Neuromuscular Block Management in Pediatric Anesthesia

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Disclosure

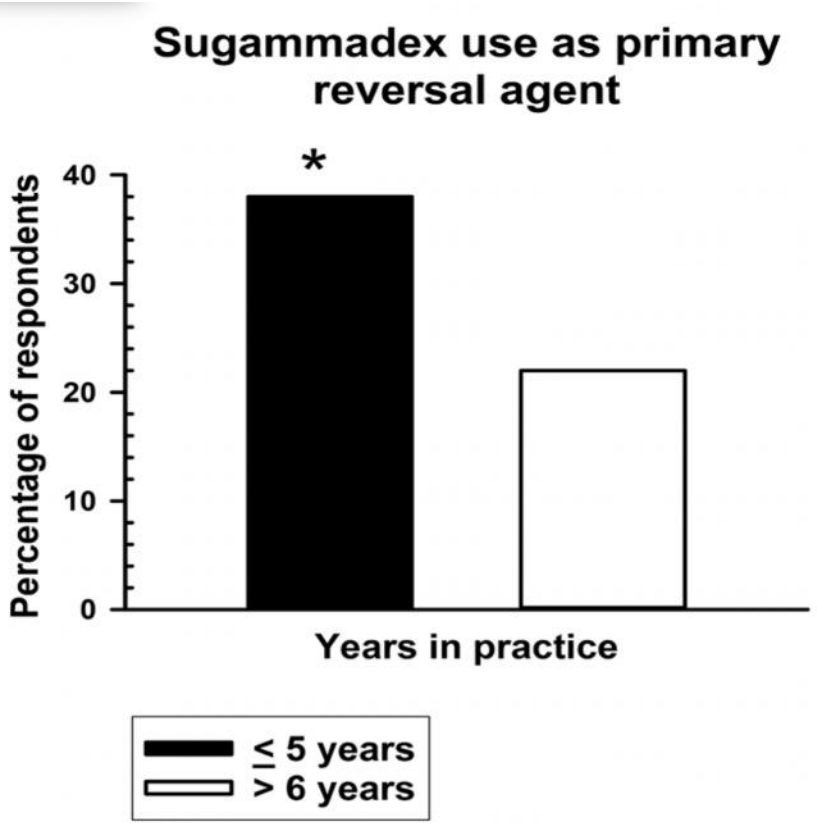
Financial Disclosure :
As a speaker I have received honorarium for this presentation.

Outline

- Monitoring
- Guidelines
- Residual block and reversal
- Sugammadex
- Future perspectives

Monitoring

A Survey of the Society for Pediatric Anesthesia on the Use, Monitoring, and Antagonism of Neuromuscular Blockade



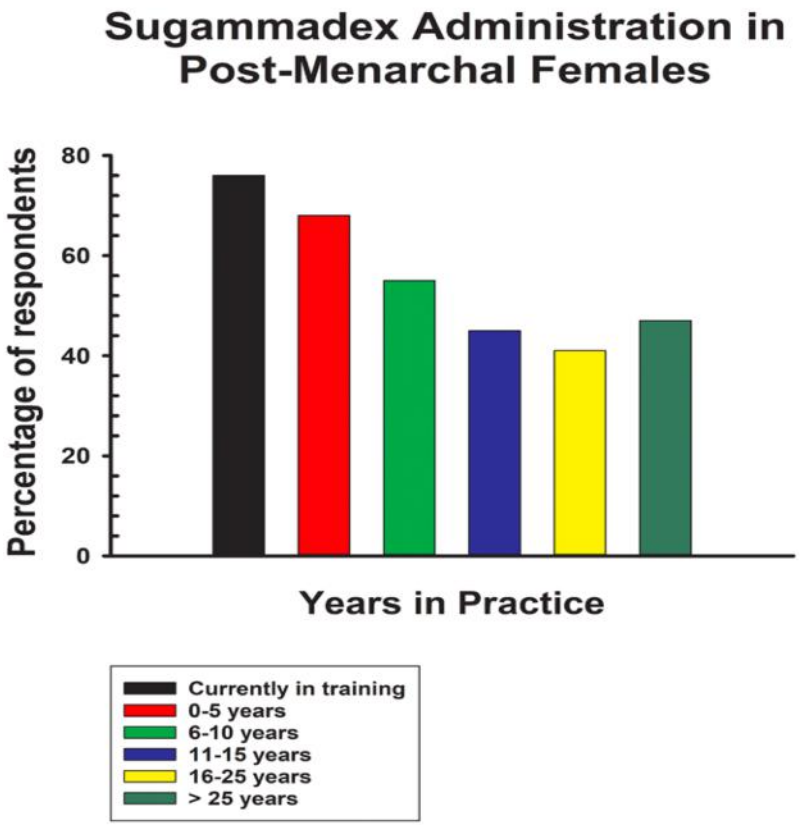


Table 3. Neuromuscular Blockade Monitoring

Parameter		N (%)
Type of TOF monitor available	Qualitative only	226 (57.7)
	Quantitative only	60 (15.3)
	Both qualitative and quantitative	91 (23.2)
	Unsure	8 (2.0)
	No monitors available	7 (1.8)
TOF monitor use Before Sugam Introduction	Always (100%)	154 (40.0)
	Mostly (50%–100%)	141 (36.6)
	Sometimes (25%–50%)	47 (12.2)
	Rarely (>0%–25%)	37 (9.6)
	Never (0%)	6 (1.6)
TOF monitor use since Sugam introduction	No longer a need	6 (1.7)
	Still routinely use	231 (67.0)
	Case-by-case basis	103 (29.9)
	Never monitored before	5 (1.4)
Preferred anatomic site for TOF monitor	Adductor pollicis	126 (32.7)
	Orbicularis oculi	33 (8.6)
	Posterior tibialis	2 (0.5)
	Does not matter—use whatever site available based on position	42 (10.9)
	Does matter—use whatever site available based on position	182 (47.3)
Encountered Sugam Failure	Yes	44 (12.8)
	No	301 (87.2)
Encountered neostigmine Failure	Yes	242 (62.9)
	No	143 (37.1)

Survey results

- ≤5 years of practice: sugammadex as primary reversal agent ([OR]: 2.08; 95% CI, 1.31-3.31)
- Only 40% of practitioners always assess NMB (train-of-four), and use was inversely correlated with years of practice (Spearman ρ = −0.11, P = .04)
- Anesthesiologists who primarily used sugammadex assess NMB less routinely (OR: 0.56; 95% CI, 0.34-0.90; P = .01).
- 38% percent did not discuss its effects on hormonal contraception with the patient and/or family, independent of anesthesiologist experience

The Recent Guidelines

2023 American Society of Anesthesiologists Practice Guidelines for Monitoring and Antagonism of Neuromuscular Blockade: A Report by the American Society of Anesthesiologists Task Force on Neuromuscular Blockade

Stephan R. Thilen, M.D., M.S. (co-chair),
Wade A. Weigel, M.D. (co-chair), Michael M. Todd, M.D.,
Richard P. Dutton, M.D., M.B.A., Cynthia A. Lien, M.D.,
Stuart A. Grant, M.D.,
Joseph W. Szokol, M.D., J.D., M.B.A., FASA,
Lars I. Eriksson, M.D., Ph.D., FRCA,
Myron Yaster, M.D., Mark D. Grant, M.D., Ph.D.,
Madhulika Agarkar, M.P.H., Anne M. Marbella, M.S.,
Jaime F. Blanck, M.L.I.S., M.P.A.,
Karen B. Domino, M.D., M.P.H.

