IMMEDIATE RESCUE REVERSAL OF ROCURONIUM-INDUCED INTENSE NEUROMUSCULAR BLOCKADE USING SUGAMMADEX IN PEDIATRIC SURGICAL PATIENTS

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ABSTRACT

BACKGROUND: The dose of Sugammadex for rescue reversal of intense neuromuscular block has not been studied in children. The only recommended dose of Sugammadex in children is 2mg/kg to reverse a shallow block.

OBJECTIVES: To assess the efficacy and safety of Sugammadex 2mg/kg and 4mg/kg as immediate rescue reversal of intense rocuronium-induced neuromuscular block in pediatric patients

METHODS: 80 children, aged 2 to 11 years old, requiring general anesthesia were enrolled in this randomized prospective study. Group 1 given Sugammadex 2mg/kg (40 subjects) while Group 2 received Sugammadex 4mg/kg (40 subjects), at the end of the procedure if PTC=0. The Recovery Time was recorded (TOF ratio ≥0.9) (Primary Outcome). Discharge readiness in the PACU was assessed using Modified Aldrete Scale (Secondary Outcome). Monitoring of adverse effects in the ward continued until 24 hours postoperatively.

RESULTS: There were significantly more patients in the Sugammadex 4mg/kg that had a recovery time of ≤2min as compared to those given Sugammadex 2mg/kg (p=0.012). There was no significant difference in the Aldrete score between the two groups (p=0.2776). All patients achieved a very satisfactory discharge score in the PACU. The adverse effects experienced by the patients in the two doses of Sugammadex in the PACU and up to 24 hours postoperatively were not significantly different.

CONCLUSION: Sugammadex 4mg/kg can be considered safe and effective as an immediate reversal agent for rocuronium-induced intense neuromuscular blockade in children.

RECOMMENDATION: Clinicians should identify if Sugammadex 6mg/kg, compared with 4mg/kg, would translate to a shorter Recovery time to a TOF ratio of 0.9. The time from TOF ratio of 0.9 to the time of extubation should be measured to increase the efficacy and safety assessment of Sugammadex in this age group.

KEYWORDS: Sugammadex, Immediate Rescue Reversal, Intense Neuromuscular Blockade

INTRODUCTION

The difficulty of airway management is usually due to either difficulty in performing adequate mask ventilation or in successfully achieving tracheal intubation[1]. Difficulty with endotracheal intubation may occur unexpectedly even under controlled situations such as during induction of anesthesia in the operating room[2]. Although some difficult airways can be predicted, even the most thorough assessment of the airway may not detect the possibility of a difficult intubation and associated problems with ventilation of the patient[2]. Failure to oxygenate by face mask or supraglottic device occurring in conjunction with failed tracheal intubation defines a failed oxygenation, "cannot intubate, cannot oxygenate" situation (CICO)[3]. CICO or CICV ("cannot intubate, cannot ventilate") situations are rare anesthetic emergencies[4], but if they happen respiratory complications[5,6] and catastrophic outcomes including cerebral anoxia and death can occur[2].

In a study by Heinrich et al[7], the incidence of difficult direct laryngoscopy

(Cormack-Lehane grade 3 or 4 views) was 4.7% in children less than one year of age and 0.7% in children older than one year. Meanwhile, Murat et al[6] cited that the frequency of unanticipated difficult tracheal intubations was 0.24% in children less than one year of age and 0.07% in children older than one year.

For more than 50 years, acetylcholinesterase inhibitors have been used to speed up the recovery from non-depolarizing neuromuscular blockade[8]. However, acetylcholinesterase inhibitors like neostigmine are ineffective against profound block[8].
The modified γ-cyclodextrin Sugammadex can reverse any degree of block induced by rocuronium, in a dose-dependent manner[8,9].

Sugammadex rescue reversal is recommended to be retained for use in unanticipated difficult airways[9,10]. When facing a CICV scenario following rocuronium induction, anesthesiologists need to have an appropriate dose of sugammadex immediately available[9].

