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SCIENTIFIC ARTICLE

Sugammadex versus neostigmine in pediatric patients: a prospective randomized study



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KEYWORDS

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Abstract

Background and objectives: Acetylcholinesterase inhibitors may cause postoperative residual curarization when they are used for reversal of neuromuscular blockade. Sugammadex reverses neuromuscular blockade by chemical encapsulation and is not associated with the side effects that may occur with the use of anticholinesterase agents. Because of increased outpatient surgical procedures postoperative residual curarization and rapid postoperative recovery have a greater importance in the pediatric patient population. The aim of this study was to compare the efficacy of sugammadex and neostigmine on reversing neuromuscular blockade in pediatric patients undergoing outpatient surgical procedures.

Methods: 80 patients, aged 2–12 years, scheduled for outpatient surgery were enrolled in this randomized prospective study. Neuromuscular blockade was achieved with 0.6 mg kg⁻¹ rocuronium and monitored with train-of-four. Group RN ($n=40$) received 0.03 mg kg⁻¹ neostigmine, Group RS ($n=40$) received 2 mg kg⁻¹ sugammadex for reversal of rocuronium. Extubation time (time from the reversal of neuromuscular blockade to extubation), train-of-four ratio during this time, time to reach train-of-four > 0.9, and probable complications were recorded.

Results: There was no significant difference between the patients' characteristics. Extubation time and time to reach train-of-four > 0.9 were significantly higher in Group RN ($p=0.001$, $p=0.002$). Train-of-four at the time of neostigmine/sugammadex injection in Group RN were significantly higher than in the RS group ($p=0.020$). Extubation train-of-four ratio was significantly lower in Group RN ($p=0.002$).

Conclusion: Sugammadex provides safer extubation with a shorter recovery time than neostigmine in pediatric patients undergoing outpatient surgical procedures.

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PALAVRAS-CHAVESugammadex;
Neostigmina;
Pediatria**Sugammadex versus neostigmina em pacientes pediátricos: Estudo prospectivo e randomizado****Resumo**

Justificativa e objetivos: Os inibidores da acetilcolinesterase podem causar curarização residual no pós-operatório quando usados para reverter o bloqueio neuromuscular. Sugammadex reverte o bloqueio neuromuscular por encapsulação química e não está associado aos efeitos colaterais que podem ocorrer com o uso de agentes anticolinesterase. Devido ao aumento dos procedimentos cirúrgicos ambulatoriais. A curarização residual e a rápida recuperação no pós-operatório são muito importantes para a população de pacientes pediátricos. O objetivo deste estudo foi comparar a eficácia de sugammadex e neostigmina na reversão do bloqueio neuromuscular em pacientes pediátricos submetidos a procedimentos cirúrgicos ambulatoriais.

Métodos: 80 pacientes, com idades entre 2-12 anos, programados para cirurgias ambulatoriais foram incluídos neste estudo prospectivo e randomizado. O bloqueio neuromuscular foi obtido com $0,6 \text{ mg kg}^{-1}$ de rocurônio e monitorizado com a interpretação da sequência de quatro estímulos. O Grupo RN ($n = 40$) recebeu $0,03 \text{ mg kg}^{-1}$ de neostigmina e o Grupo RS ($n = 40$) recebeu 2 mg kg^{-1} de sugammadex para a reversão de rocurônio. O tempo de extubação (tempo desde a reversão do bloqueio neuromuscular até a extubação), a razão da sequência de quatro estímulos durante esse tempo, o tempo para atingir uma sequência de quatro estímulos $> 0,9$ e as complicações prováveis foram registrados.

Resultados: Não houve diferença significativa entre as características dos pacientes. Os tempos de extubação e para atingir uma sequência de quatro estímulos $> 0,9$ foram significativamente maiores no Grupo RN ($p = 0,001$, $p = 0,002$). A sequência de quatro estímulos no momento da injeção de neostigmina/sugammadex foi significativamente maior no Grupo RN que no Grupo RS ($p = 0,020$). A razão entre extubação e sequência de quatro estímulos foi significativamente menor no Grupo RN ($p = 0,002$).