ANESTHESIOLOGY 2023; 138:13–41

Recommendation	Strength of Recommendation	Strength of Evidence
1. When neuromuscular blocking drugs are administered, we recommend against clinical assessment alone to avoid residual neuromuscular blockade, due to the insensitivity of the assessment.	Strong	Moderate
2. We recommend quantitative monitoring over qualitative assessment to avoid residual neuromuscular blockade.	Strong	Moderate
3. When using quantitative monitoring, we recommend confirming a train-of-four ratio greater than or equal to 0.9 before extubation.	Strong	Moderate
4. We recommend using the adductor pollicis muscle for neuromuscular monitoring.	Strong	Moderate
5. We recommend against using eye muscles for neuromuscular monitoring.	Strong	Moderate
6. We recommend sugammadex over neostigmine at deep, moderate, and shallow depths of neuromuscular blockade induced by rocuronium or vecuronium, to avoid residual neuromuscular blockade.*	Strong	Moderate
7. We suggest neostigmine as a reasonable alternative to sugammadex at minimal depth of neuromuscular blockade.	Conditional	Low
8. To avoid residual neuromuscular blockade when atracurium or cisatracurium are administered and qualitative assessment is used, we suggest antagonism with neostigmine at minimal neuromuscular blockade depth. In the absence of quantitative monitoring, at least 10 min should elapse from antagonism to extubation. When quantitative monitoring is utilized, extubation can be done as soon as a train-of-four ratio greater than or equal to 0.9 is confirmed before extubation.	Conditional	Very low

1. When neuromuscular blocking drugs are administered, we recommend against clinical assessment alone to avoid residual neuromuscular blockade, due to the insensitivity of the assessment. Strong Moderate
2. We recommend quantitative monitoring over qualitative assessment to avoid residual neuromuscular blockade. Strong Moderate
3. When using quantitative monitoring, we recommend confirming a train-of-four ratio greater than or equal to 0.9 before extubation. Strong Moderate

EJA

GUIDELINES

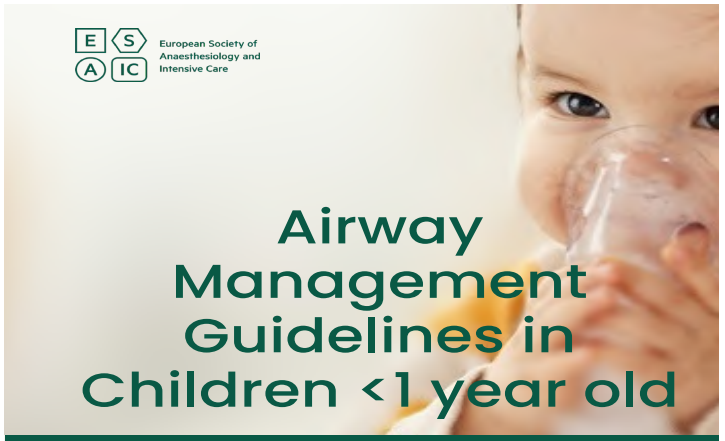
Peri-operative management of neuromuscular blockade

A guideline from the European Society of Anaesthesiology and Intensive Care

Thomas Fuchs-Buder, Carolina S. Romero, Heidrun Lewald, Massimo Lamperti, Arash Afshari, Ana-Marjia Hristovska, Denis Schmartz, Jochen Hinkelbein, Dan Longrois, Maria Popp, Hans D. de Boer, Massimiliano Sorbello, Radmilo Jankovic and Peter Kranke

Is the use of muscle relaxants necessary to facilitate tracheal intubation?

(1) We recommend using a muscle relaxant to facilitate tracheal intubation (**1A**).



Provide adequate anaesthesia/sedation for all children and paralysis if spontaneous breathing is not required

What are the strategies for the diagnosis and treatment of residual neuromuscular paralysis?

(1) We recommend the use of ulnar nerve stimulation and quantitative NMM at the adductor pollicis muscle to exclude residual paralysis. (**1B**)

(2) We recommend using sugammadex to antagonise deep, moderate and shallow neuromuscular blockade induced by aminosteroidal agents (rocuronium, vecuronium) (deep: posttetanic count >1 and TOF count 0, moderate: TOF count 1 to 3, shallow: TOF count 4 and TOF ratio < 0.4). (**1A**)

(3) We recommend advanced spontaneous recovery (i.e. TOF-ratio >0.2) before starting neostigmine-based reversal and to continue quantitative monitoring of neuromuscular blockade until a TOF ratio of more than 0.9 has been attained. (**1C**)

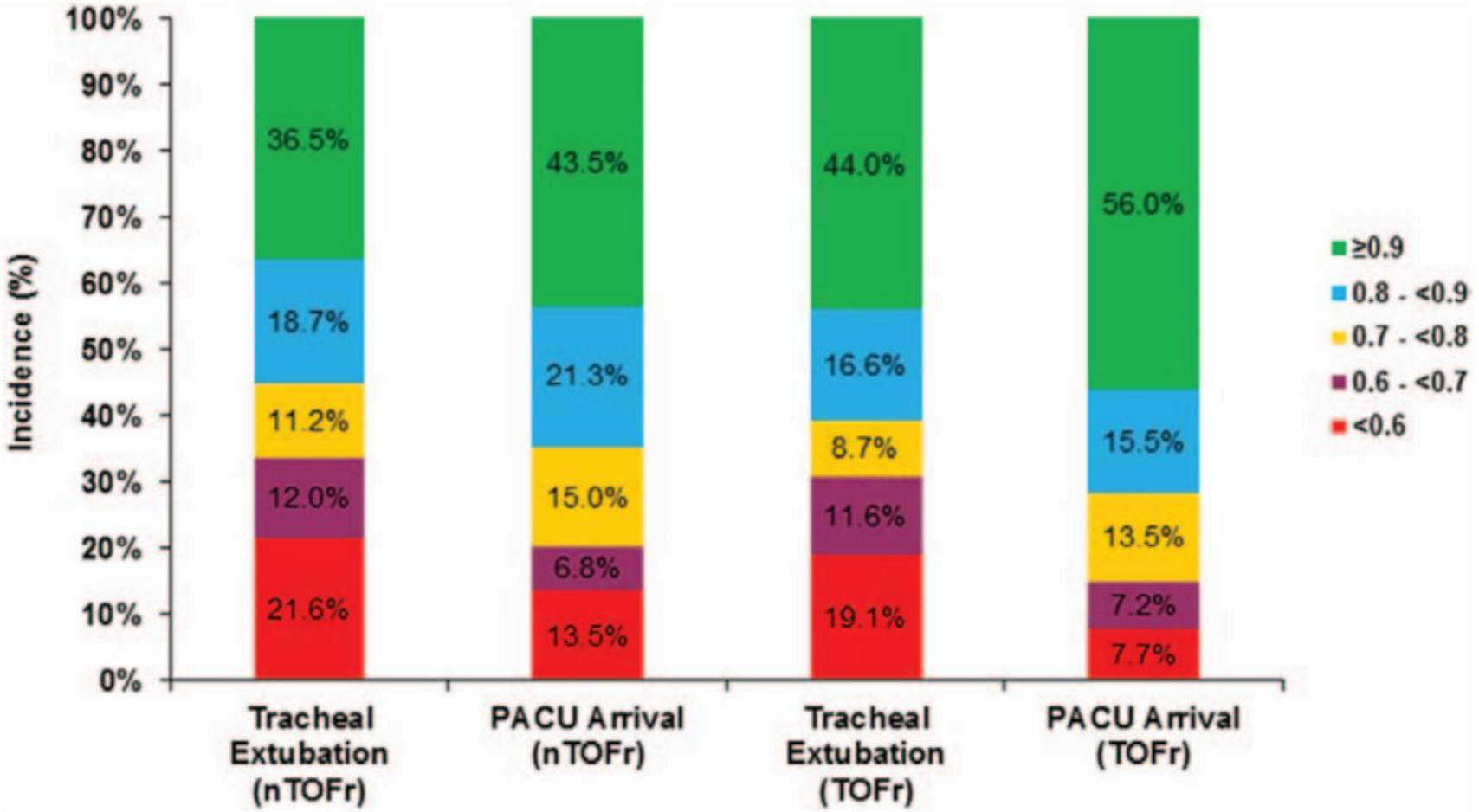
EJA

Limitations and further research

(1) Paediatric patients may also be at risk of residual neuromuscular block, but the current guidelines do not address monitoring in this patient group. This, however, should be undertaken in a specific guideline.

