Randomized comparison of sugammadex and neostigmine for reversal of rocuronium-induced muscle relaxation in morbidly obese undergoing general anaesthesia

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Editor’s key points

- The accuracy of neostigmine and sugammadex was compared to inverse rocuronium and prevent postoperative residual curarization (PORC) in morbidly obese patients.
- Sugammadex 2.0 mg kg⁻¹ corrected body weight administered at the reappearance of T2 can reverse rocuronium-induced neuromuscular block faster than neostigmine.
- Sugammadex prevents PORC in morbidly obese patients better than neostigmine.

Background. Complete and fast recovery of neuromuscular function is very important in morbidly obese patients because of the possible influence of postoperative residual curarization (PORC) on respiratory function in the postoperative period. Recent reports underline incidences of the residual influence of neuromuscular blocking agents.

Methods. Seventy morbidly obese (BMI >40 kg m⁻²) patients requiring general anaesthesia and receiving rocuronium for muscle relaxation were randomly assigned into two groups: at the end of the anaesthetic procedure, one group received sugammadex 2 mg kg⁻¹ of corrected body weight (Group SUG) and the other group received neostigmine 0.05 mg kg⁻¹ of CBW (Group NEO). At the end of surgery and when response reached a train-of-four (TOF) score of 2, patients received the study drugs. The neuromuscular function was recorded and time to achieve 90% of TOF (safe extubation) was measured. Patients were examined directly after arrival to the post-anaesthesia care unit (PACU) by a blinded investigator for the presence of PORC.

Results. Thirty-five patients received sugammadex and 35 neostigmine. Mean dose of rocuronium was 87.9 vs 85.6 mg (P>0.05), mean time to 90% of TOF was 2.7 vs 9.6 min (P<0.05), and TOF at the PACU was 109.8% vs 85.5% (P<0.05) in Groups SUG and NEO, respectively.

Conclusions. Administration of sugammadex provides fast recovery of neuromuscular function and prevents PORC in the morbidly obese, however neostigmine does not.

Keywords: morbid obesity; neostigmine; neuromuscular block; sugammadex

Accepted for publication: 1 August 2011

Maintaining a patent airway and accurate defending reflexes from the upper airway are crucial in morbidly obese patients due to their sometimes borderline vital functions. As such, a complete recovery of neuromuscular function after general anaesthesia is essential to avoid postoperative residual curarization (PORC) in the postoperative period influencing respiratory function. Unfortunately, the functions of the larynx and pharynx muscles are among the last to be restored after muscle relaxation during general anaesthesia. The frequency of PORC is revealed to be up to 60% of the anaesthetized patients.¹ Extubating the lungs of a patient with PORC can cause acute respiratory failure.² ³ Also the risk of aspiration of the lungs due to depressed reflexes from the larynx and pharynx is increased in patients with PORC.⁴ PORC could be avoided if neuromuscular function is measured routinely during anaesthesia; however, it is not frequently applied as a standard monitor in daily clinical practice.

To speed up the process of reversing muscle relaxation, inhibitors of acetylcholinesterase such as neostigmine can be administered. Their mechanism of action is based on increasing the concentration of acetylcholine in the synaptic gap. Neostigmine can be administered when the spontaneous recovery of neuromuscular function begins. Too early administration of neostigmine is not effective; on the contrary, it may produce serious side-effects from accumulation of acetylcholine in other organs, especially the brain and heart.

Frequently, PORC is clinically not detected at the moment of extubation but only discovered at the postoperative care unit using an objective measurement such as accelerometry.⁵ In many of these cases, neostigmine was administered too early, when the concentration of relaxant in synaptic gap is still high.⁶ Sugammadex is a relatively new drug selectively acting on a molecule of neuromuscular blocking agent—rocuronium or vecuronium, binding with it permanently. The complex is removed through the kidneys. Sugammadex is very effective and can reverse muscle relaxation in any stage of muscle relaxation.
In morbidly obese patients, pharmacological changes of most anaesthetic drugs are observed. Doses of most drugs may be based on ideal body weight; however, such doses may result in delayed onset and peak of action because of the greater volume of distribution. Therefore, some authors propose increasing the dose by basing it on corrected body weight (CBW). The formula is \[ \text{CBW} = \text{IBW} + 0.4 \times (\text{total body weight} - \text{IBW}).\]

The aim of this prospective randomized trial was to compare the effectiveness of neostigmine and sugammadex to speed up the recovery of neuromuscular function induced with rocuronium and for prevention of PORC. Dose calculations for sugammadex were done using CBW.