Conclusão: Sugammadex proporciona extubação mais segura com um tempo de recuperação mais curto que o de neostigmina em pacientes pediátricos submetidos a procedimentos cirúrgicos ambulatoriais.

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Background

Postoperative residual curarization (PORC) in postoperative patients is a succession of the presence of blocked nicotinic receptors.^{1,2} Even in observationally asymptomatic patients, 60–70% of these receptors can be still blocked.¹ PORC can cause delayed recovery, hypoxia, metabolic derangement and rarely death.²

Cholinesterase inhibitors are traditionally used for reversal of neuromuscular blockade (NMB). Among these agents neostigmine is the most potent and selective one.³ It should be kept in mind that cholinesterase inhibitor agents have multi-systemic side effects. Since these agents are not selective to nicotinic receptors and also stimulate the muscarinic system, there can be quite a few serious adverse effects as follows: Bradycardia, QT lengthening, bronchoconstriction, hypersalivation and increased motility.³ To avoid these effects, concomitant anticholinergic agents, such as atropine or glikopirolat, are administered to the patient before the cholinesterase inhibitors.³ Today, sugammadex is an alternative to the decurarization procedure, which was traditionally executed with cholinesterase inhibitors. PORC and the muscarinic side effects are not anticipated when using sugammadex, which has been developed so as to be selective for rocuronium and vecuronium.⁴⁻⁶

The rudimentary neuromuscular junction, the variability of fibrin fibers, the differences in drug distribution and body volume in children change their neuromuscular conduction. These factors can cause prolonged recovery and increased risk of PORC.^{7,8}

Sugammadex is proved to be a safe and superior agent in NMB reversal compared to neostigmine in adults.⁴⁻⁶ However, there is only one study in the literature concerning sugammadex administration in pediatric patients.⁹ The aim of this study was to compare the efficacy of sugammadex and neostigmine on reversing NMB in pediatric patients undergoing outpatient surgical procedures.

Methods

After approval by the local ethics committee and written informed consent was obtained from the person legally responsible for the child, this prospective, randomized, double-blind, controlled study of pediatric patients was performed. Eighty children, American Society of Anesthesiologists (ASA) physical status I, 2–12 years of age who were scheduled to undergo outpatient surgery as elective lower abdominal or urogenital procedures, were included in this study.

Table 1 Age, mean time of surgery and anesthesia.

Variable	Group RN (n = 40)	Group RS (n = 40)	p value
Age	5.07 ± 3.24	6.48 ± 2.81	0.065
Surgery duration (min)	60.37 ± 43.71 (43)	63.52 ± 39.78 (49.5)	0.341
Anesthesia duration (min)	85.50 ± 47.49 (70)	71.77 ± 40.80 (59.5)	0.108

Table 2 Evaluation of time variations.

	Group RN (n = 40)	Group RS (n = 40)	p value
Last NMB administration-reversing time (min)	44.45 ± 22.17	40.05 ± 23.29	0.390
Last NMB administration-extubation time (min)	47.70 ± 22.05	41.55 ± 23.37	0.230
Mean extubation time (min)	3.25 ± 1.79 (3)	1.15 ± 1.44 (1)	0.001 ^a

^a $p < 0.05$ (mean ± SD).

Any patients with known drug hypersensitivity, kidney failure, liver failure, diseases affecting the neuromuscular junction, or a history of malign hyperthermia, and those mentally retarded, were not included in the study.

All patients were applied 0.5 mg kg⁻¹ oral midazolam 30–45 min before surgery. Electrocardiogram (EKG), mean arterial pressure (MAP), oxygen saturation (SPO₂), heart rate and EtCO₂ (End-Tidal CO₂) (Draeger Primus, Draeger Medical, Drammen, Norway) were all monitored in the operating room. The train-of-four (TOF) equipment working with the nerve-muscle acceleromyometry principle (TOF Watch, Organon Technica, Eppelheim, Germany) was placed on the ulnar nerve trace and transducer thumbs of all the patients, and the peripheral heat sensor was placed into the palmar side of the hand.