Residual neuromuscular block

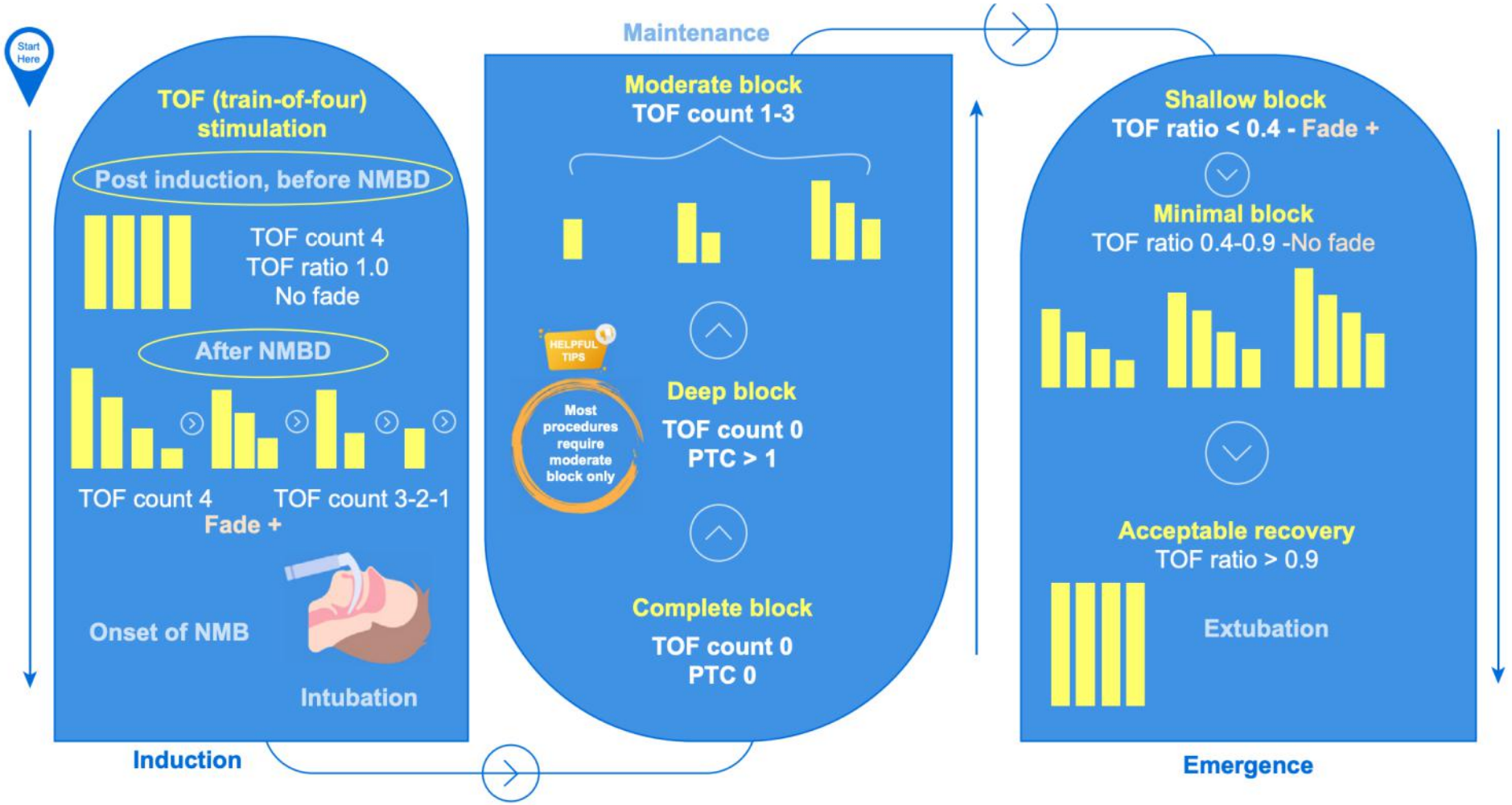
The RECITE Study: A Canadian Prospective, Multicenter Study of the Incidence and Severity of Residual Neuromuscular Blockade



Qualitative vs Quantitative

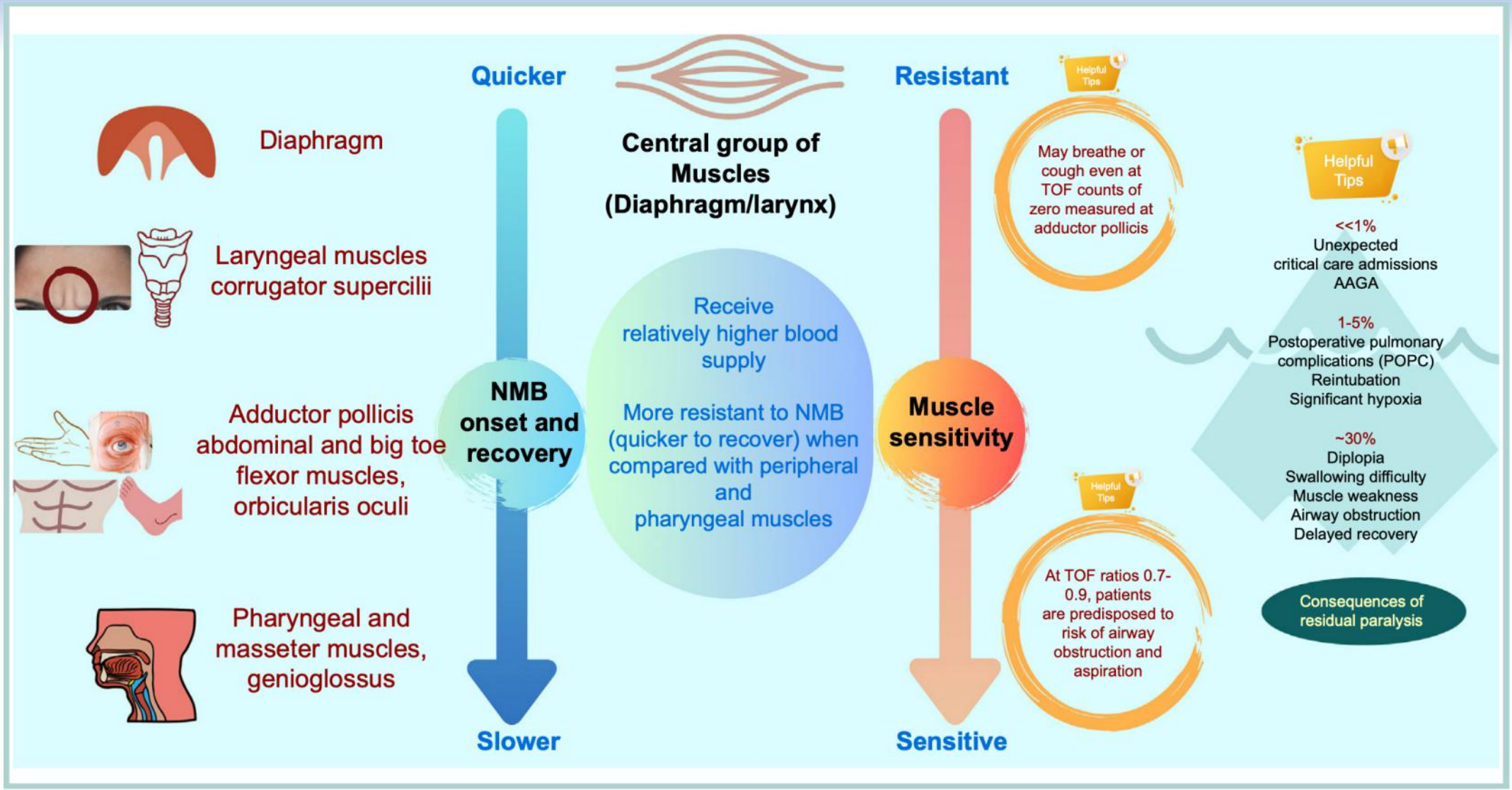
Depth of Blockade	Peripheral Nerve Stimulator and Qualitative Assessment	Quantitative Monitor
Complete	Posttetanic count = 0	Posttetanic count = 0
Deep	Posttetanic count ≥ 1; train-of-four count = 0	Posttetanic count ≥ 1; train-of-four count = 0
Moderate	Train-of-four count = 1–3	Train-of-four count = 1–3
Shallow*	Train-of-four count = 4; train-of-four fade present	Train-of-four ratio < 0.4
Minimal*	Train-of-four count = 4; train-of-four fade absent	Train-of-four ratio = 0.4–0.9
Acceptable recovery	Cannot be determined	Train-of-four ratio ≥ 0.9

