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Effectiveness of Sugammadex on muscle relaxant reversal in preterm neonates

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ABSTRACT

Background & objective: Sugammadex is a drug used to reverse the muscle relaxation effect of rocuronium. Its use is still limited in preterm neonates. The aim of this study was to compare the efficacy of Sugammadex with that of neostigmine in reversing rocuronium-induced muscle relaxation in preterm neonates and to evaluate the safety of its use in this age group.

Patients and methods: This randomized clinical trial was carried out on Sixty preterm neonates, planned for elective inguinal hernia repair under general anaesthesia. The patients were divided into two equal groups. Group N used neostigmine and group S used Sugammadex as the reversal agent for rocuronium.

Results: In Sugammadex group the mean reversal time (1.15 ± 0.42) min and the mean recovery time (17 ± 6.64) min were significantly shorter than in the neostigmine group (8.9 ± 1.6) min and (27.16 ± 9.26) min respectively, with p value <0.001.The patients in the Sugammadex group showed significantly lower heart rate than those in neostigmine group but showed no significant difference as regard mean blood pressure at 3, 6, 9,12,15 and 18 min after drug injection.There were no significant complications noted in both group

Conclusion: Sugammadex is well tolerated in the Preterm neonates with shorter recovery and reversal time when compared to neostigmine.

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KEYWORDS
Muscle relaxants; reversal; Sugammadex; preterm neonates

1. Introduction

Rocuronium, a non-depolarizing amino steroidal neuromuscular blocking drug isn't used in neonates due to concerns about lingering muscle relaxation. It has a rapid to moderate onset of action and an intermediate duration of effect. [1,2]

A selective muscle relaxant binding agent is called sugammadex. Sugammadex is a hydrophilic exterior that promotes solubility and a hydrophobic interior that encapsulates amino steroidal medicines. It is a donut-shaped cyclodextrin molecule. [3,4] Sugammadex binds to rocuronium with the highest affinity, but it also has a three-fold lower affinity for vecuronium. [5] Pancuronium is not much affected, while the benzylisoquinoliums and succinylcholine classes of muscle relaxants are unaffected. Acetylcholinesterase inhibitors like neostigmine, which compete to stop the breakdown of acetylcholine rather than directly opposing neuromuscular blockers, have long been the go-to antagonists. [6] Because Sugammadex interacts directly with steroidal relaxants, it is the only medicine now on the market that can reverse profound neuromuscular blockade. [6]

Sugammadex is a good option for rocuronium reversal since it is a modified form of cyclodextrin that is specifically designed to encapsulate rocuronium and can quickly restore neuromuscular function regardless of the degree of neuromuscular block. [7] Sugammadex does not bind to muscarinic receptors, hence it has the benefit of being free from the negative consequences that using cholinesterase inhibitors may bring about. [8]

Numerous publications addressing the prevalence of severe bradycardia, hypotension, nausea, vomiting, and other problems raised some concerns about taking Sugammadex. Although the studies indicated that both adults and children were rarely subject to such occurrences. [9,10] Concerns about the preterm neonate age group have persisted despite insufficient research, especially considering the vulnerable and undeveloped nature of this age group. [11,12]

The primary outcome was to compare the effectiveness of Sugammadex and neostigmine in reversal of effects of rocuronium in preterm newborns. The secondary outcome was to evaluate the safety of using Sugammadex in preterm newborns and to look for any potential side effects.

2. Objectives

The aim of this study was to compare the efficacy of Sugammadex with that of neostigmine in reversing rocuronium-induced muscle relaxation in preterm neonates and to evaluate the safety of its use in this age group.

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3. Setting

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4. Design

A randomized clinical trial (Clinical Trials.gov, Identifier: NCT04566796).

5. Patients and methods

Following approval from the local ethics council, this randomised clinical trial was conducted on 60 preterm newborns at the Shatby University Hospital, Alexandria University, Egypt. Under general anaesthesia, elective inguinal hernia repair was planned for each participant in the study. The research was conducted between August 2020 and February 2021. Following a thorough explanation of the trial's advantages and risks, the patient's parents or legal guardian who consented to participate provided their signed informed permission. All procedures were carried out in compliance with the 1964 Helsinki Declaration and its later amendments, as well as the institutional, national, and research committee ethical standards. The study was approved by the ethical committee of faculty Medicine, Alexandria University (No.11/2019OBSGN27) and the study protocol was registered at Clinical Trials.gov (Identifier: NCT04566796).