Vascular access was provided on the other arm, where neuromuscular monitoring was not applied. General anesthesia was induced in both groups with 5–7 mg kg⁻¹ thiopental, 1 µg kg⁻¹ fentanyl and 0.6 mg kg⁻¹ rocuronium. 90 s after the first dose of rocuronium the patients were orotracheally intubated. The first TOF ratio was 100% calibrated and measured. Maintenance of anesthesia was provided with 2% sevoflurane and 50% O₂–50% N₂O. During the operation TOF was not measured.

The effect of the neuromuscular blocker was evaluated clinically according to the increase of respiration frequency, disruption to respiration curve, and the onset of muscular movements. When necessary 0.2 mg kg⁻¹ rocuronium was administered, and the time of the last NMB dose was recorded.

At the end of surgery, sevoflurane inhalation was interrupted and switched to 100% O₂. TOF monitorization began. The children were randomly assigned to one of two groups by a computer-generated table of random numbers. When T₂ reappeared, Group RN (n = 40) received 0.01 mg kg⁻¹ atropine and 0.03 mg kg⁻¹ neostigmine and Group RS (n = 40) received 2 mg kg⁻¹ sugammadex for the reversal of the NMB.

Injection time of neostigmine or sugammadex after the last NMB and the TOF ratio at injection were recorded. Patients were clinically assessed for NMB recovery (50% of normal tidal volume, eye opening and movement) and extubated. Duration from NMB reversal to extubation was evaluated as the extubation time. The TOF ratio at

extubation and the time to reach TOF > 0.90 were recorded. Operation and anesthesia duration (time interval between induction and interruption of sevoflurane inhalation) were also recorded. Adverse effects such as bradycardia, tachycardia, QT lengthening, hypotension, nausea, vomiting, bronchoconstriction, hypersalivation, diplopia, rash, fever, or dysgeusia were noted.

Statistical analysis

In this study, statistical analyses were performed with NCSS (Number Cruncher Statistical System) 2007 and PASS 2008 Statistical Software (Utah, USA) program. For evaluation of obtained data, along with descriptive statistical methods (mean, standard deviation), an independent samples test was used for the comparison of quantitative data, and the Mann–Whitney *U* test was used for a comparison of abnormal distribution parameters between two groups. Results were considered statistically significant when the *p* value was under 0.05.

Results

Eighty patients aged 2–12 years, who underwent lower abdominal or urogenital surgery, completed this study and were included in one of the two groups. Mean age was 5.73 ± 3.11 years. There was no significant difference between the groups in age, time of surgery or time of anesthesia (Table 1).

Time for applying neostigmine or sugammadex after the last NMB and time from the last NMB to extubation were similar in both groups (Table 2).

Extubation time in Group RN was statistically higher than that in Group RS ($p = 0.001$) (Fig. 1).

TOF rate at the time of neostigmine or sugammadex injection in Group RN was significantly higher than that in Group RS ($p = 0.020$) (Table 3).

TOF rate of Group RN at extubation was significantly lower compared to Group RS ($p = 0.002$) (Table 3; Fig. 2).

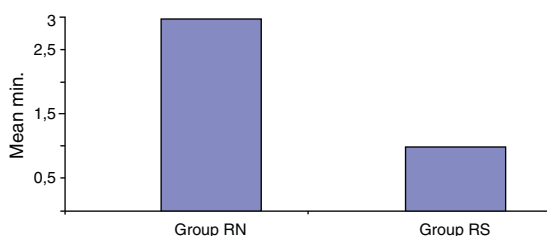
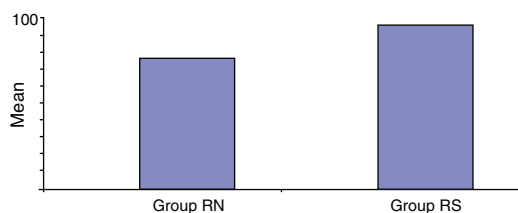
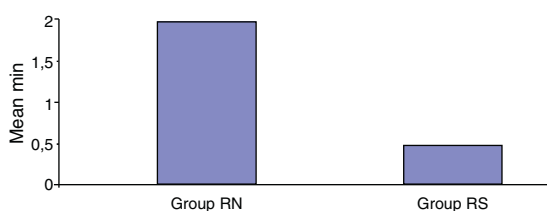
The time when TOF rate exceeded 0.90 was significantly higher in the RN Group ($p = 0.002$) (Table 3; Fig. 3).

