

Residual neuromuscular block in elderly patients after surgical procedures under general anaesthesia with rocuronium

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ABSTRACT

Background. Incomplete recovery of neuromuscular function following the administration of medium-acting, non-depolarising agents is one of the most feared complications in anaesthesia. We assessed the incidence of postoperative residual curarisation (PORC) after general anaesthesia with rocuronium in elderly and young patients, and we evaluated possible complications of postoperative residual curarisation.

Methods. This observational study included 415 patients (ASA physical status I–III) who were undergoing different surgical procedures: 184 patients were aged ≥ 65 (range: 65–89) years, and 231 patients were aged 19–57 years. No patients had renal or hepatic disorders. Patients received rocuronium for relaxation. Neuromuscular monitoring was not used intraoperatively. Neuromuscular function recovery was spontaneous. Patients were transferred to the post-anaesthesia care unit (PACU) after anaesthesia. During the first ten minutes in the post-anaesthesia care unit, the presence of postoperative residual curarisation was assessed by acceleromyography and train-of-four (TOF) stimulation. Patient well-being was monitored continuously. During hospitalisation, patient medical documentation was assessed for postoperative residual curarisation-related complications.

Results. TOF ratios were < 0.7 in 31% of all patients, whereas the block was clinically completely recovered in all patients. Postoperative residual curarisation was more frequent in elderly (44%) than younger patients (20%) ($P < 0.05$). Only 73 patients (21 elderly, 52 younger patients) had TOF ratios ≥ 0.9 . Hypoxia was more frequent in elderly patients in the PACU: 17.9% vs. 8.2% ($P < 0.05$). Postoperative residual curarisation-related pneumonia was observed in one elderly patient.

Conclusion. Residual paralysis remains a major problem in geriatric clinical anaesthesia. Neuromuscular function monitoring is obligatory, and pharmacological reversal of relaxation should be advised in geriatric patients after using relaxants for general anaesthesia.

Key words: postoperative residual curarisation, general anaesthesia, neuromuscular block, neuromuscular monitoring, postoperative pulmonary complications, geriatric patients

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Muscle relaxation is only one of the components of balanced anaesthesia. Reports on the use of curare in 25 patients by Harrold Griffith and Enid Johnson changed anaesthetic practice and heralded the start of the modern era of anaesthesiology [1]. Previously, deep inhalational anaesthesia had been the only way to provide adequate muscle relaxation, but this approach was poorly tolerated by debilitated and elderly patients.

Almost immediately after the introduction of curare, apart from the desired clinical effect, the disadvantageous influence of residual curarisation was also observed. After the introduction of muscle relaxants into routine anaesthesia, reports of postoperative asphyxia and residual curarisation were published [2].

In 1955, Beecher and Todd showed that the use of curare increases anaesthesia-related mortality six-fold [3]. The

importance of postoperative residual curarisation (PORC) and its effect on postoperative complications has been described repeatedly during subsequent decades. These studies demonstrated that the incidence of postoperative pulmonary complications was significantly more frequent for patients who had PORC in the recovery room [4–6]. This effect decreases the throughput of patients in the operating theatre and increases operating theatre costs [7].

According to demographic data, the highest level of ageing in the European community will occur between 2010 and 2020. The number of people aged 50–64 will increase by 26%, the number of people aged 65+ years is predicted to be approximately 30%, and the number of people aged 20–29 years will decrease by 20%. This effect is caused by the fact that the group of people who represent the population boom will reach middle-age.

Most anaesthesiologists currently provide care for geriatric patients and will increasingly likely be needed to do so in the future. Physiological changes that accompany ageing, including decreases in hepatic and renal blood flow and function, may impact the pharmacodynamics and pharmacokinetics of non-depolarising neuromuscular blocking agents.

Rocuronium is considered to be a safe muscle relaxant for elderly patients. The aim of this study was to determine the incidence of PORC and critical respiratory events (CRE) including hypoxia in the post-anaesthesia care unit (PACU) after general anaesthesia, and to examine the connection between ageing and residual paralysis after using rocuronium. Our research aimed to determine whether there is a need for special consideration associated with using this muscle relaxant in geriatric patients.