The closed envelope method was used to divide the study participants into two groups at random. Each group have the same number of patients (n = 30). To counteract the effects of the administered neuromuscular blocker, all the patients in the control group (Group N) received 0.02 mg/kg atropine and 0.05 mg/kg neostigmine intravenously. Sugammadex 2 mg/kg IV was administered to the study group's patients (Group S) as a reversal drug.

Patients who had a history of medication hypersensitivity or other conditions that affected the neuromuscular junction were not allowed to participate in the study. Patients with serious illnesses or congenital anomalies that could raise the risk of morbidity or fatality were also eliminated.

All the study participants underwent preoperative evaluation, which included thorough clinical examinations, regular laboratory tests, and complete medical and surgical history collection.

After using the standard monitor techniques on the patients, 4% sevoflurane was administered through face mask to produce anaesthesia in both groups. Using a multichannel monitor, the patients were monitored for non-invasive arterial blood pressure (mmHg), lead II electrocardiography, peripheral oxygen saturation (SpO2%) and end tidal CO2 (mmHg).

Using a multichannel monitor (Dräger® Infinity vista XL Germany) was attached to the patient to displaying when the TOF score hits 1, 1.5–2% isoflurane and increments of 0.2 mg/kg rocuronium were administered to maintain anesthesia. Rocuronium is used to maintain muscle relaxation.

During the procedure, the ulnar nerve was used to monitor the train-of-four (TOF) using the "TOF Watch Organon Technica, Eppelheim, Germany". The distal electrode was put on the wrist's flexor crease on the ulnar side. The flexor carpi ulnaris tendon was then placed 1–2 cm away from the proximal electrode.

The second arm, which was not attached with electrodes for neuromuscular monitoring, was used to insert intravenous access. Patients received 0.2 mg/kg of rocuronium intravenously after calibrating the first TOF ratio, and after 90 seconds, they were orally intubated.

When the TOF score hits 1, 1.5–2% isoflurane and increments of 0.2 mg/kg rocuronium were administered to maintain anaesthesia. Drager ventilator was used to regulate the ventilation and a low fresh gas flow of 1–3 litres per minute was used to sustain it. End tidal CO2 was maintained by adjusting the breathing rate (35–40 mmHg).

5.1. Pressure controlled ventilation

Ventilation maintained using Dräger Fabius plus ventilator as IPPV pressure control. Respiratory rate 25–35/min, Peep 2cmH2O, inspiratory pressure less 20 cm H2O and FiO2 40%.

When the second twitch T2 on the TOF stimulation is reached, patients were injected with the reversal agent either: 0.02 mg/kg atropine and 0.05 mg/kg neostigmine IV in Group N or with 2 mg/kg Sugammadex IV in Group S. At the ending of the operation, isoflurane was discontinued and switched to 100% O2. Patients were transported to the post-operative anaesthesia care unit (PACU) for the following two hours after extubation, which was performed only after the full reversal of muscle relaxants as measured by TOF, such as TOF ratio 0.9.

6. Outcome *measures*

Using a multi-channel monitor (Penlon Sp M5), hemodynamic parameters were continuously recorded at the following times: baseline, prior to the induction of general anaesthesia, prior to the injection of the reversal agent, and then every 3 minutes following the injection of the reversal agent until full recovery and extubation.

- **Total dose of muscle relaxant**: At the end of the operation, the total dose of muscle relaxant was calculated.

- **Assessment of reversal**: After recovery, reversal time was noted in both groups. It was specified as the interval, measured in seconds, between the start of the Sugammadex or neostigmine injection and the TOF ratio of 0.9. [13]
- **Complications**: Possible side effects of any medicine under study were identified and handled appropriately [14]
- **Evaluation of recovery**: This is accomplished by tracking the recovery period, which is defined as the period between extubation and a modified Aldrete score of 10. [15]

7. Sample size estimation

Using the software created by Rollin Brant for the Estimation of Sample Size, it was determined that 60 patients would be required in the current study to achieve a power of 80% at level of significance of 5% and to achieve a success rate of 90% (based on a simulation process) and assuming that roughly 10% of patients would have 1 or more major protocol violations or missing data.