Phases of Neuromuscular Block

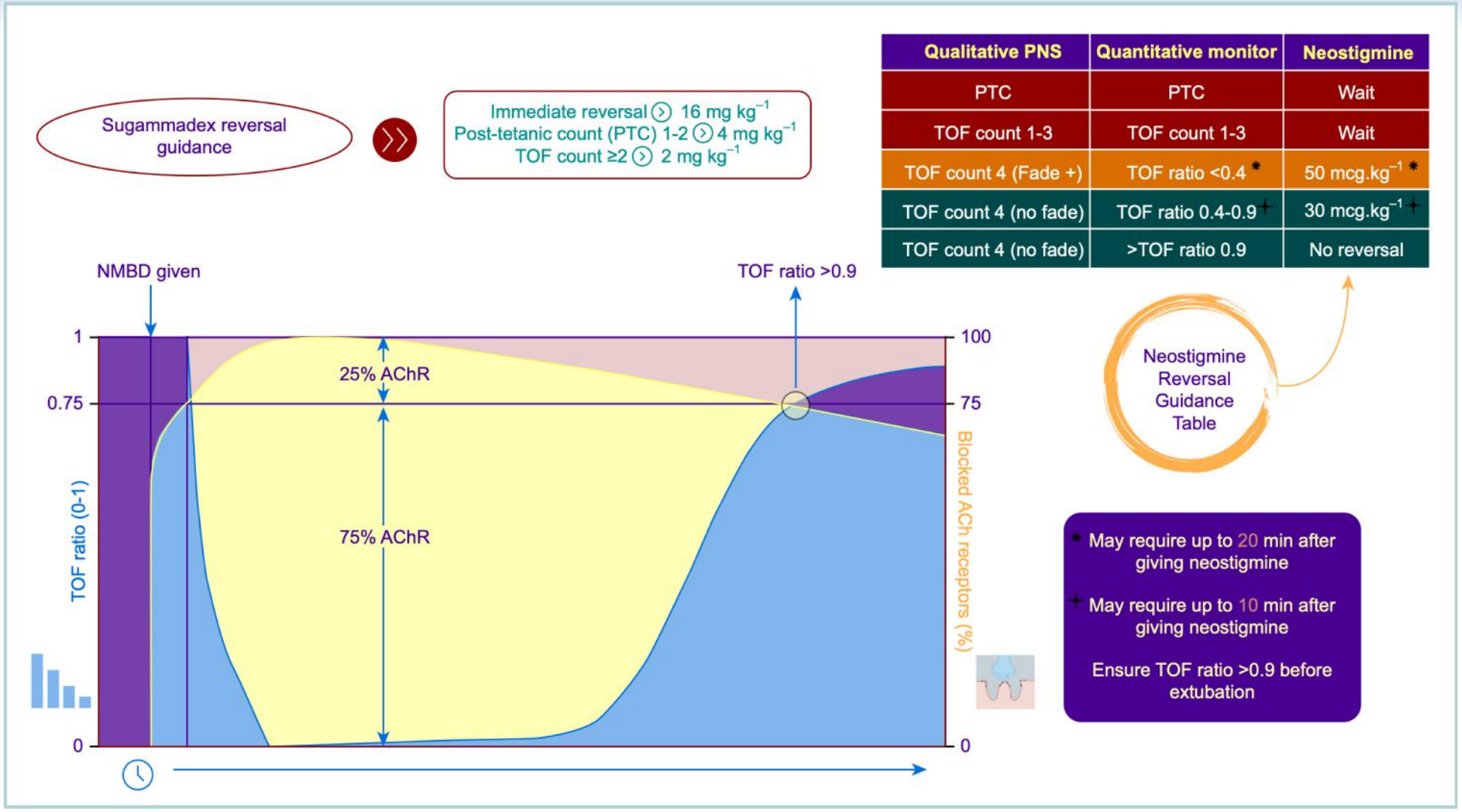


Complete (PTC = 0)
Deep (PTC 1, TOF count = 0)
Moderate (TOF count = 1-3)
Shallow (TOF ratio < 0.4)
Minimal (TOF ratio < 0.4-0.9)
Recovery (TOF ratio > 0.9)

Differential muscle sensitivity



Acetylcholine receptor occupancy and TOF ratio



Qualitative PNS	Quantitative monitor	Neostigmine
PTC	PTC	Wait
TOF count 1-3	TOF count 1-3	Wait
TOF count 4 (Fade +)	TOF ratio <0.4 *	50 mcg.kg^{-1} *
TOF count 4 (no fade)	TOF ratio 0.4-0.9 +	30 mcg.kg^{-1} +
TOF count 4 (no fade)	>TOF ratio 0.9	No reversal

The Time to Seriously Reassess the Use and Misuse of Neuromuscular Blockade in Children Is Now

J. Ross Renew, MD, FASA, FASE,* Joseph D. Tobias, MD,† and Sorin J. Brull, MD, FCARCSI (Hon)*

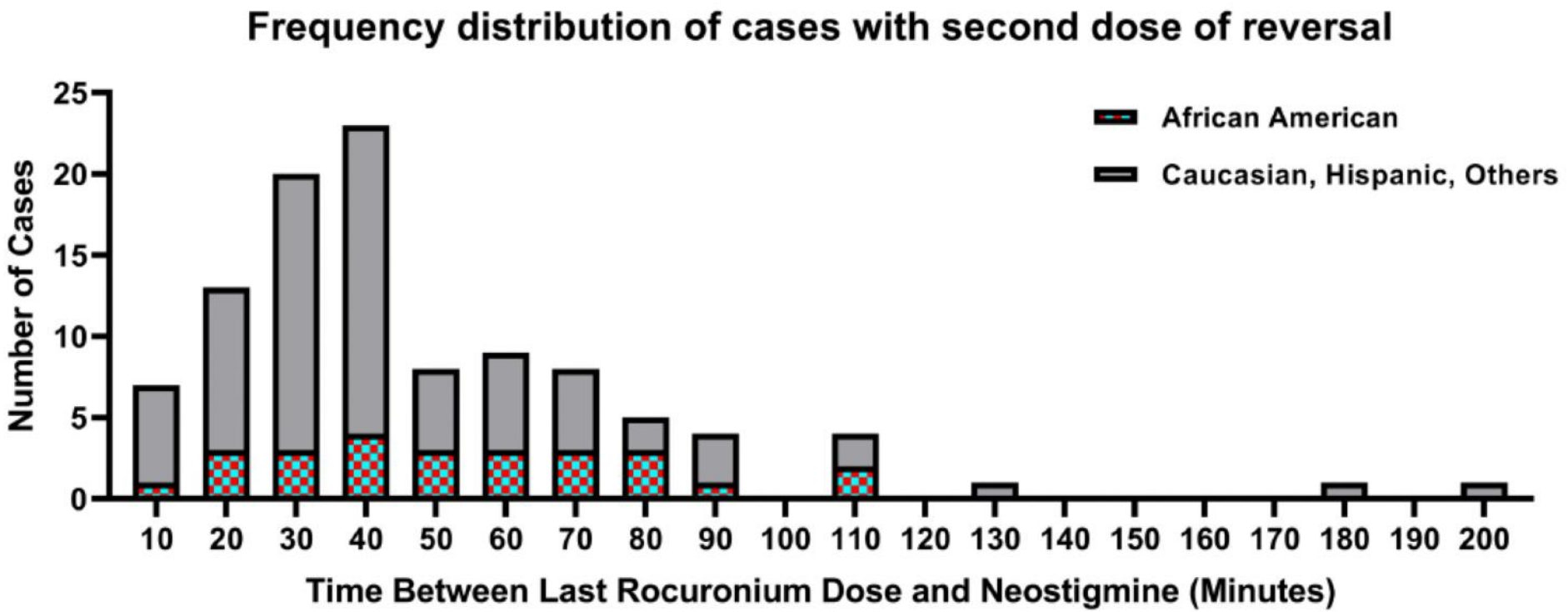
- Sugammadex dosing is frequently not based on objective neuromuscular monitoring
- Only 40% of practitioners always use a device
- The incidence of anaphylaxis to sugammadex is rare (< 0.04%)
- The most common complications associated with the use of NMBAs in pediatric patients is residual neuromuscular block (….and, maybe, re-paralysis….)

Residual paralysis

- A recently published cohort study of over 6500 pediatric surgeries that has shown that high doses of NMBAs are associated with a high risk of postoperative pulmonary complications (odds ratio [OR], 2.27; 95% CI, 1.12-4.59; P =.02), particularly in infants ≤1 year (OR, 3.84; CI, 11.35-10.94; P =.01)

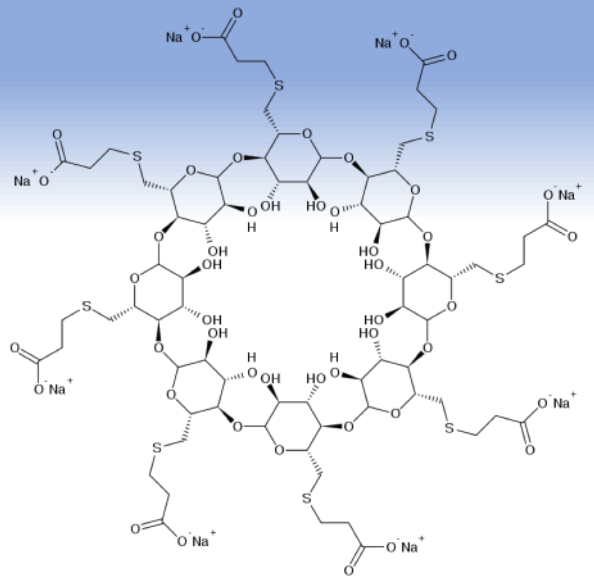
Scheffenbichler FT, Rudolph MI, Friedrich S, et al. Effects of high neuromuscular blocking agent dose on post-operative respiratory complications in infants and children. *Acta Anaesthesiol Scand*. 2020;64:156–167.