In pediatric patients with unanticipated difficult airway requiring immediate neuromuscular blockade reversal, what is the effective dose of sugammadex? Is this dose safe for the pediatric population? While sugammadex can be relied upon for immediate reversal of rocuronium-induced blockade in adults, the age-related change in efficacy of sugammadex and an adequate dose of sugammadex in pediatric patients have not been completely investigated[11]. Although a few studies have shown successful off-label use of sugammadex in younger patients[12,13,14] no recommendation is made until further data become available[15].

OBJECTIVES OF THE STUDY

General Objective

1. To evaluate the efficacy and safety of Sugammadex as an immediate reversal agent for Rocuronium-induced intense neuromuscular blockade in children ages 2-11 years old undergoing Surgical Procedures under General Anesthesia in Philippine Children's Medical Center

Specific Objectives

1. To describe the clinical profile of the patient population

2. To identify the Recovery Time (RT) from administration of Sugammadex to a TOF ratio of 0.9 in both groups (2mg/kg and 4mg/kg) (Primary Outcome)
    a. RT to TOF 0.9 ≤ 2 minutes
    b. RT to TOF 0.9 > 2 minutes

3. To assess the level of consciousness, vital signs, neuromuscular function, and pain control using the Modified Aldrete Scale in both groups

4. To investigate the adverse effects of Sugammadex during the postoperative stay in the recovery room and during the 24-hour postoperative visit (Secondary Outcome) in both groups

METHODOLOGY

This is a double-blind randomized control trial conducted in the Philippine Children's Medical Center, a specialized pediatric government hospital. The study protocol was evaluated by the Institutional Review Board and was conducted in accordance with the International Conference on Harmonization Guidelines / Good Clinical Practice, and current regulatory requirements. The subjects were screened a day prior to the procedure. History-taking and Physical examination by the investigator included a Review of Systems Checklist. A baseline PT, PTT, SGPT and creatinine were drawn from the patient (5ml blood sample). Written Assent Form and Informed Consent were obtained from the subjects and their parents by the investigator prior to the procedure and before obtaining the blood sample. The 80 subjects were randomized into two groups as follows: Group 1 – Sugammadex 2mg/kg (40 subjects); and Group 2 – Sugammadex 4mg/kg (40 subjects). Random assignment of study subjects was done using computer-generated random numbers which were prepared prior to start of recruitment. Sealed envelopes containing the assignment were placed sequentially in a box. The anesthesiologist (other than the investigator) who opened the envelope prepared the drug and administered it to avoid bias. The study dose and rescue dose of Sugammadex were prepared respectively in similar-looking tuberculin

syringes and were concealed from the investigator.

The trial comprised 4 periods, namely:

1) a screening period
2) a perianesthetic period
3) a postanesthetic period that consisted of an assessment prior to recovery room discharge
4) a postoperative visit by the safety assessor within 24h after the study drug administration

Adverse events (AEs) and serious AEs were monitored and recorded by the assessor during the said postoperative period. The investigator was the assessor in all 4 periods.

Patients were eligible for the trial if they fulfilled the following inclusion criteria: categorized as American Society of Anesthesiologists (ASA) class 1 or 2 (Appendix Table 7); age 2 years-11 years old, inpatient, scheduled to undergo a minor/major surgical procedure (extended 2 hours at most) under general anesthesia. Patients were excluded from participation in the study if they had anticipated difficult airway, cardiac disease, neuromuscular disease, liver and/or renal failure, had coagulopathy or bleeding disorders, or were using medication known to interact with rocuronium (toremifene, flucloxacillin, fusidic acid, magnesium, anticonvulsants), had a family history of malignant hyperthermia or allergy to any medication used during general anesthesia, or using an inadequate method of contraception.

