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Sugammadex versus neostigmine in pediatric cancer patients undergoing outpatient surgical procedures

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ABSTRACT

Neuromuscular blocking agents (NMBAs) are still required for the pediatric population. Residual neuromuscular block is a common complication in the early postoperative period. The objective of this study is to compare the efficacy of sugammadex versus neostigmine for reversing NMB in pediatric patients with cancer who undergo outpatient surgical procedures. This double-blinded study included 80 children with different oncological diagnoses, aged 2-18 years, scheduled for outpatient surgical procedures. They were randomly divided into two equal groups; Group N received neostigmine 0.03 mg/kg with atropine 0.02 mg/kg and Group S received sugammadex 2 mg/kg at the end of surgery. The patients were clinically assessed for NMB recovery and extubated. The primary outcome measure was the time from NMB reversal to recovery of the TOF ratio to 0.9% (recovery time). The secondary outcomes included the time between reversal injection and extubation (extubation time) and possible adverse events. The time to recovery of the TOF ratio to 0.9 and the time between reversal injection and extubation were significantly shorter in S Group ($p < 0.001$). The time to reach TOF ratio of 0.9 was not correlated with age, anesthesia time, or the dose of the neuromuscular blocker. None of the children developed respiratory depression or postoperative residual curarization. Relatively few patients developed arrhythmia, hypotension, and nausea and vomiting with no significant difference between the two groups. Sugammadex is a good alternative to neostigmine for reversal of neuromuscular block in outpatient surgical procedures in children with cancer; it safely provides faster NMB reversal and extubation time.



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INTRODUCTION

The relatively recent introduction of laryngeal masks for airway management has prejudiced the

need for muscle relaxants in pediatric anesthesia (Sanwatsarkar *et al.*, 2019). Also, the development of less-toxic, shorter-acting anesthetic drugs and adjuvants has challenged the necessity of using muscle relaxants (Meakin, 2007). However, neuromuscular blocking agents (NMBAs) will still be sometimes required to facilitate the surgeon's work and to reduce the volumes of anesthetic agents given for the pediatric population.

Unfortunately, postoperative residual curarization (PORC) is still common and usually undetected event in the early postoperative period (Cammu *et al.*, 2006) that can contribute to morbidity in patients recovering from general anesthesia (Murphy *et al.*, 2008). It is defined as the presence

of a T4/T1 ratio < 0.9 in response to the “train-of-four” (TOF) stimulation (Viby-Mogensen, 2000). The incidence of residual neuromuscular block varies widely from 38 to 64% of patients receiving intermediate-acting NMBAs (Kim *et al.*, 2002). Consequently, the use of NMBAs may be associated with postoperative respiratory complications, delayed discharge from the operating room and post-anesthesia care unit (PACU) and more extended hospital stay (McLean *et al.*, 2015). Therefore, full restoration of muscle strength is vital to guarantee a safe postoperative recovery.

Controlling the effect of NMBAs encompasses two strategies; careful monitoring of neuromuscular transmission and reversal of blockade using acetylcholine esterase inhibitors like neostigmine which increase the amount of acetylcholine in the synaptic cleft (Herbstreit *et al.*, 2010). However, due to the limitations of Anticholinesterases and complications of residual neuromuscular block, continuous research has been done to find the ideal reversal agent. The ideal agent should have a fast onset, efficient at any time, able to ensure complete recovery for light as well as profound block, and free of side effects (Hemmerling *et al.*, 2010).

Sugammadex appears to approach this ideal formula. It is a modified γ -cyclodextrin, which is water soluble with a hydrophobic cavity capable of encapsulating steroidal neuromuscular blockers. It is selective for steroidal neuromuscular blocking drugs, with little to no affinity to bind to benzylisoquinolinium neuromuscular blockers (Naguib and Johnson, 2017).

The purpose of this study is to compare the efficacy of sugammadex and neostigmine in overcoming the neuromuscular block in pediatric cancer patients undergoing ambulatory surgical procedures.