Risk factors for administration of additional reversal following neuromuscular blockade with rocuronium in children: A retrospective case–control study

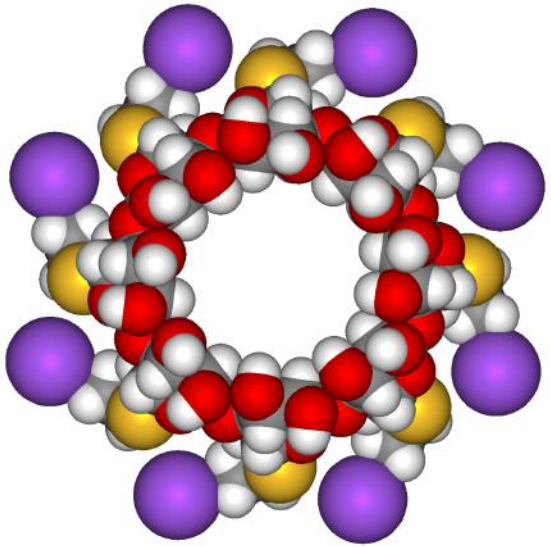


Sugammadex

PHARMACOLOGY



- Donut-shaped cyclodextrin molecule.
- Half-life of 2h in patients with normal renal function.
- It has not hepatic metabolism.
- No binding with plasma proteins or red blood cells.
- It is excreted unchanged by the ***kidneys***.

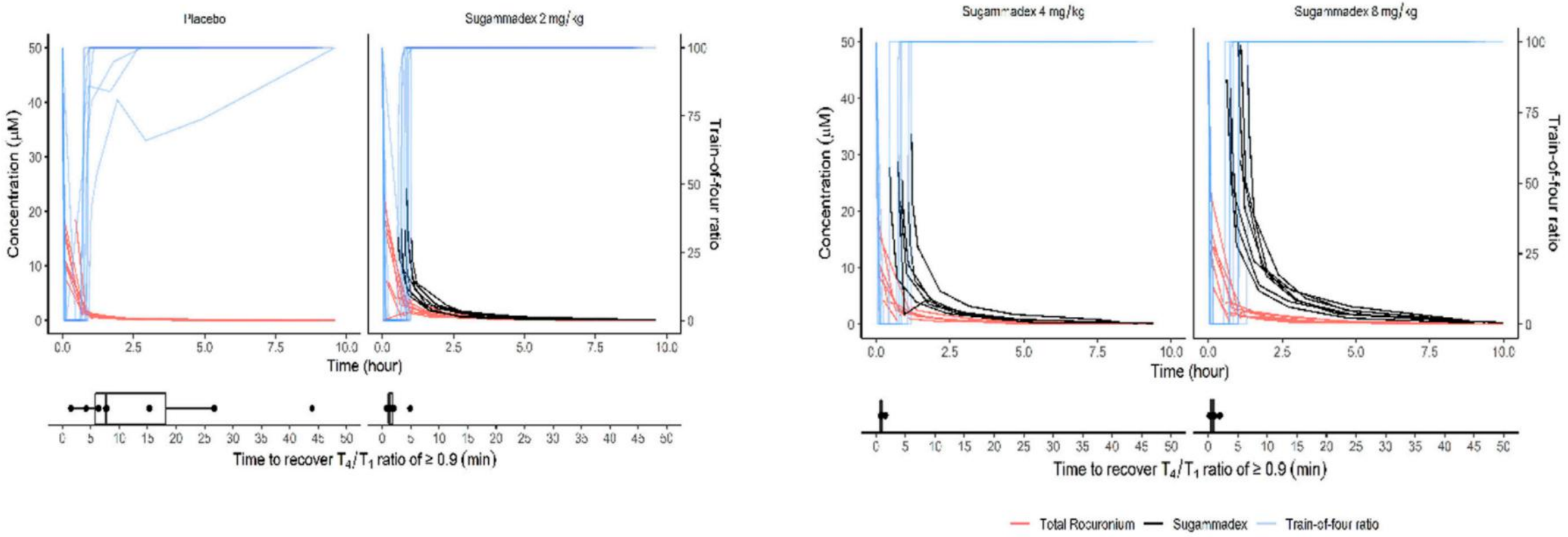


PK of sugammadex

2 mg/kg

4 mg/kg

8 mg/kg



Sang-Hwan Ji. Front. Pharmacol. 14:1127932.

SIDE EFFECTS

- Hypersensitivity and anaphylaxis: flushing, urticaria, erythematous rash, (severe) hypotension, tachycardia, swelling of tongue, swelling of pharynx, bronchospasm and pulmonary obstructive events.
- Bradycardia

- Vomiting
- Hypotension
- Headache
- Pain
- Nausea

DOSAGE

Sugammadex dosing guidelines for reversing rocuronium			
	Neuromuscular block depth	**Sugammadex dose (mg/kg)**	**Time to recovery of T_4/T_1 ratio 0.9 (minutes)**
Routine reversal	T_2	2	2
	One to two posttetanic counts	4	3
Immediate reversal	No tetany	16	1.5

Following a single intraoperative dose of rocuronium (0.6 mg/kg), sugammadex was administered within 2 minutes of reappearance of **T2** of the TOF. The median time from the administration of sugammadex to return of the **TOF ratio to 0.9** was 0.6 (n=1), 1.2 (n=4), 1.1 (n=6), and 1.2 (n=5) minutes, respectively, in infants (28days – 23months), children (2 – 11 years), adolescents (12 – 17 years), and adults (>17 years).

Grigg, Eliot Sugammadex and neuromuscular reversal: special focus on neonatal and infant populations, Current Opinion in Anaesthesiology: June 2020 - Volume 33 - Issue 3 - p 374-380

Reversal with sugammadex (**4mg/kg**) in profound residual neuromuscular blockade in neonates.

	Total Rocuronium dose (mg)	**Recovery time (min)**	**Final TOF**
1 day (n=8)			
Mean (SD)	1.6 (0.1)	1.4 (0.1)	105 (20)
Median (range)	1.7 (1.5-1.7)	1.3 (0.6-3.0)	90-152
1day–7days (n=15)			
Mean (SD)	1.4 (0.5)	1.2 (0.5)	103 (8.2)
Median (range)	1.6 (0.5-0.8)	1.2 (0.4-2.2)	97-112

Alonso A, de Boer HD, Booij L. Reversal of rocuronium-induced neuromuscular block by sugammadex in neonates (Abstract). Eur J Anaesthesiol 2014;31(Suppl 52): 163-165

SUGAMMADEX *vs* NEOSTIGMINE

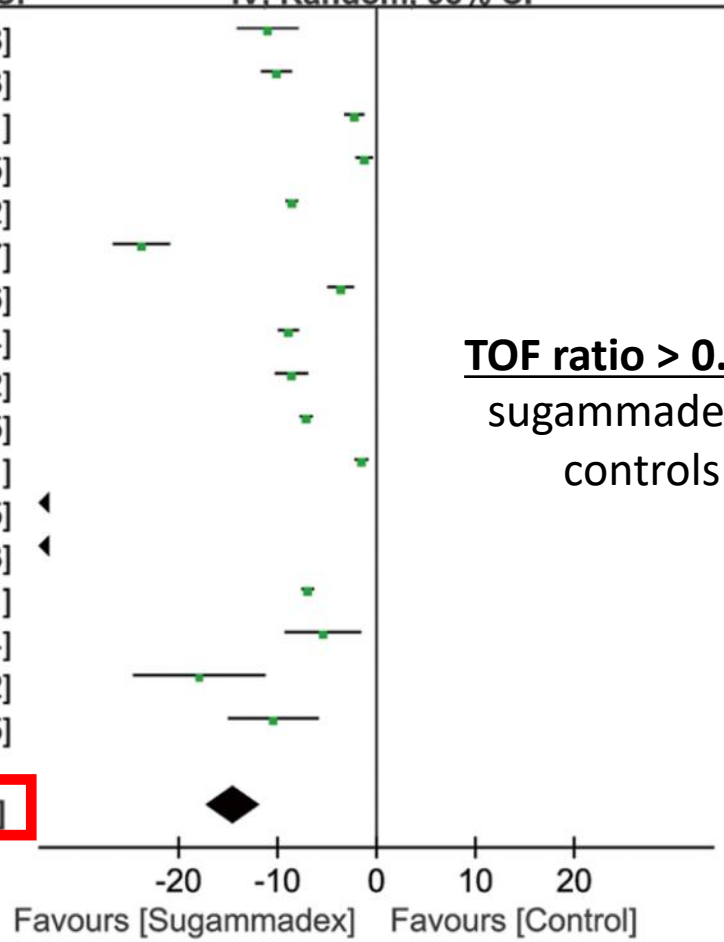
- Sugammadex provides a **faster and more complete reversal** with a lower risk of residual curarization.
- Sugammadex also has a **lower rate of postoperative respiratory complications**.

