Reversal of rocuronium induced neuromuscular block with sugammadex in patients under 2 years of age.

A series of 280 cases

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AIM: *Neuromuscular muscle relaxants are still indispensable for surgical procedures requiring general anesthesia, and the use of these agents may result in postoperative residual curarization. Sugammadex may offer a distinct advantage to pediatric patients where residual neuromuscular blockade may be poorly tolerated. Sugammadex is approved for use in adults and children over two years. This is the main reason why large-scale studies could not be conducted in the group of patients younger than two years old. This study aimed to evaluate the efficacy and safety of sugammadex for reversing deep rocuronium-induced neuromuscular blockade in children under two years of age.*
METHODS: *Pediatric patients younger than two years of age who underwent neurosurgery under sevoflurane anesthesia were included in the study. Neuromuscular block was achieved by the administration of rocuronium. It was antagonized by the administration of 5 mg/kg sugammadex and evaluated using train-of-four (TOF). Primary outcome measure was the time from sugammadex administration to return of the TOF ratio to 0,9. Postoperative adverse events were also recorded.*
RESULTS: *Two hundred eighty patients (10 day-24 months of age; 3-18 kg) were included in this study. Reversal of deep rocuronium-induced neuromuscular block with sugammadex was rapid in all patients. No residual curarization or recurarization was observed. No adverse events or hypersensitivity reactions were observed after administration of sugammadex.*
CONCLUSION: *Reversal of rocuronium-induced deep neuromuscular block in infants was rapid and safe. Sugammadex provided safe extubation in patients younger than two years of age who had undergone neurosurgery. Research Fund.*

KEY WORDS: Neuromuscular blockade, Neuromuscular monitoring, Pediatrics, Sugammadex

Introduction

Postoperative residual curarization (PORC) demonstrates the persistence of nicotinic receptors blocked postoperatively in patients. Even in visually asymptomatic patients, 60-70% of these receptors may still be blocked [1]. PORC may cause delayed recovery, hypoxia, metabolic disorder, and seldomly cause death [1]. Cholinesterase inhibitors are used to reverse neuromuscular blockade (NMB), and of these agents, neostigmine is the most selective and potent. It should not be forgotten that these agents have multisystemic adverse effects. These agents are not specific to nicotinic receptors. Since they also stimulate muscarinic receptors, they cause critical adverse effects such as bradycardia, QT prolongation, hypersalivation, bronchoconstriction [2]. To prevent these effects, the patients are given atropine before the cholinesterase inhibitor.
Sugammadex is an alternative to the decurarization procedure with cholinesterase inhibitors. Muscarinic adver-

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se effects and PORC are not expected when sugammadex, which has been developed selectively for rocuronium and vecuronium, is used. Sugammadex may provide an evident advantage in pediatric patients in whom residual neuromuscular blockade is poorly tolerated by encapsulating neuromuscular blockers of aminosteroid nature [3]. Sugammadex has been proven in many studies to be a secure and superior agent in reversing NMB compared to neostigmine in adults [4-6]. However, it is not approved for use in children under two years by The United States Food and Drug Administration (FDA) due to the lack of literature on pediatric patients and some concerns [7].

In this study, we aimed to present our clinical observation and experience regarding the antagonization of deep neuromuscular block with sugammadex in pediatric patients under two years of age undergoing neurosurgery.

Methods

This retrospective study was approved by the Baskent University Institutional Review Board and Ethics Committee (Project no: KA21/31). Patients who were operated by the neurosurgery clinic and were administered sugammadex less than two years of age at Baskent University Adana Dr. Turgut Noyan Practice and Research Center between January 2017 and January 2021 were included in this study. Exclusion criteria were emergency surgery, a known history of drug or food allergies, extreme obesity, and signs of an important clinical infection. Written informed consent was obtained from the parents of each patient. Patient information was obtained from anesthesia registration forms, patient files, and the hospital computer program called the Nucleus electronic medical information system.