8. Statistical analysis

Statistical Package for Social Sciences (SPSS for Windows, V.25, Chicago, IL, USA) was used to conduct the statistical analysis. The student's t-test, Chi square, Fisher's exact test, and paired t test were used to analyse the data. Each two-sided statistical test was run with a significance threshold of 0.05.

9. Results

Thirty-one patients were excluded from the ninety-five candidates recruited for the study Figure 1 as eleven of them did not meet the inclusion criteria and twenty refused to participate. The remaining 64 patients were randomly allocated to intervention. Four of them were discontinued to intervention due to surgical complications. Thus 30 patients were analysed in each group.

Patients' demographic data in both studied groups were comparable and showed no significant differences regarding age, weight, gestational age, and sex. Table 1.

Data of age, weight and gestational age were expressed as mean± SD and tested by independent t test.

Data of sex, expressed as number (percentage) and tested by Chi-square test.

With a p value of (0.388), the mean total dose of muscle relaxant administered did not show any statistically significant differences between the neostigmine and Sugammadex groups. as shown in Table 2.

The reversal time was significantly shorter in the Sugammadex group compared to that in the neostigmine group (1.15 ± 0.42, 8.9 ± 1.6 seconds, respectively) ($P < 0.001$) (Table 2). The Sugammadex group's recovery time was significantly much less than the neostigmine group's (17.6.64, 27.16, and 9.26 seconds, respectively). ($P < 0.001$) (Table 2), (Figure 2a & b).

Figure 3a shows the mean heart rate in both groups at different times. There was no significant difference in the means of heart rate between both groups immediately before giving the antidote to the muscle relaxant drug (Sugammadex and neostigmine) but after 3 6, 9,12,15 and 18 min from administering the drugs the patient in the Sugammadex group showed significantly lower heart rate than those in neostigmine group, with p value <0.05

Figure 3b shows the mean arterial blood pressure in both groups at different times. There was no significant difference in the means of mean arterial blood pressure between both groups immediately before giving the antidote to the muscle relaxant drug (Sugammadex and neostigmine) and after 3,6,9,12,15 and 18 min from administering the drugs.

10. Discussion

This study showed that, utilising Sugammadex instead of the conventional neostigmine to counteract the effects of rocuronium in preterm newborns has resulted in a quicker reversal and recovery period. This indicates that utilising Sugammadex leads to quicker and greater muscle recovery, which is highly important, especially in this age range. Sugammadex's unique composition and mode of action may be attributed to this. **Won et al**. [16] and **Liu et al**. [17] demonstrated the superiority of Sugammadex in providing rapid recovery in children (paediatric patient over 2 years). They also noted that using Sugammadex has led to a shorter time required to completely revers the effect of the muscle relaxant.

Even more, **Alonso et al**. [18] created a cohort of 23 newborns who received Sugammadex at a dose of 4 mg/kg. According to their analysis, the average time to return TOF to 0.9 was 1.3 minutes (range: 0.6–3.0 min). This result is quite like what we discovered, which was 1.15 0.42 minutes. Additionally, **Liu et al**. [17] discovered that Sugammadex treatment resulted in quicker recovery times across all age groups when compared to neostigmine treatment.

In contrast to our study **Franz et al**. [19] found that the average time in minutes between the end of surgery and discharge from the operating room was similar for neostigmine (19.6) min versus Sugammadex (19.4 min). This may be because our study included 53 neonates (16% of whom were under one month old) whereas Franz et al. [19] used a different age group, the youngest patient was 2 days old. Another study by **An et al**. [20] shown that Sugammadex has