No side effects occurred in both of the groups.

Table 3 TOF ratio evaluation.

	Group RN (n = 40)	Group RS (n = 40)	p value
TOF ratio before reversing	47.25 ± 38.52 (43.5)	28.62 ± 27.58 (23.5)	0.020 ^a
TOF ratio at extubation	76.95 ± 31.0	96.35 ± 21.34	0.002 ^a
Time to reach TOF ratio >0.90 (min)	1.97 ± 2.14 (1)	0.46 ± 0.70 (0)	0.002 ^a

^a $p < 0.05$ (mean ± SD).

**Figure 1** Mean extubation time difference between groups.**Figure 2** Extubation TOF ratio of the groups.**Figure 3** Mean time to reach TOF ratio >0.90 (min).

Discussion

NMB agents are still indispensable for surgical procedures requiring general anesthesia. Unfortunately applications of NMB agents entail complications, which can lead to increased mortality, such as PORC, airway obstruction, aspiration and hypoxia. Therefore, complete and rapid reversal of NMB must be ensured at the end of surgery.^{1,2,10}

NMB have a different efficacy in adults and children. NMB disperse in the extracellular area. Because the extracellular area is relatively larger in children than in adults, the neuromuscular blockers create lower plasma concentrations in children. Higher doses of NMB may be necessary to reach the same NMB level in children, as in adults.^{7,8} The neuromuscular junction in infants is not sufficiently mature. Therefore, the ion channels remain open for a longer time and the muscles can easily be depolarized. Moreover, the receptors have a lower affinity for the non-depolarizing agents.^{7,8} Because a child's diaphragm has more type I fibrins than an adult's, the diaphragm is more vulnerable to NMB than the peripheral muscles. All these factors lead to an increased risk of

post-operative apnea in pediatric patients.¹¹ At this point an NMB reversing agent with a reduced PORC risk is of great importance.^{8,9}

Vuksanaj et al.¹² investigated the pharmacokinetic properties of rocuronium in children. They stated that higher doses of rocuronium may be necessary in children for rapid onset of effect and rapid recovery. It has been ascertained that NMB reverses in a shorter time with rocuronium.^{12,13} Therefore, we preferred to use rocuronium in our study.

PORC is one of the feared complications after anesthesia. Acceleromyography is the only recommended objective method for detection of residual block.^{1,14,15} Unless the TOF ratio is ≥ 0.9 , normal vital muscle functions and spontaneous respiration are not safe.^{2,14,15} TOF monitoring was important in this study to provide an objective assessment and therefore accepted cut-off value was TOF ratio >0.9.

Sugammadex has created a new approach to the rapid reversal of NMB. In comparative studies, it has been shown that sugammadex is more effective than cholinesterase inhibitors in the reversal of NMB when rocuronium or vecuronium was administered.^{16,17} Jones et al.¹⁸ found that the time to reach 0.90 TOF ratio was 18 times shorter with sugammadex than with neostigmine in routine reversal of deep NMB. Plaud mentioned that in his study sugammadex was 10 times faster in efficiency.¹⁹

Sorgenfrei et al. compared different doses of sugammadex (0.5, 1, 2, 3, 4 mg kg⁻¹) with a placebo administration in male patients, aged 18–64 years. They analyzed the median time necessary to reach TOF 0.90 ratio after administration of sugammadex and found that with every dose of sugammadex the time to reach 0.90 TOF ratio shortened. When they compared the different sugammadex doses, they observed that the time to reach 0.90 TOF ratio was significantly shorter with sugammadex doses ≥ 2 mg kg⁻¹.²⁰ Other studies showed that ≥ 2 mg kg⁻¹ sugammadex doses are efficient.^{21,22} Debaene et al.²³ reported that a TOF measurement for the depth of NMB is important in deciding the appropriate sugammadex dose. Therefore, we administered 2 mg kg⁻¹ sugammadex, and measured the depth of NMB with TOF monitoring.