Preoperative patient characteristics, anesthesia procedures, operation types, operation times, total amount of sugammadex administered, recovery time, and postoperative complications were recorded. A standard anesthesia protocol was used in all cases. Appropriate patients were taken to the operating room after premedication with iv 0.1 mg/kg midazolam. After the patients were taken to the operating room, the patients were assessed with train-of-four (TOF) monitoring and standard monitoring methods (pulse oximetry, electrocardiography, noninvasive or invasive blood pressure, end-tidal CO_2, and temperature level). Nerve muscle block was evaluated in the adductor pollicis muscle innervated by the ulnar nerve in hand with an accelomyography device (TOF Watch SX, Organon Ltd., Drynam Road, Swords, Co. Dublin, Ireland). TOF electrodes were fixed on the distal forearm, and the transducer was fixed on the thumb. The hand and forearm were wrapped to prevent the temperature from falling below 35 °C.

After preoxygenation, anesthesia induction was provided to all patients with 5 mg/kg thiopental, 1 μg/kg fentanyl and 0.6 mg/kg rocuronium. Sevoflurane was used at a concentration of 1-2% in a 50% N_2O/O_2 mixture for maintenance of anesthesia. 0.1 mg/kg Additional muscle relaxant (0.1 mg/kg) was applied at intervals of 30 minutes. At the end of the operation, sevoflurane inhalation was stopped, 100% O_2 was administered, and TOF monitoring was started. 5 mg/kgsugammadex was administered to the patients who had deep neuromuscular block (TOF ratio, 0) with the TOF device at the end of the surgery. Sugammadex was administered to prevent residual curarization in patients under the effect of deep neuromuscular block at the end of operation and to evaluate their neurological status on the operating table in the early postoperative period.

The time from anesthesia induction to sugammadex administration was considered as the operation time, and the time from sugammadex administration to recovery of neuromuscular function (TOF ratio, 0.9) was considered as recovery time. Operation time and recovery time were recorded. Patients with Aldrete Score ≥ 8 were admitted to the postanesthesia care unit (PACU) for postoperative follow-up.

The patients who were operated due to intracranial mass and craniosynostosis were transferred to the intensive care unit for follow-up postoperatively.

Statistical Analyses

SPSS 26 was used for statistical evaluations. Descriptive statistical methods were used to analyze the data. Categorical variables were expressed as numbers and percentages, whereas numerical variables were shown as the mean and standard deviation (as median and minimum-maximum when required).

Results

Three hundred ten patients who underwent neurosurgical surgery were evaluated. However, 30 patients were not analyzed due to incomplete or lack of neuromuscular follow-up data. Two hundred eighty patients met the inclusion criteria and were included in this retrospective study. Patient characteristics including age, weight, sex, ASA status, and duration of surgery are summarized in (Table I). There were 57 newborns in the study (20% one-month-old or younger) (Fig. 1). The youngest patient was ten days old.

The most frequently performed operation was hydrocephalus (n=127; 45%) and all the types of procedures performed are listed in (Table II). Anesthetic agent consumption of the patients is shown in (Table III). The mean operative time was 94.85 ± 63.81 minutes (25-240 minutes), and the mean recovery time of TOF was 106.39 ± 33.22 seconds (70-240 seconds).

None of the patients had complications such as brady-

TABLE I - *Demographic data of the study patients and operations*

	Mean ± SD or n	Min-Max
Age (mo)	8.31 ± 6.82	1 - 24
Weight (kg)	7.62 ± 3.86	3 - 18
Gender (male/female) (n)	147 / 133	-
ASA (I/ II/ III) (n)	19 / 149 / 112	-
Operation time (min)	65.38 ± 24.40	25 - 240
Time to TOF > 0.9 (s)	106.35 ± 33.20	70 - 240
Side effects	0	0

The data are presented as mean ± standard deviation (SD), minimum-maximum range or number of patients (n); ASA (American Society of Anesthesiologists); TOF (Train-of-four)

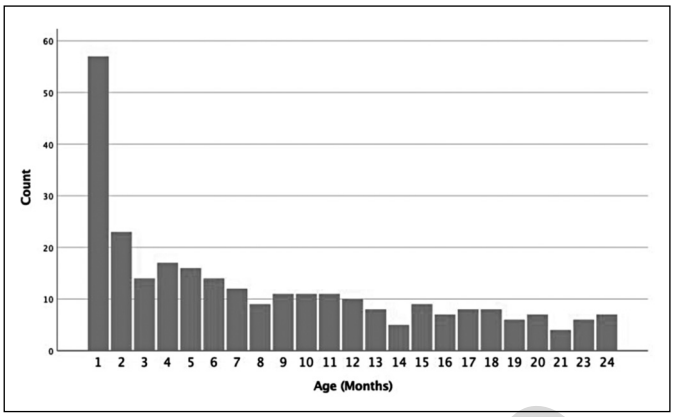

Fig. 1: Age distribution of patients receiving sugammadex.