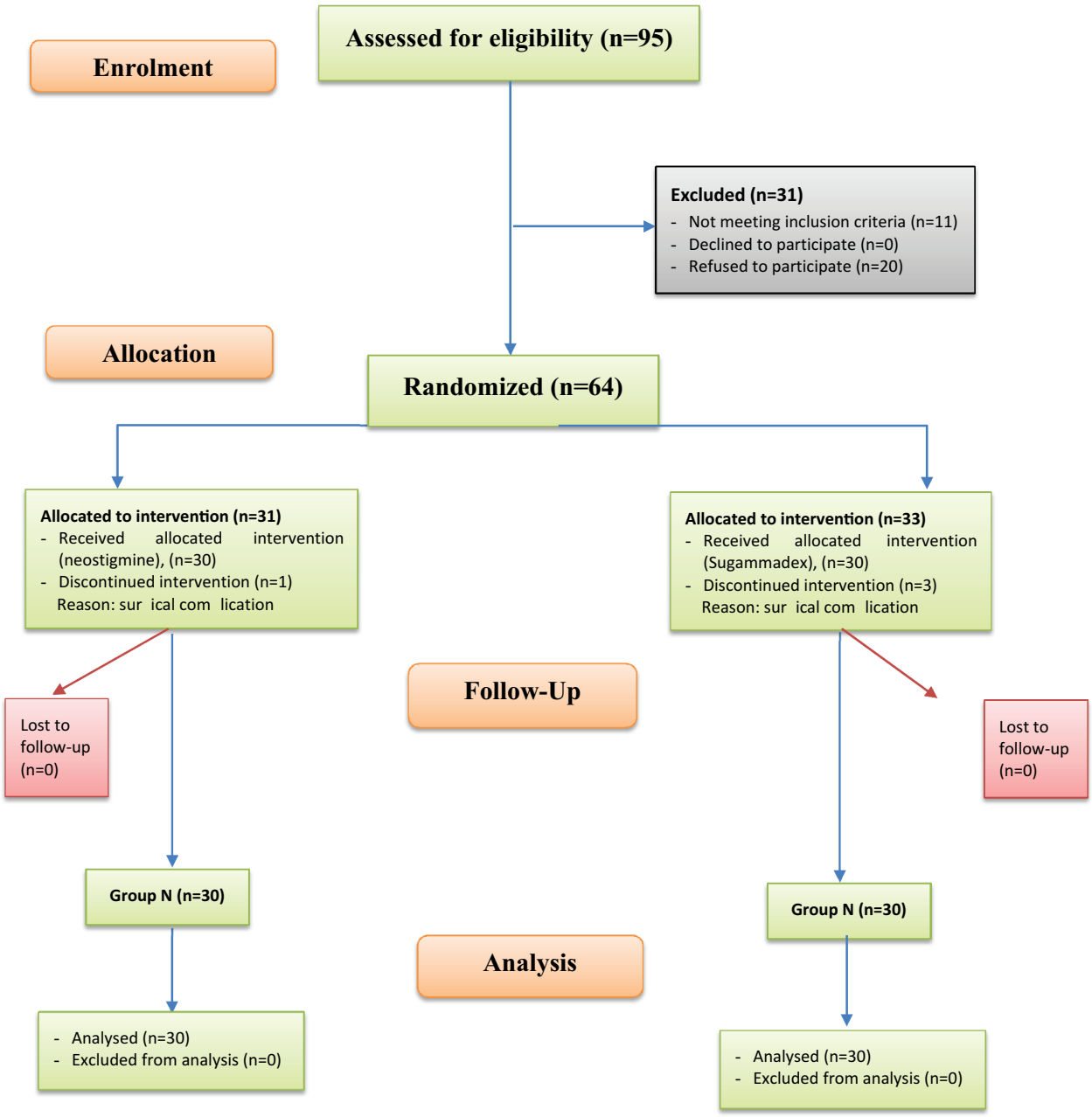

Figure 1. The CONSORT flow chart of the studied patients.

Table 1. Demographic data of the studied patients.

	Mean± SD		
	Group N (n = 30)	Group S (n = 30)	*P value*
Age/days			
Mean ±SD	13.8 ± 7.15	14.77 ± 7.69	0.616
Range	2–27	2–27	
Weight/ Kg			
Mean ±SD	2.38 ± 0.27	2.35 ± 0.29	0.649
Range	1.9–2.9	1.8–2.8	
Gestation age/weeks			
Mean ±SD	34.1 ± 0.84	33.86 ± 0.97	0.363
Range	33–36	32–35	
Sex (M: F)	23:7	20:10	0.391

a quicker recovery period than neostigmine and has no muscarinic side effects in the age range of 1 year to 11 years (in which the recovery time was up to 5 times faster for Sugammadex). [21,22]

Another study by **Abrishami et al.** [23] compared the effects of placebo, recovery after neostigmine, and Sugammadex, and concluded that regardless of the depth of the block, Sugammadex is relatively safer

Table 2. Total dose of muscle relaxant, reversal, and recovery times among the studied groups.

