sugammadex 1 mg kg^{-1} on muscle function and well-being.
- No effect was found.

Background. A train-of-four ratio (TOFR) ≥0.9 measured by quantitative neuromuscular monitoring is accepted as an indication of sufficient neuromuscular recovery for extubation, even though many postsynaptic acetylcholine receptors may still be inhibited. We investigated whether antagonism with sugammadex after spontaneous recovery to TOFR≥0.9 further improves muscle function or subjective well-being.

Methods. Following recovery to TOFR≥0.9 and emergence from anaesthesia, 300 patients randomly received either sugammadex 1.0 mg kg^{-1} or placebo. Fine motor function (Purdue Pegboard Test) and maximal voluntary grip strength were measured before and after surgery (before and after test drug administration). At discharge from the postanaesthesia care unit, well-being was assessed with numerical analogue scales and the Quality-of-Recovery Score 40 (QoR-40).

Results. Patients' fine motor function [6 (SD 4) *vs* 15 (3) pegs (30 s)$^{-1}$, $P<0.05$] and maximal voluntary grip strength (284 (126) *vs* 386 (125) N, $P<0.05$) were significantly lower after anaesthesia compared with the pre-anaesthesia baseline. After sugammadex or placebo, motor function was significantly improved in both groups but did not reach the preoperative level. There was no difference between groups at any time. Global well-being was unaffected (QoR-40: placebo, 174 *vs* 185; sugammadex, 175 *vs* 186, $P>0.05$).

Conclusions. Antagonizing rocuronium at TOF≥0.9 with sugammadex 1.0 mg kg^{-1} did not improve patients' motor function or well-being when compared with placebo. Our data support the view that TOFR≥0.9 measured by electromyography signifies sufficient recovery of neuromuscular function.

Clinical trial registration. The trial is registered at ClinicalTrials.gov (NCT01101139).

Keywords: neuromuscular blocking agent; postoperative residual paralysis; quantitative neuromuscular monitoring; sugammadex

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The use of neuromuscular blocking agents (NMBAs) during anaesthesia is associated with the risk of residual neuromuscular block and respiratory complications.[1] In the early 1970s, Ali and colleagues[2 3] promoted the development of quantitative neuromuscular monitoring. They introduced the train-of-four ratio (TOFR) as an objective index of adequate recovery from neuromuscular block. In addition, clinical recovery from neuromuscular block was evaluated by the ability to lift the head.[3] Based on their findings, recovery to a TOFR of 0.7 was initially recommended before tracheal extubation.[3] According to current expert opinion, a TOFR≥0.9 measured by quantitative neuromuscular monitoring indicates sufficient recovery from neuromuscular block.[4] This threshold was suggested based on recovery of respiratory function,[5 6] leading to intense discussion on whether recovery to TOFR=0.9 is indeed sufficient for extubation.[7] In this context, other aspects of residual neuromuscular block, such as muscle weakness and discomfort in the postanaesthesia care unit (PACU), were gradually ignored, although they have a significant impact on patients' postoperative rehabilitation and may be critical for street readiness.[8 9]

After absence of any twitch depression detectable by neuromuscular monitoring, approximately 75% of postsynaptic acetylcholine receptors are still occupied by non-depolarizing NMBAs.[10 11] The magnitude of residual NMBA effects at the neuromuscular junction, however, cannot be quantified by current methods of neuromuscular monitoring.[10 11] Therefore,

we hypothesized that the remaining block at TOFR≥0.9 is the reason for the patients' feeling of muscle weakness and compromised subjective well-being.

This study was designed to examine whether fine motor skills, maximal voluntary contraction force, and patients' well-being can be improved by eliminating rocuronium with a dose of sugammadex 1.0 mg kg^{-1} after spontaneous recovery to TOFR≥0.9.

Methods

Patients

The trial was registered at ClinicalTrials.gov (NCT01101139) and approved by the local ethics committee (Ethikkommission der Fakultät für Medizin der Technischen Universität München, Munich, Germany; study coordinator, M.B.). After written informed consent, we enrolled 300 patients (ASA I–III) scheduled for elective low-risk surgical procedures under general anaesthesia. Patients were excluded if they participated in another randomized clinical trial, if their age was <18 or >65 yrs, if they had a history of neuromuscular diseases or malignant hyperthermia, if they had significant hepatic or renal dysfunction, if they were allergic to anaesthetics, NMBAs, or sugammadex, if they had a psychiatric disorder, or if they were pregnant or breastfeeding.