METHODS

The study protocol was approved by the University Ethics Committee (protocol number: RNN/704/10/KB, 14 December 2010, Chair: Professor Przedzislav Polakowski). A total of 415 patients (ASA I–III physical status) who gave their written consent were included in this observational study. Patients were excluded from the study if they were pregnant, had a BMI > 35 kg m⁻², hepatic, renal and/or neuromuscular disorders (peripheral neuropathy or myasthenia gravis), or were unable to communicate. Patients who were receiving medications potentially interacting with rocuronium (known or suspected to be capable of affecting normal neuromuscular transmission) were also excluded. The most important criterion taken into consideration while dividing patients into groups was the patient's age. Patients were divided into two groups: group A, patients aged ≥ 65 years, and group B, patients aged < 65 years.

Premedication consisted of oral midazolam 7.5 mg for all the young and elderly patients who required the procedure, 1–2 hours before surgery. Heart rate, indirect blood

pressure, and oxygen saturation by pulse oximetry were monitored in all patients.

Anaesthesia was induced with thiopental 5 mg kg⁻¹ or etomidate 0.3 mg kg⁻¹ (for young patients with cardiovascular diseases and all elderly patients). Pain was managed with fentanyl. Patients received rocuronium 0.6 mg kg⁻¹ for endotracheal intubation. After receiving rocuronium, all patients were manually ventilated by mask with oxygen for 1.5 min and intubated. After intubation, patients received intermittent positive pressure ventilation with a 50% air/50% O₂ mixture at a tidal volume of 6–8 mL kg⁻¹, a frequency of 10–12 min⁻¹ and end-tidal carbon dioxide of 30–35 mm Hg. Repeated doses of rocuronium 0.15 mg kg⁻¹ were given during surgery after 30–40 min. Anaesthesia was maintained with sevoflurane (end-tidal concentration 1–1.5%). Neuromuscular monitoring was not used intraoperatively. Patients did not receive neostigmine at the end of anaesthesia. The anaesthesiologist allowed for spontaneous recovery of neuromuscular function.

Each patient left the operating room based on the decision of the treating anaesthetist, according to the following clinical indicators of adequate neuromuscular function: the ability to sustain a head lift for five seconds, to sustain a firm hand-grip or tongue protrusion, and to cough effectively. In the recovery room, an anaesthesiologist other than the one who administered the muscle relaxant performed an assessment of neuromuscular function during the first ten minutes after admission to the PACU. Train-of-four (TOF) ratios were quantified using acceleromyography (TOF-Watch®, Organon, Netherlands). The patient's hand was immobilised, and two surface electrodes were placed on cleaned skin over the ulnar nerve at the wrist. The evoked response of the thumb was measured after TOF stimulation (four pulses of 0.2 ms duration over two seconds at a frequency of 2 Hz, 50 mA intensity). All of the patients were continuously observed. Blood pressure, heart rate, blood saturation and overall mood were observed and controlled. Hypoxia during examination was defined as a decrease of blood saturation below 90% in spite of administering oxygen, with or without the symptom of shortness of breath.

During hospitalisation, the patient's medical documentation was examined to assess the presence of any pulmonary complications associated with the anaesthesia.

Variables studied are reported as the mean, range, standard deviation and relative frequencies. Statistical comparisons were performed using the chi-squared test for categorical data and two-sample t-test for continuous data. Where there was evidence of abnormality, the nonparametric Mann-Whitney *U*-test was used. Normality was examined by the Shapiro-Wilk test. Statistical analyses were performed using STATISTICA 10 software. A *P* value < 0.05 was considered statistically significant.

RESULTS

Patients were divided into two groups depending on age: group A, patients aged ≥ 65 years (184 patients, among whom 112 patients were aged > 70 years), and group B, 231 patients aged < 65 years (age range: 19–57 years). The total number of women in both groups was similar (group A: 64%; group B: 61.2%). Patients were mostly ASA physical status I or II ($n = 256$). The mean duration of anaesthesia was 118 ± 32.1 min (group A) and 108 ± 24.3 min (group B). Respective rocuronium doses were 75 ± 12.7 mg (group A) and 82.2 ± 16.4 mg (group B). Table 1 presents the different types of surgical procedures. The percentages of the patients in groups A and B who reached three ranges of the value TOF (< 0.7 ; $0.7-0.9$ and > 0.9) are presented in Table 2.