The study was planned to compare a continuous outcome variable from independent control and experimental subjects with 1 control per 1 experimental subject. Based on previous study conducted by Sparr et al entitled, "Early Reversal of Profound Rocuronium-induced Neuromuscular Blockade by Sugammadex in a Randomized Multicenter Study", the response variable is normally distributed with a standard deviation of 0.95. If the true difference of the means between the 2 groups is 0.6, a sample size of 40 experimental subjects and 40 control subjects were needed to be able to reject the null hypothesis that the population means of the experimental and control groups were equal with 0.8 power. The type I error associated with the test was 0.05.

Data Collection Procedure

Upon arrival of the patient at the operating room with the parent, noninvasive automatic monitoring devices for arterial blood pressure, oxygen saturation, and electrocardiography were applied. The neuromuscular monitoring device was applied by placing two small electrocardiography (ECG) electrodes on the wrist over the ulnar nerve to stimulate the adductor pollicis muscle. The acceleration transducer was placed on the thumb to record evoked motor responses. Neuromuscular monitoring was performed in accordance with Good Clinical Research Practice with TOF-Watch®SX, Organon Ireland Ltd after administration of propofol. Alternate site for neuromuscular monitoring included the posterior tibial nerve. The negative electrode (black) was placed over the inferolateral aspect of medial malleolus while the positive electrode (red) was placed 2-3cm proximal to the negative electrode. This stimulated the flexor hallucis brevis muscle to elicit plantar flexion of the big toe. However, this was not utilized in the study since all patients were accessibly monitored on their upper extremities. Induction of General Anesthesia was performed using the following agents: atropine 0.02mg/kg, fentanyl 2mcg/kg, midazolam 0.1 mg/kg, and propofol 2mg/kg IV while patients received 100% oxygen through an anesthesia facemask. The TOF Watch was calibrated after induction and before the neuromuscular blocker was administered. Tracheal intubation was performed with rocuronium 1 mg/kg. Anesthesia was maintained with 2.5-3% end-tidal concentration of sevoflurane. Monitoring of the depth of neuromuscular block intraoperatively was obtained every 20 minutes using the TOF Watch, and an intense level of neuromuscular blockade (TOF 0, PTC 0)[80] was maintained all throughout the procedure until the end. Incremental dose of Rocuronium 0.2mg/kg was given when the first response to the PTC was detected[100]. At the end of the procedure, level of paralysis was verified. If the PTC showed 0, the subject was given one of the sugammadex treatment doses: 2mg/kg or 4 mg/kg.

If the PTC was ≥1, the subject was given top-up dose of Rocuronium 0.2mg/kg. To verify intense blockade, a repeat PTC was performed 6 min after the first take of PTC to avoid underestimation of block. If PTC was

equal to 0, then the patient was given either of the sugammadex doses based on the randomization prepared. Neuromuscular monitoring was continued after administration of the reversal agent Sugammadex. TOF monitoring was obtained every 15 seconds and the patient's airway remained intubated until the standard for safe extubation (TOF ≥0.9)[76] was achieved. Patient remained anesthetized with Sevoflurane at 2-2.5% end-tidal concentration during TOF monitoring and was discontinued after TOF 0.9 was reached. The time from sugammadex administration to recovery (RT) of neuromuscular function (TOF ratio ≥ 0.9) was recorded (Primary Outcome). If Recovery Time (RT) of ≤2 minutes was achieved, patient was extubated. If RT exceeded 2 minutes, an incremental single dose of sugammadex 2 mg/kg was given intravenously. The Recovery Time to TOF ≥0.9 was recorded, and patient was only extubated at this TOF value. The investigator facilitated the perianesthetic period, but during this time, another anesthesiologist maintained the patient so that the investigator focused on the recording of Recovery Time to TOF ≥0.9. This subject was included in the Intention to Treat Group, and results were analyzed. They were monitored in the postanesthetic period in the recovery room as well as 24 hours postoperatively.