TABLE II - *Operation indications of the patients*

Operation Types	N (%)
Hydrocephalus	127 (45.4%)
EVD	36 (12.9%)
Meningomyelosel	47 (16.8%)
Intracranial tumor	55 (19.6%)
Craniosynocytosis,	15 (5.4%)

The data presented as number of cases (n) and percentage (%); External ventricular drainage (EVD)

cardia, tachycardia, vomiting, laryngospasm, bronchospasm, rash, or hypersensitivity during or after extubation. No medication was reported for anaphylaxis or bradycardia. Sixty-nine patients who were operated due to intracranial tumor and craniosynocytosis were transferred to the intensive care unit and 211 patients to the PACU.

Discussion

This study is an important step in evaluating the effective and safe use of sugammadex in patients younger than two years of age. Sugammadex was found to be effective and safe in reversing rocuronium-induced deep neuromuscular blockade in this particular age group.

Neuromuscular blockers are widely used in clinical anesthesia. Administration of these drugs is associated with the risk of residual neuromuscular blockade (RNMB). It has been reported that RNMB occurs in approximately 28% of general anesthesia cases, especially in children [8]. In infants, rudimentary neuromuscular connectivity, variability of fibrin fibers, differences in body volume, and drug distribution alter neuromuscular transmission. These factors can lead to long-term recovery, PORC, and an increased risk of postoperative apnea [3]. Hence, agents that antagonize the effect of NMB are of great importance to reduce the risk of PORC. For this purpose, sugammadex is a specially developed agent to reverse the effects of steroidal muscle relaxants.

Neostigmine is well known to act slowly when administered to reverse deep neuromuscular block [9]. Rapid and smooth reversal of neuromuscular block is of particular importance for long-term surgeries, especially in specialized surgeries such as neurosurgery. It is essential to maintain deep NMB throughout the surgery and subsequently to allow for early neurological evaluation of the patient, thus accelerating the diagnosis and treatment of a life-threatening complication. Since sugammadex binds to rocuronium molecules in a 1:1 ratio, it has no effect on plasma cholinesterase or muscarinic receptors and does not produce a muscarinic effect [10]. Sugammadex has been shown in numerous comparative studies to create a novel approach for the rapid reversal of NMB [11-12]. However, these studies were predominantly conducted in adults. Data on its use in the pedi-

TABLE III - *Consumption of the anesthetic agents of the study patients*

	Mean ± SD	Min-Max
Induction dose of thiopental (5 mg/kg)	38.17 ± 19.19	15 - 90
Induction dose of fentanyl (1 g/kg)	7.67 ± 3.87	3 - 18
Induction dose of rocuronium (0.6 mg/kg)	4.56 ± 2.31	1.8 – 10.8
Total rocuronium consumption (mg)	6.45 ± 4.03	1.8 – 22.1
Total sugammadex consumption (5 mg/kg)	38.17 ± 19.19	15 - 90

The data are presented as mean ± standard deviation (SD), minimum-maximum range

atric population are limited. In studies evaluating the efficacy and occurrence of adverse events, especially in the group of patients younger than two years, either the number of patients is very small or in the form of case reports. The main reason being non-approval of its use by the FDA in this age group.

A study by Plaud et al. is significant since it is the first to evaluate the effectiveness of sugammadex in children [13]. In this study, different pediatric age groups and adults were evaluated in terms of possible side effects and time to reach 0.90 TOF ratio. The time to reach a TOF ratio of 0.90 with 2 mg/kg sugammadex has been reported to be 1.2 minutes in both pediatric and adult patients. In this study, the total number of infant patients was eight, and vomiting was reported in 7 of them [13]. In another study evaluating 26 patients under the age of one year, deep neuromuscular block with rocuronium was antagonized with 3 mg/kg sugammadex, and the meantime for the TOF ratio to reach 90% was reported as 1.9 minutes [14]. Contrary to Plaud et al., vomiting was not observed in this study. The use of sugammadex can facilitate the rapid reversal of neuromuscular blockade when an early and detailed neurological examination is required in patients. In our study, 5 mg/kg sugammadex was administered to 280 pediatric patients for this purpose, and the mean recovery time was determined as 1.5 minutes.