The measured TOF ratio in the PACU was < 0.7 for 31% of all patients, and this level of TOF ratio appeared more often in group A patients ($P < 0.05$). Although all patients in the PACU received oxygen via nasal catheter as standard, 33 patients in group A (17.9%) and 19 patients in group B (8.2%) had hypoxaemia in the recovery room and required ventilation support ($P < 0.05$). We detected one case of pneumonia with atelectasis (in a group A patient) on the second day after surgery which, after analysis of all possible causes of this complication, was determined to be a result of PORC.

DISCUSSION

Muscle relaxants are considered to be safe drugs in skilled hands. However, the problem of residual paralysis is becoming increasingly common. A number of papers indicate that residual curarisation results in pulmonary complications. There is a relationship between residual paralysis and CRE [8]. Many anaesthetists do not readily recognise this problem, as it is often not appreciated that PORC is a stable danger outside of the operating theatre. Furthermore, the majority of the effects of PORC (such as pneumonia and atelectasis) only become apparent on the second and third days after surgery, and they are generally

treated by surgeons. In many countries, monitoring neuromuscular transmission and administration of antidotes are not part of current routine practice. For example, in Poland, although neuromuscular monitoring is obligatory during anaesthesia, most anaesthesiologists do not use it routinely. The National Health Service in Poland is to enter into a contract of anaesthetic service on the condition that the hospital or surgery is equipped with neuromonitoring. Some anaesthetists still question the use of neuromuscular transmission monitors. There are differences in the use of monitoring and reversal between different countries.

In France, apparently 74% of anaesthetists use neuromuscular transmission monitoring, but the block was reversed in only 31% of cases [9]. In the United Kingdom, only 10% of doctors routinely use monitoring, and 62% do not monitor neuromuscular transmission at all [10]. In Germany, the decision to extubate the trachea was based on clinical signs in 62.4% of cases, whereas the decision was based on monitoring neuromuscular transmission in only 6% of cases [11].

Rocuronium is an aminosteroidal neuromuscular blocking drug with an intermediate duration of action. The occurrence of the non-depolarising block is caused by binding of the muscle relaxant to nicotine receptors in the post-synaptic membrane and competition with acetylcholine. Relaxants that belong to this group also bind to the pre-synaptic receptors. Binding of non-depolarising agents to presynaptic receptors plays a leading role in the occurrence of PORC because the administration of cholinesterase inhibitors has no effect on the receptors [12, 13].

As far back as 1948, Gray and Halton noticed the wide inter-individual variability of tubocurarine, noting that factors such as age, body weight, physical condition and drug tolerance were involved [14]. Additionally, with the newer muscle relaxants belonging to the steroidal muscle relaxant group, there is wide variability in the degree of effect and in the duration of action. Numerous factors contribute to this

Table 1. Types of surgical procedure according to age group

Group	Abdominal	Endocrinological	Laparoscopic	Vascular
Group A	93	25	36	30
Group B	65	42	85	39

Group A: patients aged ≥ 65 years; group B: patients aged < 65 years

Table 2. Percentage of the patients in groups A and B who reached three ranges of the value TOF

Group	TOF ratio < 0.7	$0.7 < \text{TOF ratio} < 0.9$	TOF ratio > 0.9
Group A	44%	45%	11%
Group B	20%	57%	23%

Group A: patients aged ≥ 65 years; group B: patients aged < 65 years

variability, including age, depth of anaesthesia, drug interactions, concurrent disease and body composition [15–21].