PATIENTS AND METHODS

This double-blinded study included 80 children with different oncological diagnoses, aged 2-18 years, class I or II of the American Society of Anesthesiologists (ASA), planned for outpatient surgical procedures (dental surgery, strabismus correction, enucleation, port-a-cath insertion, etc...). The study has received approval from the local ethical committee. The person legally responsible for the child had signed a formal informed consent. Research procedures were applied according to the Helsinki declaration 2013.

Exclusion criteria included a history of hepatic or renal failure, the neuromuscular disorders, known drug hypersensitivity or history of malignant hyper-

thermia.

The children were randomly divided into two equal groups. Group N received neostigmine 0.03 mg/kg and atropine 0.02 mg/kg. Group S received sugammadex 2 mg/kg at the end of surgery only when T2 reappeared on TOF stimulation. Randomisation was done through a Microsoft Excel created random number table. The neuromuscular blocker (NMB) reversal syringes were prepared and coded by an independent anesthesiologist not involved in patient care or the collection of results, and delivered them to the clinical staff. The anesthesiologists responsible for the train of four (TOF) monitoring and results collection were blinded to the administration of NMB reversal.

Anesthesia

All patients received intravenous midazolam (0.05 mg/kg) as a premedication. Standard monitoring was implemented in the operating room, including electrocardiography (ECG), noninvasive arterial pressure measurement (NIBP), pulse oximetry (SpO₂), and End-Tidal CO₂ (EtCO₂). The degree of neuromuscular blockade (NMB) was monitored by the TOF pattern of nerve stimulation. TOF scan using the Nerve-muscle acceleromyography principle (TOF Draeger Medical Systems, Inc. 16 Electronic Avenue, Danvers, MA 01923 USA) was placed on the ulnar nerve to trigger stimulation of the adductor pollicis muscle.

After adequate pre-oxygenation, anesthesia was induced with fentanyl 2 μ g/kg IV, propofol 1.5-2.5 mg/kg, and rocuronium 0.6 mg/kg to facilitate tracheal intubation. Maintenance of anesthesia was conducted with minimum alveolar concentration (MAC) of 1.2-2% isoflurane in air/oxygen mixture (1:1). Each 10 minutes, The TOF was measured. Rocuronium (0.15 mg/kg) was given when the TOF count became ≥ 1 . Throughout the procedure, Normothermia was preserved by the warming effect of air blankets.

Paracetamol was administered at the end of surgery for both groups, in a dose of 10 mg/kg IV. At the end of the procedure, patients were shifted to 100% O₂ under TOF monitoring. When T2 reappeared, Group N received 0.03 mg/kg of neostigmine and 0.02 mg/kg of atropine and Group S received 2 mg/kg sugammadex for the NMB reversal. Patients were clinically assessed for NMB recovery (sustained head-lift for 5 seconds or sustained handgrip for 5 seconds and extubated).

Using the modified Aldrete scoring system, patients were evaluated every 15 min until they were eligible for discharge from the PACU. The criterion used

for discharge of patients was to achieve a modified Aldrete score of 9.

Respiratory complications, as desaturation ($SpO_2 < 90\%$), respiratory depression ($RR < 8$), or PORC and other adverse events, including postoperative nausea and vomiting (PONV), bradycardia, hypotension, arrhythmia, nausea, vomiting, and rash, were noted. Patients were monitored for at least two hours in the post-anesthesia care unit (PACU).

The primary outcome measure was the time from NMB reversal to recovery of the TOF ratio to 0.9% (recovery time). The secondary outcomes included the time between reversal injection and extubation (extubation time), injection time (from last dose of NMB to reversal administration), TOF ratio before reverse, TOF ratio at extubation, length of anesthesia (time period between induction and cessation of isoflurane inhalation) and possible adverse effects such as PORC, arrhythmias, hypotension, nausea, vomiting or rash.