In another recent study involving 331 infant patients, 2 mg/kg of sugammadex was administered for 223 cases, 4 mg/kg for 98 cases, and 16 mg/kg for 10 cases. No side effects were reported in this study in which different doses were compared [15]. Also, in the same study, a successful antagonism with 16 mg/kg sugammadex was reported in 10 patients in the neonate group, and detailed information about the conditions was not given [15]. Considering the bradycardia tendencies in infant groups, no cardiovascular side effects were reported, even at high doses. Alonso et al. presented data supporting the rapid antagonism of NMB with sugammadex (4 mg/kg) in 23 neonate patients aged from birth to 1 month, and no adverse events were reported. In the same study, it was reported that the reversal of rocuronium-induced deep neuromuscular block with sugammadex was rapid, and the TOF ratio was 0.9 within 1.4 minutes [16]. In our study, no adverse events (e.g., bradycardia, anaphylaxis, etc.) were observed in 57 newborns aged between 10 days to 1 month. Considering that the cardiac output of newborns is heart rate dependent, it is reassuring that bradycardia didn't occur in this age group or was not severe enough to require treatment. Bradycardia will always be a cause for concern in the neonatal group, but the use of neostigmine has similar concerns.

The most frequently reported and feared side effect for sugammadex is hypersensitivity, which has played a major role in delaying FDA approval in the infant group. However, no cases of anaphylaxis were reported in Franz et al.'s study, which included 331 infants [15]. In a retrospective study conducted in a large group of pediatric patients, the rate of anaphylaxis with the use of sugammadex was reported as 0.1% [17]. In this recent comparative study, it was underlined that the incidence of anaphylaxis was not different from the neostigmine group (0.1%) [17]. In our study, which included 280 patients, no anaphylaxis and/or hypersensitivity reactions were detected. This may be due to the insufficient number of our patients to detect sugammadex-associated anaphylaxis. Or there may be a lower incidence of anaphylaxis in the infant patient group.

A meta-analysis of 575 pediatric patients reported a reduced risk of bradycardia with the use of sugammadex compared to neostigmine, but no difference in the incidence of other side effects such as nausea, vomiting, or bronchospasm [7]. Sarı et al. reported that they did not detect any side effects (hypersensitivity and bradycardia) related to sugammadex in 24 infant patients administered with sugammadex [18].

A number of case reports of laryngospasm after administration of sugammadex are available in the literatüre [19,20]. There has been no systematic review of this infrequent side effect. However, the need for further studies is clear, especially given the use of an agent capable of reversing deep neuromuscular block during difficult airway. Another analysis study indicating a statistically significant relationship between sugammadex and bronchospasm (44 cases) supports this view [21]. In our study, complications such as vomiting, bradycardia, tachycardia, laryngospasm, bronchospasm, rash, or hypersensitivity were not detected during or after extubation with 5 mg/kg sugammadex.

The main limitation of our study is that it was retrospective, there was no control group with neostigmine, and the patients were not randomized. Another important limitation is that the patients studied were isolated neurosurgery patients performed in a single center that did not represent the general population. In addition, we think that the patient group in the study was neuromuscularly healthy infants, which is another significant limitation of the study. Our study would be more impactful if we had patients diagnosed with neuromuscular disease or using drugs that inhibit neuromuscular transmission.

The data obtained from our study support the use of sugammadex in the pediatric population under two years of age. The incidence of clinically significant bradycardia or anaphylaxis appears to be extremely rare or nonexistent. We believe that potential risks can be balanced with optimal respiratory mechanics and rapid return to neuromuscular strength.

In conclusion, this study is an important step in evaluating the efficacy and safety of sugammadex in young pediatric patients. Large-scale retrospective observations and prospective comparative studies will offer more power to detect possible advantages over neostigmine for patients under two years of age.

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