Ageing is accompanied by several physiological and anatomical changes, including a reduction in the number of motor neurons in the spinal cord and a loss of muscle fibres. These effects are accompanied by a decrease in the size of type 2 muscle fibres. Despite these changes, an augmented twitch response is obtained by stimulating a motor nerve because of an increase in the size of the motor unit. In addition to an increase in size, there are also changes within the motor unit. The number of preterminal axons is increased, as is the distance between the preterminal axon and the motor endplate. Additionally, the folds of the motor endplate at the neuromuscular junction are flattened. Changes with advancing age extend beyond the motor endplate. Ongoing denervation leads to proliferation of extra-junctional receptors in the elderly. In a rat model, the acetylcholine concentration in a motor nerve terminal was lower in older animals than that found in younger animals. However, the release of acetylcholine increased due to an increased number of nerve terminals per motor endplate [22–25].

What is the significance of these changes? Is there resistance to neuromuscular blockers because of the proliferation of extra-junctional receptors as observed in disuse atrophy, or is there increased sensitivity to non-depolarising blockers because of the decreased release of acetylcholine from pre-junctional neurons and the greater distance between the pre- and post-terminal components of the neuromuscular junction?

Interestingly, differences in the dynamics of neuromuscular blockers do not appear to be due to changes in the neuromuscular junction. The dose of relaxant causing 95% neuromuscular block (ED_{95}) is similar in elderly and young patients. Many investigators have shown that when elderly patients have the same plasma concentration of neuromuscular blocker as younger adults, they also have the same degree of neuromuscular block [26]. Differences in dynamic behaviour, therefore, appear to be due to differences in the pharmacokinetics of the compounds in the aged patient population.

Pharmacodynamic modelling has demonstrated that geriatric patients have a slower biophase equilibration, which may be an additional reason for a slower onset of maximal effect [27]. Typically, doses of non-depolarising neuromuscular blocking agents larger than their ED_{95} are used to facilitate endotracheal intubation to speed the onset of block. Increasing multiples of the ED_{95} of gantacurium, a new short-acting muscle relaxant, or rocuronium administered above $1 \times ED_{95}$ will shorten the onset of 100% block by approximately one minute [28]. However, there is a limit to the degree to which onset can be shortened, even in young adults. Additionally, with the exception of rocuronium, no compound has an onset of effect that approaches

that of succinylcholine. These limitations, coupled with the slower onset of neuromuscular block in the elderly, may lead clinicians to administer even larger doses of neuromuscular blocking agents in an attempt to further shorten the onset of effect. Overdosing non-depolarising neuromuscular blocking agents exposes patients to an increased risk of the side effects of the compound, such as histamine release or vagolysis, as well as an increased duration of action.

For compounds that are eliminated through the kidney or the liver, recovery of neuromuscular function occurs as the drug is redistributed from the neuromuscular junction to storage sites. With the administration of larger or repeated doses, recovery increasingly occurs during the elimination phase rather than the redistribution phase, and is increasingly prolonged.

Rocuronium also has a prolonged duration of effect in geriatric patients when administered as a bolus, whether for intubation or as a maintenance dose. In the elderly, clearance of rocuronium is decreased by almost 30% compared to young adults, explaining its prolonged action in this patient population [29]. Rocuronium is safe in geriatric patients only when doses are 30% lower, for either intubation or maintenance of block, than is recommended for young adults. In elderly patients, it is recommended to use a specific rocuronium-induced neuromuscular blockade reversal agent, sugammadex, at the end of surgery to prevent occurrence of PORC [30].

CONCLUSIONS

The incidence of residual paralysis upon arrival in the PACU is high when neuromuscular function is allowed to recover spontaneously, and it is a major problem in geriatric clinical anaesthesia. Neuromuscular function monitoring during anaesthesia is obligatory, and pharmacological reversal of neuromuscular blockade should be a routine standard in the geriatric population.

Residual paralysis of elderly people occurs in 90% of cases if neuromuscular transmitters are not monitored. Pharmacokinetics and pharmacodynamics of drugs are slower in elderly patients than in young patients. To reach the same safe effect of anaesthesia, the dose of rocuronium should be reduced to one third of the prescribed one. After surgery, monitoring of patients aged 65 and older should be continued for longer than young patients. Attention should be paid to suction and clearing the mouth cavity of patients who are still sleeping to prevent microaspiration of saliva from entering the bronchial tubes and causing pneumonia.

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