	Studied groups		
	Group N (n = 30)	Group S (n = 30)	P value
Total dose of muscle relaxant (mg)			
Mean ±SD	0.47 ± 0.047	0.46 ± 0.049	0.388
Range	0.4–0.5	0.4–0.5	
Reversal time (in sec)			
Mean ±SD	8.9 ± 1.6	1.15 ± 0.42	<0.001*
Range	5.5–11	0.5–2	
Recovery time (in sec)			
Mean ±SD	27.16 ± 9.26	17 ± 6.64	<0.001*
Range	15–45	10–30	

Data were expressed by using mean ±SD.
P value for comparing between the two studied groups using t-test
*: statistically significant at p ≤ 0.05.

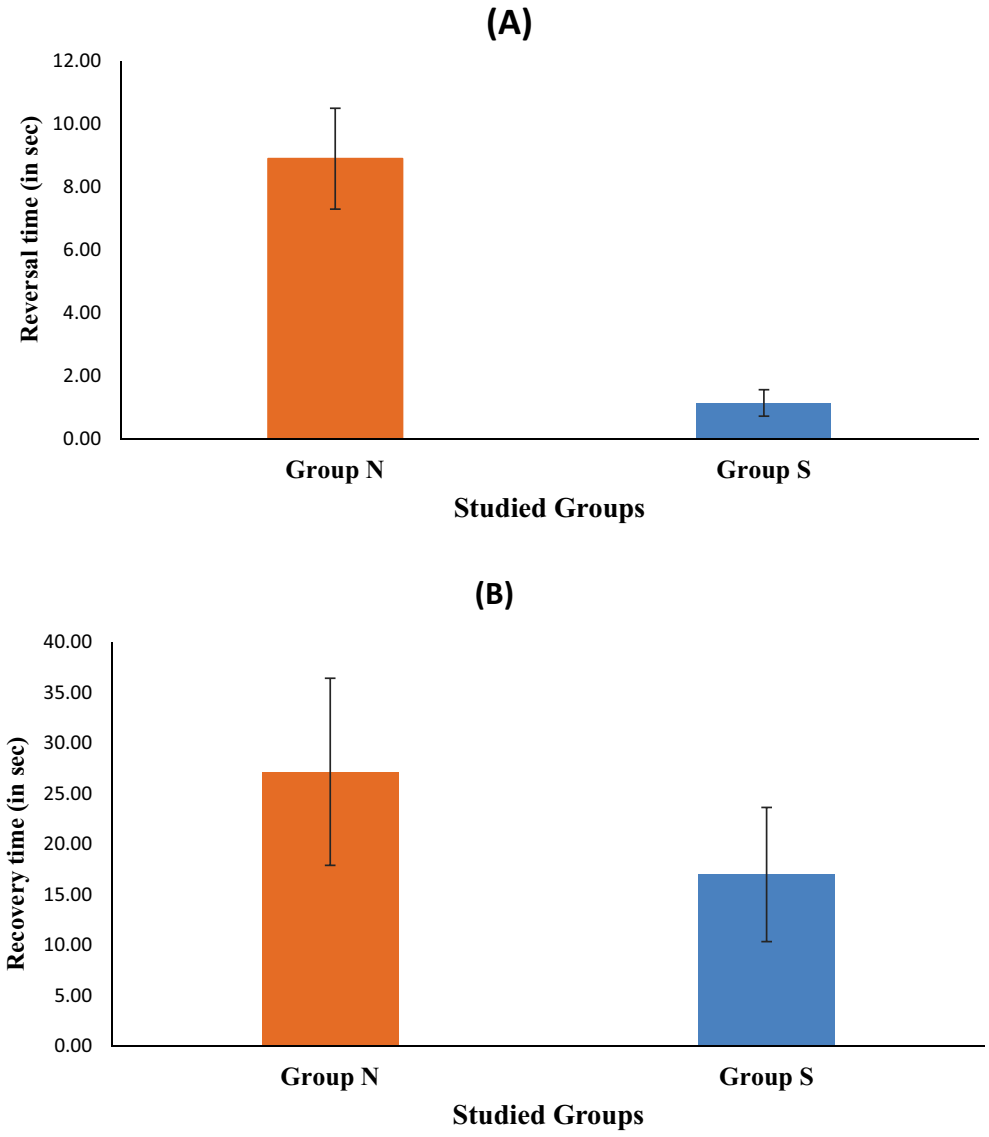

Figure 2. a, b. Reversal and recovery times distribution among the studied groups.

and produces faster reversal of rocuronium-induced neuromuscular blockade.