**Methods**

**Study design and patients’ selection**

This study was approved by the Medical University of Lodz Ethics Committee (RNN/356/09/KB, May 12, 2009, Prof. P. Polakowski) and registered with SYNABA—The Polish Clinical Trials Authorization, www.nauka-polska.pl (ref. 252922). Morbidly obese patients (BMI ≥40 kg m\(^{-2}\)) undergoing elective bariatric surgery were included in this prospective randomized study. Written consent was obtained from every participant. The exclusion criteria were: lack of consent, co-existing muscular diseases, and severe cardiovascular diseases (NYHA >2). Patients were divided into two groups: administration of sugammadex (SUG) or neostigmine (NEO). The randomization was performed by the investigator using previously prepared envelopes. The randomization method is shown in Figure 1.

**Anaesthesia and neuromuscular block**

General anaesthesia was induced identically in both groups using propofol 1.5–2.0 mg kg\(^{-1}\) CBW. For intraoperative analgesia, fentanyl 0.05 mg kg\(^{-1}\) CBW was used. For maintenance of anaesthesia, the patient’s lungs were ventilated with a mixture of oxygen, air, and desflurane in vol% depending upon the age of the patient, clinical response, and to keep bispectral index values between 40 and 60. The ventilation parameters were adjusted to maintain a normocapnia. Muscle relaxation was induced using rocuronium (Esmeron, Organon, USA) 1.0 mg kg\(^{-1}\) CBW. When train of four (TOF) reached a score of 1, a maximum of two additional doses of rocuronium 0.06 mg kg\(^{-1}\) CBW was given. The standard anaesthesia monitoring consisted of ECG, non-invasive arterial pressure, pulse oximetry, gas monitoring, and monitoring of neuromuscular function. The body temperature and temperature of skin were controlled and maintained over 35°C and over 32°C, respectively. At the end of surgery and when two responses were achieved on the TOF stimulation, one of the study drugs was administered in fast bolus and the time was recorded. Hereby, sugammadex 2 mg kg\(^{-1}\) CBW or neostigmine 0.05 mg kg\(^{-1}\) CBW together with atropine 0.02 mg kg\(^{-1}\) CBW were administered in the SUG or NEO group, respectively. The time to achieve 90% of TOF was measured. Thereafter, hypnotic drug administration was stopped.

**Fig 1** Flow diagram of attrition numbers in each group.
Monitoring of neuromuscular function

The neuromuscular function was monitored using accelerometry (TOF-Watch Device, Organon, Oss, The Netherlands) and following the good clinical research practice (GCRP) guidelines for pharmacodynamic neuromuscular studies. The electrodes were placed on the patient’s skin over the ulnar nerve after careful preparation at 2–3 cm apart. The accelerometer sensor was placed on the tip of the thumb. The arm was placed in such a way that the movement of the thumb with the accelerometer was not limited. Before tracheal intubation, supramaximal stimulation was performed followed by single-twitch stimulation (1 Hz). After intubation, the stimulation was changed to TOF. The result is displayed as the number of responses when less than four responses are received and as a per cent of the 4th response to 1st response when all four responses to stimulation are present. The measurements were recorded every 15 s. In the second phase of the study, after admission to the postoperative unit, PORC was measured using TOF stimulation by the blinded investigator. Neuromuscular function monitoring at the post-anesthesia care unit (PACU) was executed using the same apparatus as used on that particular patient during anaesthesia.

Statistics

The statistical analysis was performed using Microsoft Excel software. The unpaired Student’s t-test was used for testing pairs with unequal variations. A P-value of <0.05 was considered as significant.

Results

There was no difference in patient characteristic data and the total dose of rocuronium between the groups (Table 1). The mean time to achieve 90% on TOF was 3.5 times shorter in the SUG group (P<0.05). TOF at the PACU was higher in the SUG group and reached over 90% in every case; however, in the NEO group, it did not. In the SUG group, two patients reported a side-effect being a strange taste in the mouth. No other complications of sugammadex administration were noted. In the NEO group, we observed profound bradycardia in three cases which required additional administration of atropine. Patients did not complain of discomfort caused by TOF stimulation at the PACU, probably due to the early administration of postoperative pain medication.

Discussion

The morbidly obese patient is especially susceptible for critical respiratory events in the postoperative period, including airway obstruction, hypoventilation, hypercapnia, hypoxia, and acute respiratory failure in the postoperative period. The presence of PORC is one of the factors increasing the risk of critical respiratory events. PORC is also associated with increased risk of pulmonary complications such as lung inflammation caused by ineffective swallowing and coughing and inaccurate protective reflexes from the larynx and pharynx, resulting in the aspiration of secretions.