Khuenl-Brady et al.²⁴ compared neostigmine with sugammadex in a randomized multicentre study where it was applied to reverse the medium NMB obtained with rocuronium or vecuronium in adults. In the rocuronium group, the duration from sugammadex or neostigmine administration to reach 0.90 TOF ratio was found to be 1.4 min with sugammadex and 17.6 min with neostigmine. In a study of Blobner et al.,²⁵ 11% of patients in the neostigmine group reached the 0.90 TOF ratio in 5 min and 98% of the patients in the sugammadex group reached the 0.90 TOF ratio in 5 min. We analyzed the reversal of medium NMB and the time to reach

0.90 TOF ratio, which was 0.46 min in the sugammadex group and 1.96 min in the neostigmine group.

Della Rocca et al.²⁶ reported that the pharmacokinetic effects of sugammadex were the same in children and adults. Plaud et al. compared the efficiency and safety of sugammadex in infants (28 days–23 months old), in children (2–11 years old), in adolescents (12–17 years of age), and in adults (18–65 years of age). Doses of 0.5, 1, 2, 4 mg kg⁻¹ sugammadex and a placebo were compared in patients after NMB achieved with rocuronium. The different age groups were evaluated for possible side effects, time to reach TOF 0.90 ratio, electrocardiographic variations, sugammadex and rocuronium plasma levels. When ≥ 2 mg kg⁻¹ sugammadex was applied, the time to reach TOF 0.90 was significantly shorter than in the placebo group. In infants, children, adolescents and adults NMB reversal time with sugammadex, and sugammadex-rocuronium concentrations were similar. Reappearance of block, insufficient reversal of NMB and QT lengthening were not observed in any of the groups. This was the only prior study which evaluated the efficiency of sugammadex in children.⁹ In our study, sugammadex 2 mg kg⁻¹ was administered to 2–12-year-old pediatric patients. In the study performed by Plaud et al., the time to reach 0.90 TOF ratio was found to be 1.2 min in both pediatric and adult patients who were given 2 mg kg⁻¹ sugammadex. However, the number of patients included in that study is insufficient. Therefore, it is necessary to conduct a comprehensive study involving large infant and pediatric patient groups.

In our study the extubation times were significantly higher in the neostigmine group compared to the sugammadex group. TOF ratios of the neostigmine group in the process of NMB reversal were confirmed to be higher than those of the sugammadex group. Despite that difference, the TOF ratios in the neostigmine group were significantly lower at the extubation than in the sugammadex group. The extubation TOF mean was 76.95 ± 31.0 for the neostigmine group and 96.35 ± 21.34 for the sugammadex group. Time to reach TOF rates over 0.90 was found to be prolonged as four times in the neostigmine group compared to the sugammadex group. Results in our study were similar to previous studies.^{18,19}

No significant effects on heart rate were recorded with sugammadex; however, neostigmine caused significant increases in the mean heart rate in the second, fifth and tenth minutes after administration.¹⁸ In our study, we did not conduct a hemodynamic comparison. However, the potential side effects of bradycardia, tachycardia, hypotension and hypertension were observed in neither of the groups.

Conclusion

Lower abdominal and urogenital surgery make up a large proportion of the pediatric surgery outpatient operations. This brings NMB reversal and PORC avoidance to great importance, especially when dealing with younger children. Our study indicated that the administration of sugammadex for the reversal of rocuronium induced NMB is making faster and also safer NMB reversal possible, when compared with a traditional drug, as neostigmine is.

Conflicts of interest

The authors declare no conflicts of interest.

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