The current study proved that there was no difference in heart rate between baseline and before receiving Sugammadex or neostigmine. At 3, 6, 9, 12, 15, and 18 minutes after administering Sugammadex, it was statistically significantly lower among patients in group S, although it remained within the normal range, with no bradycardia detected at any time. With no statistically significant differences between the two groups at any point, the mean blood pressure was also comparable. No group experienced hypotension at any point.

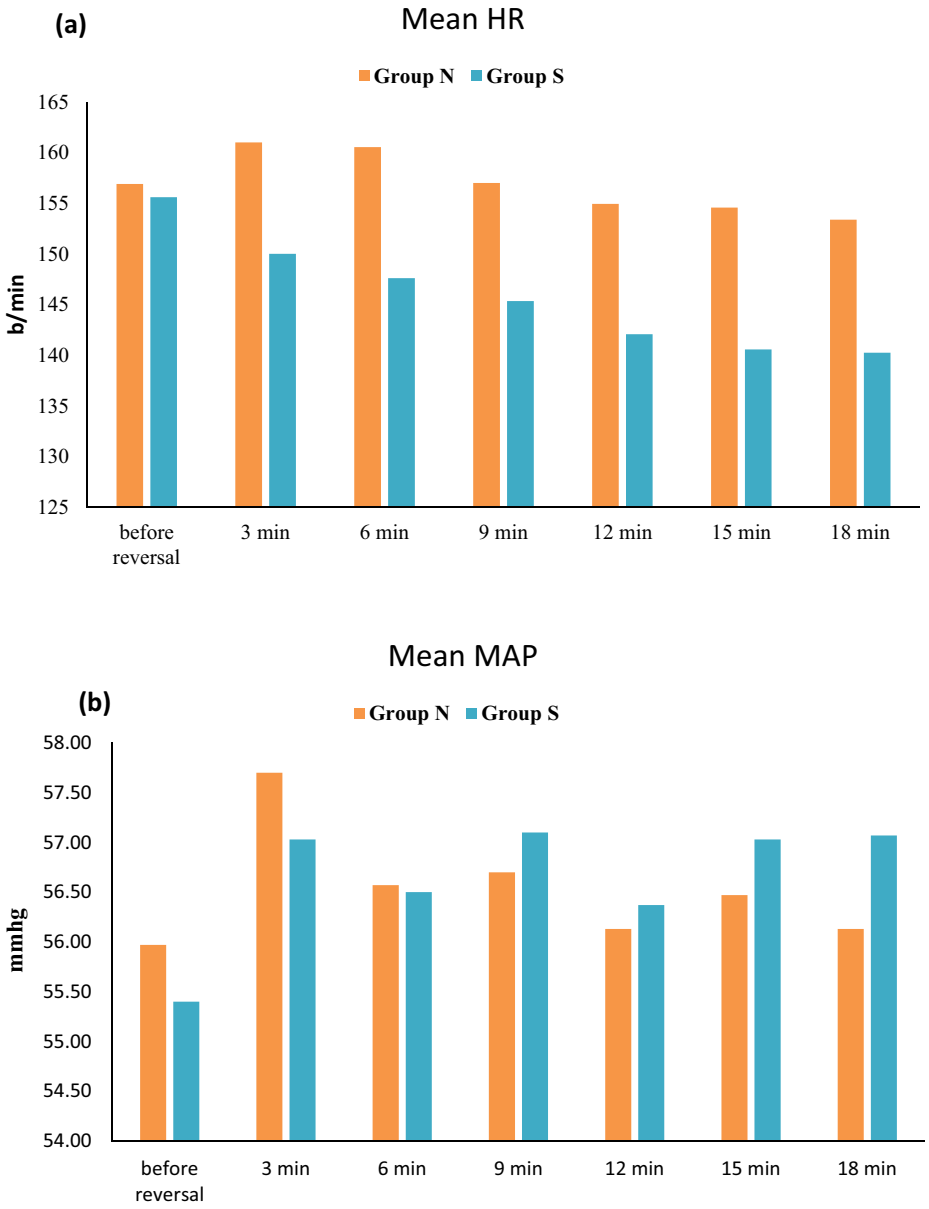

Figure 3. Mean heart rate (a) and mean arterial pressure (b) before reversal and 3–18 minutes after reversal.