(A)

Study or Subgroup	Sugammadex Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alvarez-Gomez JA 2012	1.2	0.73	49	12.2	10.9	47	6.0%	-11.00 [-14.12, -7.88]
Ammar AS 2017	2.5	0.8	30	12.6	4.3	30	6.4%	-10.10 [-11.67, -8.53]
An J 2019	1.3	0.84	30	3.53	2.73	30	6.4%	-2.23 [-3.25, -1.21]
El sayed M 2016	0.41	0.58	35	1.64	2.59	35	6.5%	-1.23 [-2.11, -0.35]
Gaona D 2012	1.11	0.3	15	9.66	1.2	15	6.5%	-8.55 [-9.18, -7.92]
Ghoneim AA 2015	1.4	1.2	20	25.16	6.49	20	6.0%	-23.76 [-26.65, -20.87]
Güzelce D 2016	1.68	0.97	16	5.3	2.98	21	6.4%	-3.62 [-4.98, -2.26]
Hu J 2020	2.2	1	20	11.1	2.2	20	6.4%	-8.90 [-9.96, -7.84]
Hussein AA 2020	2.5	0.93	40	11.1	5.33	40	6.3%	-8.60 [-10.28, -6.92]
Jiang Y 2020	1.4	0.2	30	8.5	1.8	30	6.5%	-7.10 [-7.75, -6.45]
Kara T 2014	0.46	0.7	40	1.97	2.14	40	6.5%	-1.51 [-2.21, -0.81]
Li L 2020	3.4	1.2	30	76.2	20.5	30	4.4%	-72.80 [-80.15, -65.45]
Li XB 2020	4.2	1.4	30	108.2	26.7	30	3.5%	-104.00 [-113.57, -94.43]
Mohamad Zaini RH 2016	1.41	0.71	40	8.36	1.93	40	6.5%	-6.95 [-7.59, -6.31]
Ozgun C 2014	1.13	7.62	30	6.53	7.62	30	5.7%	-5.40 [-9.26, -1.54]
Plaud B 2009	3.39	6.37	47	21.3	10.9	11	4.6%	-17.91 [-24.60, -11.22]
Veiga RG 2011	1.06	0.3	14	11.5	7.4	10	5.5%	-10.44 [-15.03, -5.85]
Total (95% CI)			**516**			**479**	**100.0%**	**-14.42 [-17.08, -11.75]**

Heterogeneity: Tau² = 28.44; Chi² = 1374.09, df = 16 (P < 0.00001); I² = 99%

Test for overall effect: Z = 10.60 (P < 0.00001)



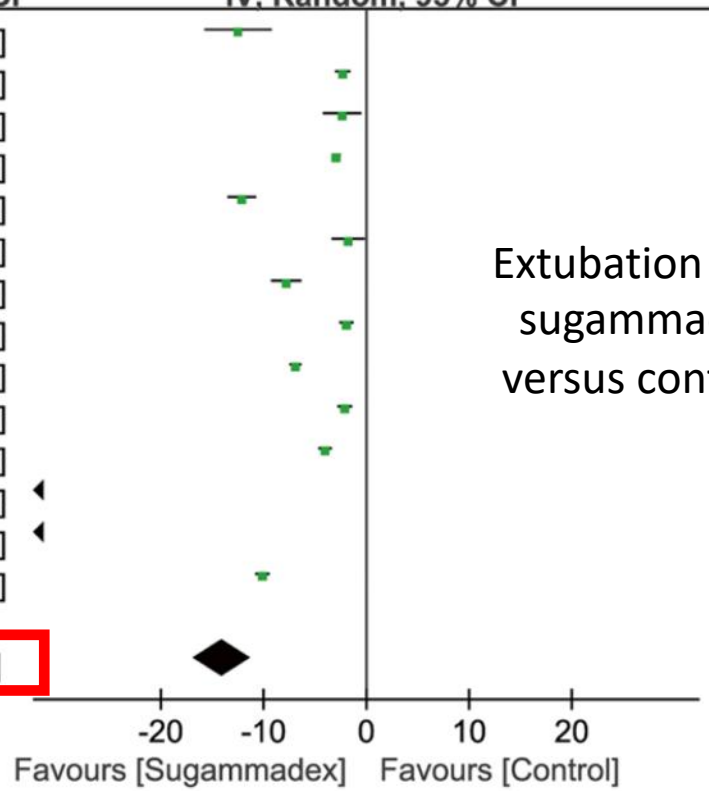
TOF ratio > 0.9 for sugammadex vs controls

Lang et al. BMC Pediatrics (2022) 22:295

Study or Subgroup	Sugammadex Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Alvarez-Gomez JA 2012	3.3	3.2	49	15.8	11.01	47	7.0%	-12.50 [-15.77, -9.23]
Ammar AS 2017	2	0.8	30	4.3	1.9	30	7.7%	-2.30 [-3.04, -1.56]
An J 2019	6.23	3.48	30	8.58	3.89	30	7.5%	-2.35 [-4.22, -0.48]
El sayed M 2016	1.25	0.59	35	4.21	1.18	35	7.7%	-2.96 [-3.40, -2.52]
Gaona D 2012	2.07	0.5	15	14.19	2.7	15	7.6%	-12.12 [-13.51, -10.73]
Güzelce D 2016	4.3	2.48	16	6.06	2.47	21	7.5%	-1.76 [-3.37, -0.15]
Hu J 2020	5.9	2.8	20	13.7	1.9	20	7.6%	-7.80 [-9.28, -6.32]
Hussein AA 2020	2.5	0.9275	40	4.4502	2.0173	40	7.7%	-1.95 [-2.64, -1.26]
Jiang Y 2020	3.8	1.1	30	10.7	1.2	30	7.7%	-6.90 [-7.48, -6.32]
Kara T 2014	1.15	1.44	40	3.25	1.79	40	7.7%	-2.10 [-2.81, -1.39]
Korkmaz MO 2019	4.82	0.85	35	8.83	1.79	35	7.7%	-4.01 [-4.67, -3.35]
Li L 2020	31	6.4	30	125.5	21.6	30	4.6%	-94.50 [-102.56, -86.44]
Li XB 2020	66.3	6.5	30	171.6	23.1	30	4.4%	-105.30 [-113.89, -96.71]
Mohamad Zaini RH 2016	1.76	0.55	40	11.88	2.21	40	7.7%	-10.12 [-10.83, -9.41]
Total (95% CI)			**440**			**443**	**100.0%**	**-13.98 [-16.70, -11.26]**

Heterogeneity: Tau² = 24.89; Chi² = 1670.05, df = 13 (P < 0.00001); I² = 99%

Test for overall effect: Z = 10.07 (P < 0.00001)