Starting before transfer to the recovery room (after tracheal extubation), patients were assessed by the investigator every 15 minutes for an hour for clinical signs of residual and recurrence of neuromuscular blockade in the postoperative period until PACU discharge. This included an assessment of the patient's level of consciousness, vital signs, pain control, and adverse effects using the Modified Aldrete Scale[94] (Appendix Table 3) (Secondary Outcome). The Modified Aldrete Scoring was used to assess discharge readiness from the recovery room. Adverse effects such as nausea, vomiting, bleeding, flushing, urticaria, and pyrexia were noted.

Then within 24 hours post operatively, the subject was reassessed in the ward every 8 hours by the investigator. The presence of adverse events described above was investigated (Secondary Outcome). During the said post-operative visit, a physical examination was done, and vital signs were noted.

In the event of complications arising from the study (may or may not be directly related to Sugammadex) such as prolonged/recurrent curarization, bradycardia, anaphylaxis, and other adverse effects mentioned above, the Department of Pediatric Anesthesia of this institution was responsible to provide intervention.

Primary outcome was the Recovery Time (RT) defined as the time from administration of Sugammadex to recovery of neuromuscular function measured by a TOF ratio of 0.9. TOF monitoring at this time was done every 15 seconds. Secondary outcome were the clinical signs of neuromuscular recovery, pain control, level of consciousness, and vital signs. This was done every 15 minutes in the Recovery Room. The Modified Aldrete Scale was used as reference. Measurement of Secondary Outcome extended into the 24-hour postoperative visit and included an assessment of adverse drug effects every 8 hours.

Because of the unreliability of visual/tactile assessment of neuromuscular function[95], a quantitative device such as a TOF-Watch® SX, Organon Ireland Ltd was used in this study. In an article by McGrath[76], a nerve stimulator should be battery operated and be able to deliver a constant current, up to a maximum of 80 mA. At a constant voltage, current will vary depending on the resistance of the skin. The skin should always be cleansed with alcohol adequately before applying the electrodes. The nerve stimulator should be capable of delivering a variety of pattern of stimulation including: single twitch (at 1 Hz); TOF twitch stimulation (usually 2 Hz with at least a 10 second interval between trains); tetanic stimulation at 50 Hz for up to 5 s; and double-burst stimulation (DBS). The ideal stimulator also enabled monitoring of the evoked responses. In this study, a PTC value of 0 was obtained before Sugammadex administration, and a TOF ratio of 0.9 or greater was the goal prior to extubation.

Data were encoded and analyzed using Stata 14 MP. Baseline characteristics of the two groups were presented in tabular form. Continuous variables such as age and weight were reported as mean±standard deviation, and t-test was used for comparison between the two groups. On the other hand, categorical variables

such as ASA score were reported as frequency and percentages, and chi-square test was used for comparison between the two groups. The association between the two treatment groups and the recovery time as well as adverse events was analyzed using χ^2 test, while the association between the Aldrete scores between the two groups was analyzed using Mann-Whitney test. A p-value of <0.05 was considered statistically significant.

RESULTS

There were a total of 80 patients included in the study, of which 40 were given 2 mg/kg Sugammadex dose and another 40 patients were given 4 mg/kg Sugammadex dose. The mean age of the patients in the two groups was 6 ranging from a little over 2 years to 11 years of age. There were more males than females but no significant difference in sex distribution was noted between the two groups.