The Sugammadex group did not experience any additional complications. These results supported the notion that administering Sugammadex in preterm newborns is safe.

In this concern, **Liu et al**. [17] conducted a meta-analysis of 10 studies involving a total of 575 paediatric patients, which revealed no differences in the occurrence of additional adverse effects like nausea and vomiting or bronchospasm following Sugammadex injection compared to neostigmine. The lack of a consistent definition of bradycardia among studies and the existence of sizable disparities within trials despite sensitivity and subgroup analyses were both criticised by the authors of this meta-analysis. Another study by **Gaver et al**. [24] hypotension and bradycardia were observed following Sugammadex injection. Bradycardia has been seen less frequently than neostigmine, although it can be a serious issue in paediatric patients whose cardiac output is dependent on heart rate. To examine the postoperative adverse effects between patients who received Sugammadex 2 versus 4 mg/kg, **Simonini et al**. [25] retrospectively looked at 423 paediatric patients. Within 30 minutes post-intubation, this study observed no change in the incidence of problems such delirium, laryngo- spasm, bradycardia, or nausea. **Lang et al**. [26] stated that there was no increase in the incidence of pain, bronchospasm, laryngospasm, apnoea, or oxygen desaturation, but there was a substantial decrease in the incidence of bradycardia and dry mouth in patients who took Sugammadex.

The two cases in our study in group N desaturated following extubation were caused by laryngeal spasms, and they were manged accordingly.

This study's limitation came from the fact that only individuals who were generally healthy were included, even though people in this age group frequently have health issues. Therefore, if a patient has a condition that affects the pharmacodynamic or

pharmacokinetic properties of the drug, the results and safety of Sugammadex shown in this study may not be correct.

11. Conclusion

We concluded that in preterm newborns, sugammadex can be used safely to reverse the action of rocuronium. When compared to neostigmine, the use of Sugammadex in preterm newborns causes a faster recovery from the effect of the muscle relaxant rocuronium.

12. Recommendations

We recommend utilising Sugammadex as a rocuronium reversal medication in premature neonates. However, trials with larger samples should continue to be conducted to identify any complications that can arise when the medication is used on a broader scale.

Data sharing statement

All data and materials included in this work are available

Ethics approval and consent to participate

Our local Ethics Committee approved our study and a written consent for participation was obtained from all patients.