Table 1

| Table 1 Physical characteristics and patient data; pharmacology data. Values are mean (so) (range). *P<0.05 compared with the SUG group |
|----------------|--------------------------|
| SUG group | NEO group |
| **Age (yr)** | 38.1 (10.3) (19–57) | 38.9 (9.6) (22–63) |
| **Height (cm)** | 171.4 (10.3) (150–196) | 168.9 (7.4) (157–188) |
| **Weight (kg)** | 141.8 (27.4) (100–212) | 139.8 (21.5) (100–192) |
| **BMI (kg m⁻²)** | 47.8 (5.9) (40–66) | 45.5 (5.9) (40–64.5) |
| **CBW (kg)** | 91.1 (16.2) (65–125) | 88.0 (13.2) (71–123.6) |
| **Rocuronium (mg)** | 87.9 (18.8) (65–125) | 85.6 (20.7) (71–150) |
| **Time to 90% TOF (s)** | 2 min 44.1 s | 9 min 37.7 s* |
| **TOF at PACU (%)** | 109.8 (18.1) (94–161) | 85.5 (18.2) (44–120)* |

PORC may increase the incidence of thrombotic complications because of decreased movement of the patient. PORC is encountered more often in patients with comorbidities and especially in the elderly, morbidly obese. PORC is not only a morbidly obese than in non-obese anesthetized patients (33% vs 26%). Reliance on clinical symptoms to determine reversal of neuromuscular function is not effective and only monitoring the neuromuscular function can prevent PORC. Evidence-based medicine dictates that during the monitoring of neuromuscular function, a level of TOF below 90% is considered as PORC. Sugammadex is an effective reversal agent of neuromuscular block and prevention of PORC due to its beneficial pharmacological profile. It is a cyclodextrin permanently binding with rocuronium and vecuronium hereby blocking the neuromuscular paralysis. Its action differs from commonly used acetylcholinesterase-blocking agents such as neostigmine which are not binding directly on the neuromuscular blocking agents’ molecule. Sugammadex is able to remove the relaxant molecule from the synaptic gap, so it can be administered at every stage of neuromuscular block, including deep block. Sugammadex can also be used to treat the symptoms of PORC. The recommended dose of sugammadex depends on the depthness of the neuromuscular block: 16 mg kg⁻¹ for a deep block, 4 mg kg⁻¹ for a shallow block (by the end of the duration of action of the neuromuscular blocking agent), and 2 mg kg⁻¹ to speed up recovery of neuromuscular function, when at least two responses on TOF stimulation are achieved. Obesity does not affect the action of sugammadex.

The recommended dosing by the manufacturer is based on real body weight. We decided to use CBW after the recommendations of previous authors. In the case of neostigmine in the morbidly obese, Suzuki and colleagues used a dose of 0.04 mg kg⁻¹ of real body weight. We used a dose of 0.05 mg kg⁻¹ of CBW which showed to be sufficient without causing a high incidence of side-effects. We achieved an even faster recovery of TOF 90% than Suzuki and colleagues (9.5 vs 25.9 min). In the neostigmine group (10%), we observed a
dangerous profound bradycardia after administration of the study drug in three patients.

As for sugammadex, we achieved similar results as others describing a 1.9–2.5 min to achieve an adequate reversal of muscle relaxation, in contrast to neostigmine where more than 9.5 min is required.14 15 Although those studies were performed using non-obese study populations, our results are comparable.

In most patients, the administration of neostigmine is not preventing PORC, but the administration of sugammadex is.9 The lower TOF scores at the PACU in the NEO group are difficult to explain. A possible hypothesis is that the half-life of neostigmine may be shorter than that of rocuronium. The reversal of the neuromuscular function depends in this case on the concentration of acetylcholine in the synaptic gap. If the concentration of acetylcholine decreases, it is possible that the rocuronium molecule may bind again to the receptors. In the SUG group, we observed typical side-effects of sugammadex administration: chemical taste in the mouth.16 17 There were no other complications of the use of sugammadex. In the NEO group, there were a few cases of bradycardia. The administration of atropine together with neostigmine is a standard in Poland to prevent this complication. The use of glycopyrrolate might be considered as an alternative.

In conclusion, the results of this study confirm that sugammadex 2.0 mg kg\(^{-1}\) CBW administered at the reappearance of T2 can rapidly and effectively reverse rocuronium-induced neuromuscular block and prevent PORC in morbidly obese patients. Sugammadex was significantly faster reversing rocuronium-induced neuromuscular block than neostigmine. Sugammadex was safe and well tolerated. Neostigmine provoked some side-effects and did not eliminate the occurrence of PORC.

Acknowledgements
The authors would like to thank Ms Alicja Pawlak MD PhD, Mr John A’Court, Przemysław Dobielski MD, and Robert Gluszcz MD for language correction of this manuscript.

Declaration of interest
T.G. is a member of the national advisory committee on introduction of sugammadex into clinical practice. T.G. has received an honorarium from MSD Company for lectures during scientific meetings on use of neuromuscular blocking agents in general anaesthesia.

Funding
The study was sponsored by government grant no. N N403 3755 33.

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