Clinical Profile

More than half of the patients were classified as ASA 1 (58.8) and the rest were classified as ASA 2. The mean weight of the patient was 21 kgs in both groups. The mean surgery time was observed to be at 2.0 hours ranging from less than 1 hour to more than 5 hours. There were 95% of the patients in the Sugammadex 2 mg/kg group who were given Sugammadex rescue compared to only 75% in the Sugammadex 4 mg/kg group (*p-value*=0.012). The mean recovery time to a TOF ratio 0.9 was 321 seconds in the group given Sugammadex 2mg/kg *vs.* 229 seconds in those given Sugammadex 4 mg/kg. Recovery time in patients who received 4mg/kg was significantly faster than those who received 2mg/kg (Table 1)

Table 1. Clinical Profile of the Patient Population

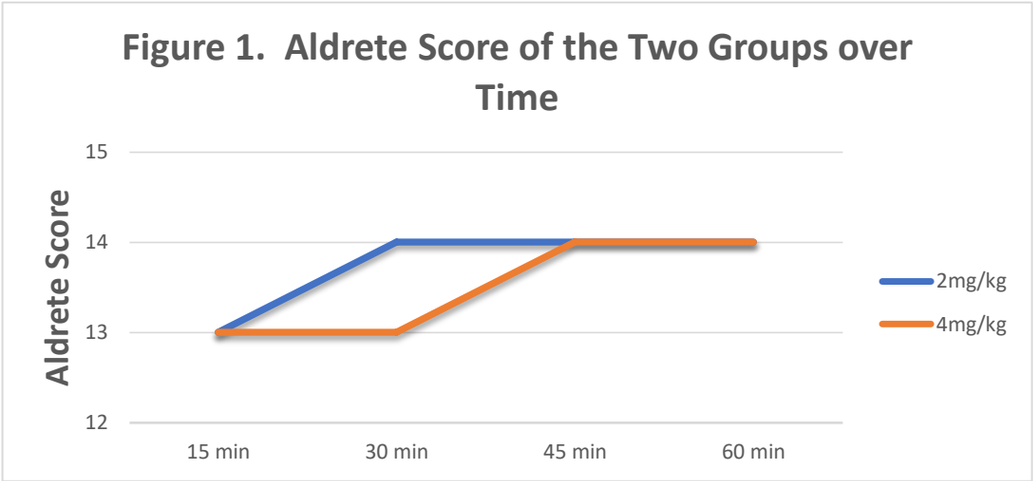
Variable	Sugammadex 2 mg/kg N=40	Sugammadex 4mg/kg N=40	p-value
Age (yrs)	6.46±3.08	6.26±3.08	0.7815
Sex Male Female	 26 (65%) 14 (35%)	 27 (67.5%) 13 (32.5%)	0.813
ASA 1 2	 23 (57.5%) 17 (42.5%)	 24 (60%) 16 (40%)	0.820
Weight (kg)	21.21±8.38	21.90±11.11	0.7556
Surgery time (min)	120.18±67.16	121.68±79.0	0.9273
Sugammadex Rescue Yes No	 38 (95%) 2 (5%)	 30 (75%) 10 (25%)	 0.012
Recovery time to TOF 0.9 (sec)	321.23±223.93	229.33±170.46	0.0422
Modified Aldrete Score	13.6±0.31	13.56±0.26	0.2766

The Recovery Time, from administration of Sugammadex to TOF ratio of 0.9, of 2 minutes or less was compared in terms of dosage, particularly 2 mg/kg and 4 mg/kg. The recovery time of 2 minutes or less occurred in about 5.0% of the patients given 2mg/kg while the same occurred in 25.0% of the patients given 4mg/kg. There were significantly more patients in the group given Sugammadex 4mg/kg that had a recovery time of ≤ 2min as compared to those given Sugammadex 2mg/kg (Table 2).

Table 2. Recovery Time (RT) from administration of Sugammadex to a TOF ratio of 0.9 in both groups (2mg/kg and 4mg/kg)

Recovery Time to TOF 0.9	Sugammadex 2mg/kg N=40	Sugammadex 4mg/kg N=40	p-value
≤ 2min	2 (5%)	10 (25%)	0.012
>2 min	38 (95%)	30 (75%)	

The median Modified Aldrete Score was also compared between the 2 groups. It is similar in the 2 groups. Aldrete score was recorded at 15-minute intervals in both groups. There was no significant difference in the Aldrete score between the two groups (p=0.2776).