Authors' contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure statement

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References

[1] Chaves-Cardona H, Hernandez-Torres V, Kiley S, et al. Neuromuscular blockade management in patients with COVID-19. Korean J Anesthesiol. 2021 Aug 1;74 (4):285–292.
[2] Baillard C, Clec'h C, Catineau J, et al. Postoperative residual neuromuscular block: a survey of management. Br J Anaesth. 2005 Nov 1;95(5):622–626.
[3] Nag K, Singh DR, Shetti AN, et al. A revolutionary drug in neuromuscular pharmacology. Anesthesia, essays and research. 2013 Sep;7(3): 302.
[4] Kovac AL. Sugammadex: the first selective binding reversal agent for neuromuscular block. J Clin Anesth. 2009 Sep 1;21(6):444–453.
[5] Asztalos L, Szabó-Maák Z, Gajdos A, et al. Reversal of vecuronium-induced neuromuscular blockade with low-dose sugammadex at train-of-four count of four: a randomized controlled trial. Anesthesiology. 2017 Sep;127(3):441–449.
[6] Grigg E. Sugammadex and neuromuscular reversal: special focus on neonatal and infant populations. Curr Opin Anesthesiol. 2020 Jun 1;33(3):374–380.
[7] Blobner M, Eriksson LI, Scholz J, et al. Della Rocca G Prins ME. Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. Eur J Anesthesiol. 2010;27:874–881.
[8] Suy K, Morias K, Cammu G. Effective reversal of moderate rocuronium- or vecuronium-induced neuromuscular block with sugammadex, a selective relaxant binding agent. Anesthesiology. 2007;106(2):283–288.
[9] Bilgi M, Demirhan A, Akkaya A, et al. Sugammadex associated persistent bradycardia. Int J Med Sci Public Health. 2015;3:372e4.
[10] Bhavani SS. Severe bradycardia and asystole after sugammadex: a report of 2 cases. Br J Anaesth 2018; 121: 95e6
[11] Hristovska AM, Duch P, Allingstrup M, et al. safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults. Cochrane Database Syst Rev. 2017;8(8):Cd012763.
[12] Fierro C, Medoro A, Mignogna D, et al. Bradycardia and Asystole after Sugammadex Administration in an Elderly Patient. Medicina (B Aires). 2021;57(1):79.
[13] Eriksson LI. Evidence-based practice and neuromuscular monitoring: it's time for routine quantitative assessment. Anaesthesiol. 2003;98(5):1037–1039.
[14] Gaszynski T, Jakubiak J, Szlachcinski L, et al. Administration of neostigmine does not prevent from post-operative residual curarisation. Eur J Anaesthesiol. 2008;25(Sup 44):137.
[15] Tanaka M, Sato M, Saito A, et al. Reevaluation of rectal ketamine premedication in children. Anesthesiology. 2000;93(5):1217–1224.
[16] Won YJ, Lim BG, Lee DK, et al. Sugammadex for reversal of rocuronium-induced neuromuscular blockade in pediatric patients: a systematic review and meta-analysis. In: Medicine. Vol. 95 (Wolters Kluwer Health); 2016 Aug. p. 34.
[17] Liu G, Wang R, Yan Y, et al. The efficacy and safety of sugammadex for reversing postoperative residual neuromuscular blockade in pediatric patients: a systematic review. Sci Rep. 2017 Jul 18;7(1):1–9.
[18] Alonso A, de Boer HD, Booij L. Reversal of rocuronium-induced neuromus- cular block by

sugammadex in neonates. Eur J Anaesthesiol. 2014;31 (Suppl52): 163–165 .

[19] Franz A, Chiem J, Martin LM, et al. Case Series of 331 doses of Sugammadex compared to Neostigmine in patients under 2-years-old. Pediatr Anesth. 2019;29 (6):591–596.

[20] An J, Lee JH, Kim E, et al. Comparison of sugammadex and pyridostigmine bromide for reversal of rocuronium-induced neuromuscular blockade in short-term pediatric surgery: a prospective randomized study. In: Medicine. Vol. 99 (wolters Kluwer Health); 2020 Feb. p. 7.

[21] Ammar AS, Mahmoud KM, Kasemy ZA. A comparison of sugammadex and neostigmine for reversal of rocuronium-induced neuromuscular blockade in children. Acta Anaesthesiol Scand. 2017 Apr;61(4):374–380.

[22] Katz RL. Pyridostigmin (mestinon) as an antagonist of d-tubocurarine.J American SocAnesthesiologists 1967 May 1 (Vol. 28, No. 3, pp. 528–534). The American Society of Anesthesiologists

[23] Abrishami A, Ho J, Wong J, et al. Sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular blockade. In: Cochrane Database of Systematic Reviews (john wiley & Sons). 2009. p. 4.

[24] Gaver RS, Brenn BR, Gartley A, et al. Retrospective analysis of the safety and efficacy of sugammadex versus neostigmine for the reversal of neuromuscular blockade in children. Anesthesia Analg. 2019 Oct 1;129 (4):1124–1129.

[25] Simonini A, Brogi E, Calevo MG, et al. Sugammadex for reversal of neuromuscular blockade in paediatric patients: a two-year single-centre retrospective study. Anaesth Crit Care Pain Med. 2019 Feb 25;38 (5):529–531.

[26] Lang B, Han L, Zeng L, et al. safety of sugammadex for neuromuscular blockade reversal in pediatric patients: an updated meta-analysis of randomized controlled trials with trial sequential analysis. BMC Pediatr. 2022 Dec;22(1):1–2.