Statistical methods:

Statistical analysis was done using version 22 of IBM® SPSS® Statistics (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or as a median and range. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to investigate the relationship between qualitative variables. comparison between the two groups was made using independent sample t-test or Mann-Whitney test for quantitative data. Spearman-rho method was used to test the correlation between numerical variables. A p-value < 0.05 was considered significant.

RESULTS

The two groups were comparable in age, sex, and body weight (Table 1). The anesthesia time and total dose of NMB between the two groups were not significantly different.

Also, there was no statistically significant difference between the two groups in the time of injection of the reversing drug ($p = 0.227$). TOF ratio in N Group was significantly higher in N Group before reversal injection ($p=0.005$), and significantly lower after reversal injection ($p < 0.001$). The time to achieve a TOF ratio of 0.9 was significantly shorter in S Group ($p < 0.001$). Similarly, the time between reversal injection and extubation was significantly shorter in S Group (Table 2).

The time to achieve a TOF ratio of 0.9 was not correlated with age, anesthesia time, or the dose of the neuromuscular blocker (Table 3).

None of the children in the two studied groups developed postoperative desaturation, respiratory depression, or postoperative residual curarization. Relatively few patients developed arrhythmia, hypotension, and nausea and vomiting with no significant difference between the two groups.

DISCUSSION

In general anesthesia, complete recovery from neuromuscular blocker is essential to avoid its potentially serious adverse effects, including impaired respiration, compromised laryngeal or pharyngeal function, aspiration, and PORC (Murphy and Brull, 2010). A recent study in a pediatric population confirmed that residual neuromuscular block (RNB) is common in the operating room (48%) and postoperative care units (27%). The authors found a relationship between age and RNB, where every year of increasing age was associated with an 8% risk reduction in the incidence of RNB (Klucka et al., 2019).

Therefore, administration of effecting reversal agents is vital, especially in younger age groups. The current study compared the relatively new sugammadex with the conventional reversal agent, neostigmine in children with various types of cancer subjected to outpatient surgical procedures. The need for rapid and successful NMB reversal is more pronounced in cases of outpatient procedures, especially in the pediatric population. The study demonstrated that sugammadex is superior to neostigmine in terms of significantly shorter recovery time from NMBAs and extubation time. Both drugs were not associated with serious postoperative respiratory complications of residual curarization. Adverse events were minor, with no significant difference between the two groups.

Few previous studies investigated the safety and efficacy of sugammadex in the pediatric population. A recent retrospective study compared sugammadex to neostigmine in a large cohort of children. The authors reported significantly shorter reversal time in sugammadex-treated groups except for infants 1-12 months of age. The greatest difference was observed in the neonates. Fewer side effects were observed with sugammadex (Gaver et al., 2019). (Kara et al., 2014) compared the efficacy of sugammadex 2 mg/kg and neostigmine 0.03mg/kg in 80 children aged 2 to 12 years subjected to outpatient surgery. In agreement with the current study, significantly shorter time to reach train-of-four > 0.9 and extubation time in children treated with sugammadex (Kara et al., 2014). Another prospective randomized study included 60 children

Table 1: Baseline characteristics of the two studied groups

	Group N n=40	Group S n=40	p-value
Age (years)	6.1 (2.1- 18.0)	8.5 (3.2-16.0)	0.262
Sex (male/female)	18/22	19/21	0.823
Weight (kg)	17.7 (10.5-55.8)	23.1 (12.5-48.0)	0.149

Data were expressed as median (range) or ratio

Table 2: Characteristic of anesthesia and recovery of the two studied groups

	Group N n=40	Group S n=40	p-value
Anesthesia time (minutes)	60 (25-120)	65 (25-110)	0.809
Total dose of NMBA (mg)	15.0± 3.3	15.4± 2.7	0.530
Injection time (minutes)	46.5 (25.0-85.0)	53.5 (25.0-85.0)	0.227
TOF ratio before injection of reversal	41.18± 15.89	31.63± 13.79	0.005
TOF ratio at extubation	64.62± 7.88	90.62± 5.76	< 0.001
Time to TOF ratio 0.9 (minutes)	10.5 (2.0-25.0)	2.5 (0.5-4.5)	< 0.001
Time from reversal to extubation (extu- bation time) (minutes)	4.4 (0.3- 9.0)	2.5 (0.5-4.5)	< 0.001