Extubation time sugammadex versus controls

Lang et al. BMC Pediatrics (2022) 22:295

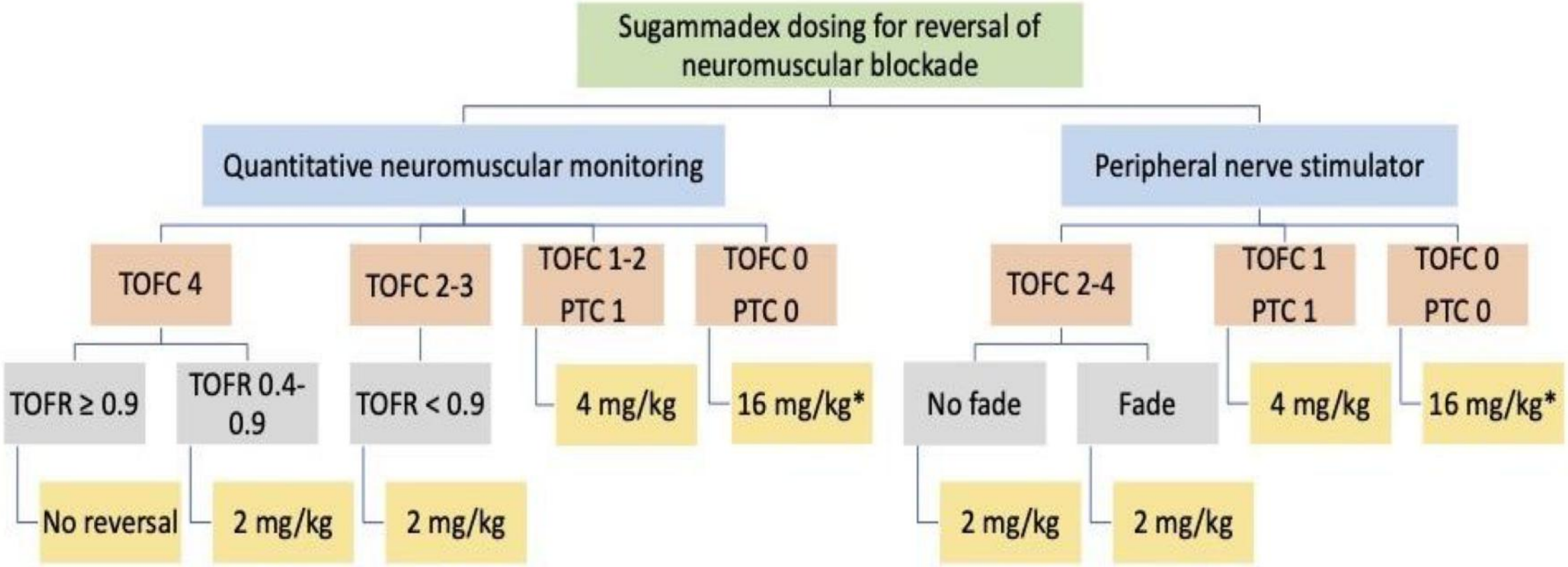
Adverse effects	Number of studies (Reference no.)	Patients in Sugammadex group (Incidence, %)	Patients in Control group (Incidence, %)	I^2 (%)	Risk ratio with [95% CI]	*P* value
PONV	13 (23,25,28,29,32–40)	33/431 (7.66%)	69/393 (17.56%)	21	0.30 [0.20, 0.46]	< 0.00001*
Bradycardia	4 (25,26,33,40)	0/124 (0%)	15/122 (12.30%)	0	0.09 [0.02, 0.46]	0.004*
Pain	2 (23,39)	8/67 (11.94%)	5/31 (16.13%)	0	1.21 [0.46, 3.17]	0.70
Bronchospasm/ Laryngospasm	3 (25,28,34)	1/114 (0.88%)	4/112 (3.57%)	0	0.45 [0.10, 1.96]	0.29
Dry mouth	2 (33,35)	3/60 (5%)	25/60 (41.67%)	0	0.14 [0.05, 0.38]	0.0001*
Apnea	2 (34,40)	0/65 (0%)	2/65 (3.08%)	0	0.33 [0.04, 3.12]	0.34
Oxygen desaturation	3 (34,35,38)	3/95 (3.16%)	8/95 (8.42%)	0	0.41 [0.12, 1.37]	0.15

* Significant difference between groups ($P < 0.05$)

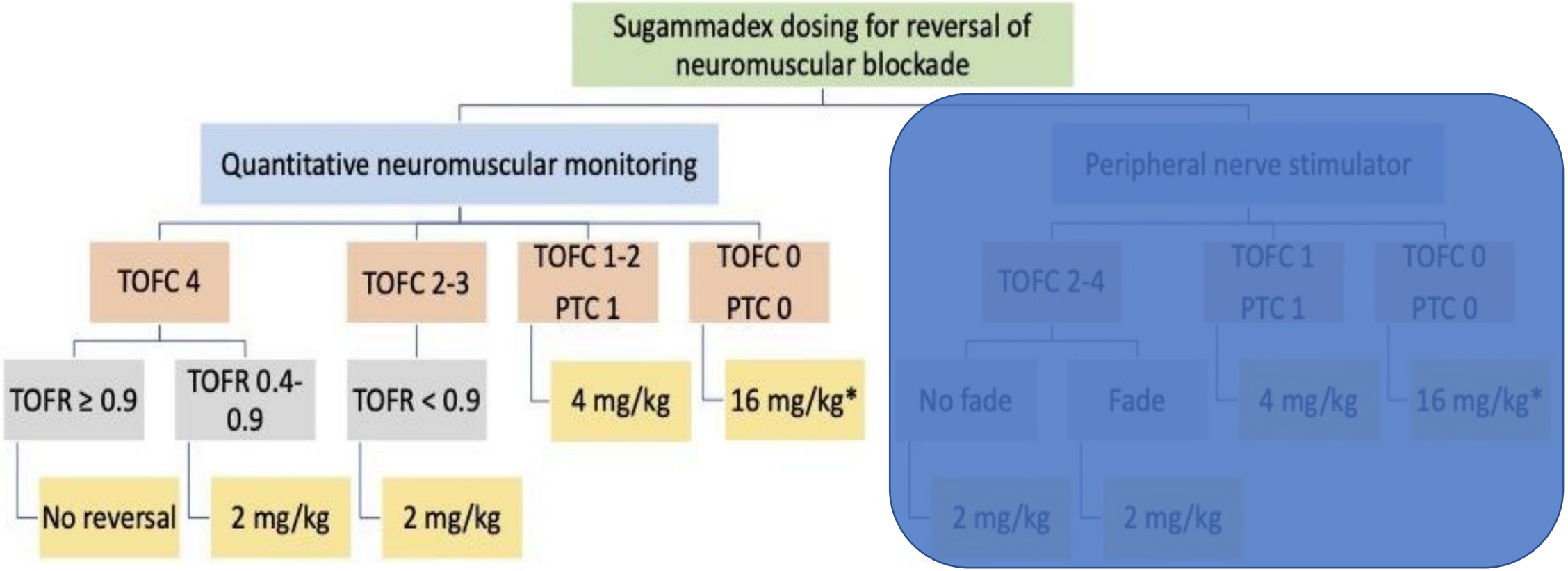
PONV postoperative nausea and vomiting, *CI* confidence intervals

Lang B, Han L, Zeng L, Zhang Q, Chen S, Huang L, Jia Z, Yu Q, Zhang L. Efficacy and 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 May 19;22(1):295.