The incidence of adverse effects in the PACU and during the 24-Hour Postoperative Period was compared between the 2 groups. The adverse effects experienced by the patients in the two doses of Sugammadex in the PACU and up to 24 hours postoperatively were not significantly different (Table 3).

Table 3. Adverse effects of Sugammadex in the Recovery Room and during the 24-Hour Postoperative Period in both groups

Adverse events	Sugammadex 2mg/kg N=40	Sugammadex 4mg/kg N=40	p-value
PACU adverse events Yes No	 9 (22.5%) 31 (77.5%)	 6 (15%) 34 (85%)	0.390
Ward adverse events Yes No	 7 (17.5%) 33 (82.5%)	 5 (12.5%) 35 (87.5%)	0.531

The most common adverse effects were vomiting, followed by low normal heart rate and hypertension. No significant difference was noted in the adverse effects between the two doses since a minimum sample size of 200 patients is needed to detect such a difference. No deaths occurred in the study (Table 4).

Table 4. Incidence of the Most Common Adverse Effects by Treatment Group in the PACU and During the 24-Hour Postop Period

Adverse event	Sugammadex 2mg/kg N=40		Sugammadex 4mg/kg N=40	
	PACU	Ward	PACU	Ward
Vomiting	2	4	2	2
Nausea	1	0	0	1
Low-normal Heart Rate	3	1	2	2
Hypertension	1	1	1	0
Bradycardia	1	0	1	0
Fever	1	1	0	0
Total	9	7	6	5

DISCUSSION

At the end of the procedure all 80 subjects reached a TOF ratio of 0.9. Between the 2 groups (Sugammadex 2mg/kg and 4mg/kg), there were more subjects (10 vs. 2) in the Sugammadex 4mg/kg group who achieved a Recovery Time to TOF ratio of 0.9 in less than 2 minutes. The observations in our study were consistent with the pharmacokinetics of Sugammadex showing a linear, dose-dependent relationship[15]. In a study by Plaud et al., when Sugammadex was administered at reappearance of T2 for the reversal of rocuronium-induced neuromuscular blockade in pediatric and adult surgical patients, a clear dose-response relationship was observed for children, adolescents, and adults with median times to a TOF ratio of 0.9 ranging from 4.6 to 0.6 min as the dose of Sugammadex increased from 0.5 mg/kg upwards[13]. Same findings were supported in two phase II studies[18,104] wherein a rapid and dose-dependent reduction in the mean time to recovery of the TOF ratio to 0.9 was shown from approximately 4.0 to 1.1 min with Sugammadex doses of 0.5–4.0 mg/kg, respectively, when administered at reappearance of T2 in adult patients with neuromuscular blockade induced by 0.6 mg/kg rocuronium[13,18,104]. Sugammadex dose of 4mg/kg was shown to be significantly more effective than Sugammadex 2mg/kg in children for the immediate rescue reversal of intense neuromuscular blockade. However, a clinical observation was made during the study. When the TOF ratio was ≥0.9 some patients still had abdominal breathing. A time lag of approximately 2-3 minutes was noted between the objective display of TOF ratio ≥0.9 and the clinical improvement from abdominal breathing to adequate chest rise and good tidal volume. Thus, a good clinical judgment as regards to the clinical parameters for extubation has to be exercised in correlation with the TOF reading especially in this population. A limitation of the study was that the time interval from the TOF reading of 0.9 to extubation was not recorded. This could have given us a deeper insight about the efficacy and safety profile of the particular study dose of Sugammadex.