Study design

This study was a single-centre, randomized, controlled, double-blinded trial. Following recovery to TOFR≥0.9 and emergence from anaesthesia, all patients were randomly assigned to receive either sugammadex or saline in the PACU. The surgical and anaesthesia team, including the postanaesthesia care team, were blinded to the group assignment. Only the study coordinator, who prepared the study medication labelled with the randomization code, was unblinded to group assignment. He was not involved in any testing or care taking of the patients.

Preoperative assessment

After preoperative assessment and written consent, patients performed initial testing of gross and fine motor function and completed a well-being questionnaire. Maximal voluntary muscle strength was measured using hand dynamometry (Jamar Plus+Hand Dynamometer™; Patterson Medical, Sammons Preston, Bolingbrook, IL, USA). Before testing, the study assessor demonstrated the handling of the hand dynamometer and coached patients through the procedure. They were asked to choose a hand and to press the hand dynamometer once, with maximal force (measured in newtons).[12 13] The Purdue Pegboard was used to test fine motor skills (Purdue Pegboard Test™; Lafayette Instrument Company, Lafayette, IN, USA)[14] and was also demonstrated to each participant before testing. By using the dominant hand, patients placed 3-cm-long pegs in a row on a wooden board; as many and as fast as they could within 30 s. Preoperative well-being was measured by the Quality-of-Recovery Score 40 (QoR-40).[15 16] This patient-assessed questionnaire evaluates the quality of recovery after surgery and anaesthesia. It encompasses the following five dimensions that have been identified to be clinically relevant: emotional state, physical comfort, psychological support, physical independence, and pain. As a result of its high validity, reliability, and responsiveness, the questionnaire is a valuable tool to assess well-being in the perioperative period and is recommended for clinical use and research.[15 16]

Anaesthesia

Patients received no premedication. After arrival in the preoperative area, an i.v. cannula was placed in a proximal forearm vein in order to avoid interference with the muscle function tests, and an infusion of Ringer's acetate solution was administered. Standard anaesthesia monitoring, including pulse oximetry, non-invasive blood pressure, and electrocardiography, was established. To prevent postoperative nausea and vomiting, patients were given dexamethasone (8 mg) i.v. After the Entropy™ Module (GE Datex-Ohmeda Entropy™; GE Healthcare, Milwaukee, WI, USA) was set up to monitor depth of hypnosis, anaesthesia was induced with fentanyl (0.1–0.2 μg kg^{-1}) and propofol (2–3 mg kg^{-1}). After patients became apnoeic, their lungs were ventilated by facemask with 100% oxygen.

Neuromuscular monitoring was performed using evoked electromyography of the adductor pollicis muscle with a NMT module in an S/5 GE Datex Light monitor (GE Datex Medical Instrumentation, Inc., Tewksbury, MA, USA). In brief, the forearm was immobilized, and surface skin electrodes were placed over the ulnar nerve proximal to the wrist. After 3 min of calibration, the ulnar nerve was stimulated with supramaximal train-of-four stimulation at 20 s intervals and the evoked electromyogram of the adductor pollicis muscle recorded. Following the calibration of the neuromuscular monitoring with stable TOFR (0.97–1.0), rocuronium 0.6 mg kg^{-1} was injected i.v., and tracheal intubation was performed at TOFR=0.

After intubation, anaesthesia was maintained with remifentanil and sevoflurane according to the clinical needs monitored with the Entropy™ Module (GE Datex-Ohmeda Entropy™; GE Healthcare) and the preference of the responsible anaesthetist. Ventilation with 40–50% oxygen in air was controlled to maintain normocapnia (end-tidal carbon dioxide tension 4.6–6 kPa). During surgery, maintenance doses of rocuronium were given if required to improve mechanical ventilation or surgical conditions. Oropharyngeal temperature was kept ≥36°C using a forced air-warming device.

At the end of surgery, neuromuscular function was allowed to recover spontaneously. Paracetamol (Perfalgan™ 1 g 100 ml^{-1}; Bristol-Myers Squibb, NY, USA) was administered for preventive analgesia, and Ondansetron-hameln 2mg/ml (Hameln Pharmaceuticals GMBH, Hameln, Germany) for additional prophylaxis of postoperative nausea and vomiting. Remifentanil infusion and sevoflurane inhalation were discontinued. At TOFR≥0.9, the trachea was extubated and patients were immediately transferred to the PACU.

Only after spontaneous recovery to a TOFR≥0.9 and emergence from anaesthesia were patients eligible for randomization in the PACU in order to avoid dropouts because of secondary exclusion criteria (e.g. requirement for an antagonistic agent because of insufficient spontaneous neuromuscular recovery; please see also Fig. 1) and organizational problems.