Data were expressed as mean ± SD or median (range)

NMBA: Neuromuscular blocking agent

Table 3: Correlation between the time to achieve a TOF ratio of 0.9 and age, anesthesia time, and neuromuscular blocker dose

	Correlation coefficient	Time to TOFR 0.9
		p-value
Age	0.007	0.949
Anesthesia time	-0.089	0.433
Total dose of NMB	-0.232	0.038

Table 4: Postoperative complications in the studied groups

	Group N n=40	Group S n=40
Arrhythmia	3 (7.5%)	3 (7.5%)
Hypotension	3 (7.5%)	4 (10.0%)
Nausea	2 (5.0%)	2 (5.0%)
Vomiting	3 (7.5%)	2 (5.0%)

Data were expressed as number (%)

aged 3–12 years with a history of bronchial asthma undergoing outpatient lower abdominal or urogenital surgeries. Similar results were observed as a significantly shorter time of NMB reversal and time of extubation with sugammadex. Minor complications were more common in the neostigmine group (Nada, 2017).

Several studies compared sugammadex with neostigmine in adults. Similar findings were reported in these studies. Plaud found that sugammadex was ten times more rapid than neostigmine without concomitant administration of atropine (Plaud, 2009). Another study found it 18 times faster in recovery from profound rocuronium-induced NMB (Jones et al., 2008). In a randomized trial in 304 women undergoing elective laparoscopic gynecological surgery, (Paech et al., 2018) compared sugammadex with neostigmine. The reversal was more rapid with sugammadex with comparable postoperative nausea or vomiting (Paech et al., 2018).

In a multicenter study, time to reach a TOF ratio >0.9 was 1.4 min with sugammadex and 17.6 min with neostigmine (Khuenl-Brady et al., 2010). Other investigators reported comparable results in adults (Blobner et al., 2010). Pooled analysis on data from 26 multicenter, randomized, studies including 1855 adults was performed to compare sugammadex with neostigmine or placebo. Sugammadex provided a rapid reversal of rocuronium and vecuronium-induced NMB (Herring et al., 2017).

However, investigating safety and efficacy of sugammadex in the pediatric population is essential as owing to the different behavior of NMB in adults and children. The NMB is dispersed within the extracellular area, which is relatively larger in children than in adults. Therefore, NMBAs produce lower plasma levels in children. Besides, neuromuscular junction in children is relatively immature. Thus, doses of NMBAs have to be increased in children to provide the same degree of the block as in adults. (Vuksanaj and Fisher, 1995) found that higher doses of rocuronium may be needed for rapid onset of effect in children (Vuksanaj and Fisher, 1995). The diaphragm contains mainly type I fibrin fibers in children making them more susceptible to NMB compared with other muscles. These factors collectively increase the risk of complications in children (Meretoja, 2010).

In the current study, we used a sugammadex dose of 2 mg/kg. This was based on previous studies. Different doses of sugammadex were compared in adult males ranging from 0.5 to 4 mg/kg. The authors found that the time to reach a TOF ratio > 0.9 was

significantly shorter, with sugammadex doses ≥ 2 mg/kg (Sorgenfrei et al., 2006). Also, other studies confirmed the efficiency of doses ≥ 2 mg/kg (Hogg and Mirakhur, 2009).

To the best of our knowledge, this is the first study that investigates sugammadex in pediatric cancer patients subjected to outpatient surgical procedures related to their condition.

CONCLUSIONS

The administration of sugammadex for the reversal of neuromuscular block in outpatient surgical procedures in children with cancer appears to be a good alternative Sugammadex safely provides faster NMB reversal and extubation time compared to traditional drugs as neostigmine

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Conflicts of interest

None to be declared

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