Eventhough a time lag interval was observed between the TOF reading of ≥0.9 and improved clinical respiratory parameters for some patients in the higher dose group Sugammadex 4mg/kg, no patients developed residual neuromuscular blockade or recurarization in the PACU and within the 24-hour postoperative period in the two groups. All of the patients achieved a very satisfactory recovery discharge criteria based on Modified Aldrete Scale in the PACU. No adverse effects in the PACU and within the 24-hour postoperative period that led to discontinuation of a treated patient from the study. The median Modified Aldrete Scale was 14 in the two groups, out of a total score of 14. No scores below 1 were noted for the individual variables related to consciousness, activity, respiration, hemodynamics, oxygen saturation, pain, as well as nausea and vomiting. Minor or isolated adverse effects in the PACU include the following: 2 patients developed mild bradycardia[108](Appendix Table 8) which was responsive to single dose of atropine, 5 patients had low normal heart rate but were still given single dose atropine to achieve near-baseline value, 1 patient with nausea, 5 patients with vomiting (one of which was the same patient who developed low normal heart rate), 2 patients developed hypertension but asymptomatic, 1 patient had fever (37.9°C) which was controlled with tepid sponge bath. Similar side-effects were noted within the 24-hour postoperative period. The following were: mild vomiting (n=6, not likely to be related with Sugammadex alone), nausea (n=1), low normal heart rate (n=3, one was transient and no longer required atropine), hypertension (n=1, same patient who developed hypertension in PACU [130-140/60-70mmHg - 120/60mmHg] but continuously remained asymptomatic), and mild fever (n=1, 37.8°C). The most commonly occurring adverse effects in the two groups were vomiting and a low normal heart rate. The intensity of these adverse effects was described as mild to moderate. They were easily manageable and were not considered life-threatening. Furthermore, no serious adverse events suggestive of hypersensitivity and/or suspected anaphylaxis were observed during the study. The occurrence of adverse effects while in the PACU and during the 24-hour postoperative period did not differ significantly in the two groups. Sugammadex 4mg/kg was well-tolerated in children. The safety information collected in this study adds to the profile of Sugammadex established in previously published studies. In a study performed by

Plaud et al. and Sari et al.[13,92] across the different age groups (infants, children, and adolescents) the most common side effects were acute postoperative nausea / vomiting and pain related to the surgery. They could not directly correlate the side effects with Sugammadex[13,92]. An observation in our study was that the side effects of Sugammadex were usually noted within the first 15 to 30 minutes of administration. It is suggested that it should be diluted and given slowly especially in this population in order to minimize the occurrence of side effects.

CONCLUSION

The dose of Sugammadex 4mg/kg was shown to be statistically effective in regaining spontaneous respiration in less than 2 minutes compared with Sugammadex 2mg/kg. All pediatric patients who received Sugammadex 2mg/kg and 4mg/kg, respectively, achieved Good Recovery Parameters in the PACU. Comparison of adverse effects both in PACU stay and during 24-hours postoperatively yielded no significant difference. The most frequently observed adverse effects were vomiting and low normal heart rate which was the same in both groups. The clinical severity of adverse effects was considered as mild to moderate. Sugammadex 4mg/kg compared with Sugammadex 2mg/kg can be considered safe and effective as an immediate reversal agent for rocuronium-induced intense neuromuscular blockade in children.

RECOMMENDATION

While Sugammadex 4mg/kg showed statistically significant result compared with Sugammadex 2mg/kg in reversing an intense neuromuscular blockade in children, further study should be done to identify whether increasing the dose of Sugammadex from 4mg/kg to 6mg/kg, comparing the two groups, would translate to a shorter Recovery time to a TOF ratio of 0.9, thus, a faster return to spontaneous respiration. The time from arriving at a TOF ratio of 0.9 to the time of extubation should also be measured and compared between the two groups to increase the efficacy and safety assessment of Sugammadex in this age group. More documentation about the efficacy and safety profile of Sugammadex 6mg/kg in this special population should be performed and compared with the 4mg/kg. This effort could set the initial steps until the safe and appropriate dose for the immediate reversal of intense neuromuscular blockade in children will be established. This will indeed be lifesaving for many of our children who would be found in the real clinical scenario of an unanticipated difficult airway.

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