Sugammadex dosages

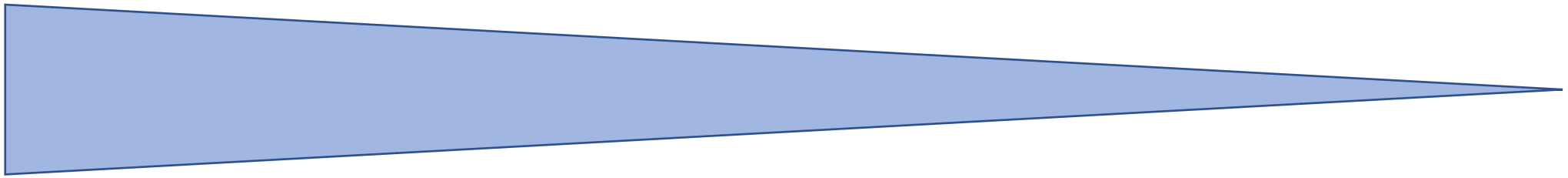


Sugammadex dosages



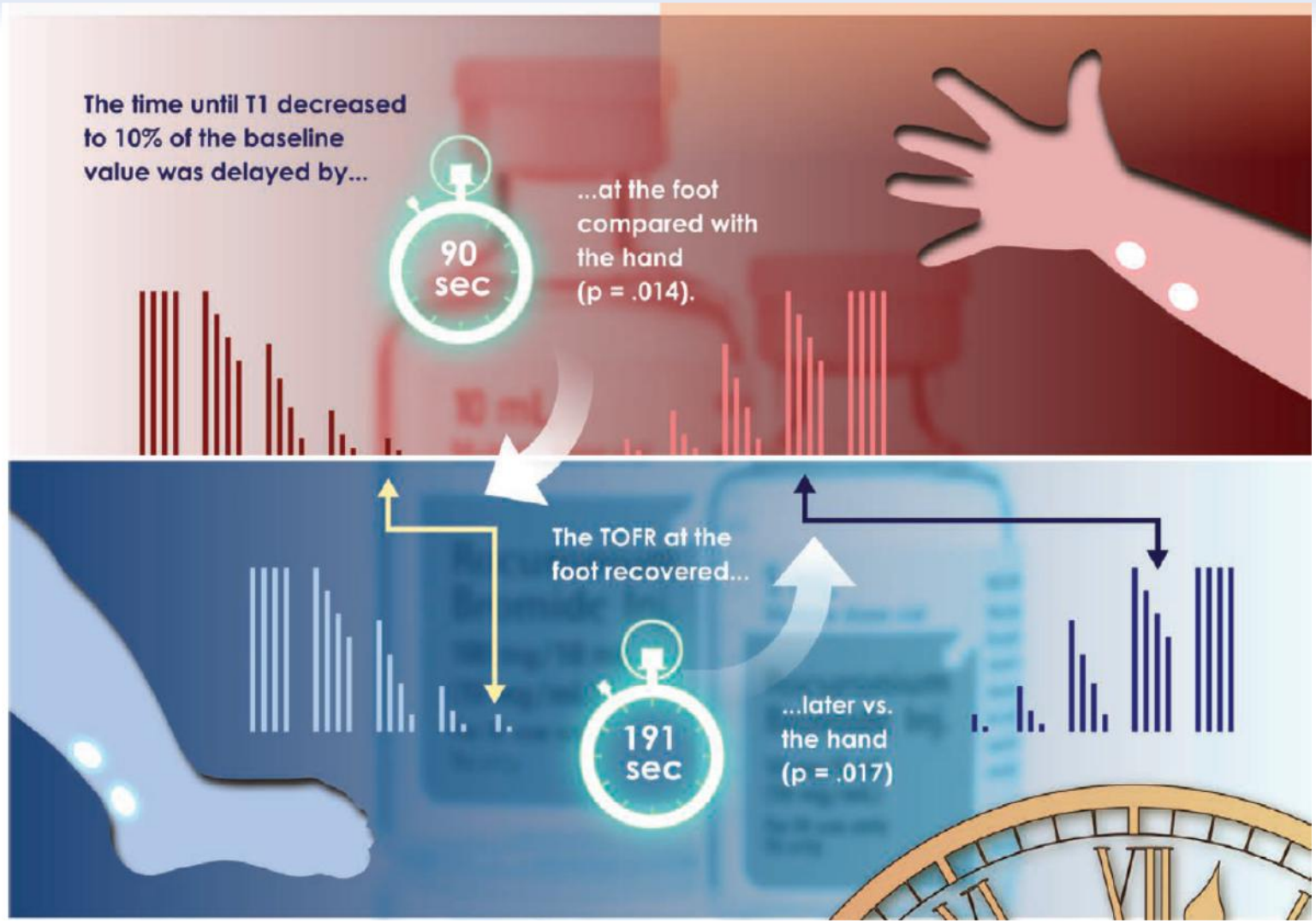
Reversal of rocuronium

PTC	0	1-2	-	-	-	-	-	-
Twitches	0	0	1	2	3	4	4	4
TOF-ratio	-	-	-	-	-	0.2	<0.9	>0.9



Sugamma dex mg/kg	8 (16)	4	2	2	(2)	(2)	(2)	-
Neostigimine mcg/kg	-	-	wait	wait	wait	50	20-50	--

Tobias JD, et al. Pediatric intraoperative electromyographic responses at the adductor pollicis and flexor Hallucis Brevis muscles: A prospective, comparative analysis. *Anesth Analg*. 2024;139:36–43.



Future directions

Patient-directed strategy

- Incidence of sugammadex anaphylaxis is rare (<1/10,000 anaesthesia)
- PK of NMBAs is variable in infants and neonates
- PRAEs related to residual paralysis are frequent
- Lack of studies on NMBA monitoring in children
- Paediatric guidelines are work in progress (ESAIC)

Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents III: The 2023 Geneva revision

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ASPA 2024

Before administering Bridion®, please read the full prescribing information

SCAN TO DOWNLOAD
THE FULL PRESCRIBING INFORMATION at https://quest3plus.bpfk.gov.my/pmo2/index.php

Selected Safety Information for BRIDION® (Sugammadex Sodium)

INDICATIONS Reversal of neuromuscular blockade induced by rocuronium or vecuronium. For the pediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents. DOSAGE AND METHOD OF USE Sugammadex should only be administered by, or under the supervision of an anesthetist. Sugammadex should be administered intravenously as a single bolus injection. The bolus injection should be given rapidly, within 10 seconds, into an existing intravenous line. The recommended dose of sugammadex depends on the level of neuromuscular blockade to be reversed. Adults Routine reversal A dose of 4 mg/kg sugammadex is recommended if recovery has reached at least 1-2 post tetanic counts (PTC) following rocuronium or vecuronium induced blockade. Median time to recovery of the T4/T1 ratio to 0.9 is around 3 minutes. A dose of 2 mg/kg sugammadex is recommended, if spontaneous recovery has occurred up to at least the reappearance of T2 following rocuronium or vecuronium induced blockade. Median time to recovery of the T4/T1 ratio to 0.9 is around 2 minutes. Immediate reversal of rocuronium-induced blockade A dose of 16 mg/kg sugammadex is recommended. Re-administration of sugammadex A repeat dose of 4 mg/kg sugammadex is recommended. Renal impairment For mild and moderate renal impairment (creatinine clearance 30 and <80 ml/min), the dose recommendations are the same as for adults without renal impairment. For patients with severe renal impairment (including patients requiring dialysis (CrCl <30 ml/min)), the use of sugammadex is not recommended. Elderly patients Same dose recommendation as for adults should be followed. Obese patients In obese patients, including morbidly obese patients, the dose of sugammadex should be based on actual body weight. The same dose recommendations as for adults should be followed. Hepatic impairment For mild to moderate hepatic impairment, no dose adjustments are required. Pediatric populations (Children and adolescents) Bridion 100 mg/ml may be diluted to 10 mg/ml to increase the accuracy of dosing in the pediatric population. Routine reversal A dose of 2 mg/kg is recommended for reversal of rocuronium induced blockade at reappearance of T2 in children and adolescents (2-17 years). Immediate reversal Immediate reversal in children and adolescents has not been investigated. CONTRAINDICATIONS Hypersensitivity to the active substance or to any of the excipients. WARNINGS AND PRECAUTIONS Should neuromuscular blockade reoccur following extubation, adequate ventilation should be provided. Bleeding risk has not been studied systematically at higher doses than sugammadex 4 mg/kg, thus, coagulation parameters should be carefully monitored in patients with known coagulopathies and those using anticoagulants who receive a dose of 16 mg/kg sugammadex. The use of lower than recommended doses may lead to an increased risk of recurrence of neuromuscular blockade after initial reversal and is not recommended. When rocuronium 1.2 mg/kg is administered within 30 minutes after reversal with sugammadex, the onset of neuromuscular blockade may be delayed up to approximately 4 minutes and the duration of neuromuscular blockade may be shortened up to approximately 15 minutes. Recommended waiting time in patients with mild or moderate renal impairment for re-use of 0.6 mg/kg rocuronium or 0.1 mg/kg vecuronium after routine reversal with sugammadex should be 24 hours. A nonsteroidal neuromuscular blocking agent should be used for patients requiring neuromuscular blockade prior to passing the recommended waiting time. Sugammadex is not recommended for use in patients with severe renal impairment, including those requiring dialysis. Due to the administration of sugammadex, certain medicinal products could become less effective due to a lowering of the (free) plasma concentrations. Due to the administration of certain medicinal products after sugammadex, theoretically rocuronium or vecuronium could be displaced from sugammadex. Patients should be closely monitored for hemodynamic changes during and after reversal of neuromuscular blockade. Patients with severe hepatic impairment should be treated with great caution. Sugammadex should not be used to reverse block induced by nonsteroidal neuromuscular blocking agents and steroidal neuromuscular blocking agents other than rocuronium or vecuronium. Clinicians should be prepared for the possibility of drug hypersensitivity reactions (including anaphylactic reactions) and take the necessary precautions. If more than 2.4 ml solution needs to be administered, this should be taken into consideration by patients on a controlled sodium diet. PREGNANCY AND LACTATION Pregnancy Caution should be exercised when administering sugammadex to pregnant women. Lactation Caution should be exercised when administering sugammadex to a breast-feeding woman. ADVERSE EVENTS In the subset of Pooled Placebo-controlled trials where subjects received anesthesia and/or neuromuscular blocking agents, the following adverse events occurred in 2% of subjects treated with sugammadex and at least twice as often compared to placebo including airway complication of anesthesia, anesthetic complication, procedural hypotension, procedural complication and cough. In post-marketing, isolated cases of marked bradycardia and bradycardia with cardiac arrest have been observed within minutes after administration of sugammadex. A limited database suggests that the safety prole of sugammadex (up to 4 mg/kg) in pediatric patients was similar to that in adults.