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Safety Use of Muscle Relaxant and Reversal Agents

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Outline

1

Postoperative Pulmonary Complications (PPCs)

2

**Residual Neuromuscular Blockade, The
Reversal of Residual Block and PPCs**

3

Sugammadex VS Neostigmine

Mechanisms of PPCs

- Postoperative pulmonary complications (PPCs): composite outcome
- General anesthesia:
 - Central respiratory depression
 - Impaired ventilatory responses to hypercapnia and hypoxia
 - Respiratory muscle function changes (even no NMBAs)
 - reduced FRC, atelectasis

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Residual Neuromuscular Blockade and PPCs

- Increased oxygen desaturation
- Impaired upper airway patency, Airway obstruction, Reintubation
- Impaired peripheral chemoreflex, hypoxic respiratory drive, despite full reversal
- Impaired pulmonary function test
- 4-fold incidence of misdirected swallowing.
- Postoperative aspiration pneumonia.

Sundman. Anesthesiology, 2000, Murphy. Anesthesiology, 2008, Murphy. Anesth Analg, 2010
Gross-Sundrup. BMJ, 2012, Asai. Anesthesiology, 2014, Cedborg. Anesthesiology, 2014
Murphy. Anesthesiology, 2015, Bulka. Anesthesiology, 2016, Fernandez-Bustamante. JAMA Surg, 2017
Broens. Anesthesiology, 2020

Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications

- High-dose NMBAs: increased risk of postoperative respiratory complications. (OR 1.28, $p = 0.02$)
- Neostigmine: increased respiratory complications, dose-dependent. (OR 1.19, $p=0.017$)
- Appropriate neostigmine (60 mcg/kg when TOF ≥ 2): decreased postoperative respiratory complications. (OR 0.79, $p = 0.002$)

Nondepolarizing Neuromuscular Blocking Agents, Reversal, and Risk of Postoperative Pneumonia

- Intermediate-acting NMBAs, compared with No NMBAs:
 - 1.79-fold postoperative pneumonia (95%CI 1.08 – 3.07)
- NMBAs without neostigmine, compared with NMBAs with neostigmine:
 - 2.26-fold postoperative pneumonia (95%CI 1.65 – 3.03)

Bulka et al. Anesthesiology, 2016

Intermediate-Acting Nondepolarizing Neuromuscular Blocking Agents and Risk of Postoperative 30-Day Morbidity and Mortality, and Long-term Survival

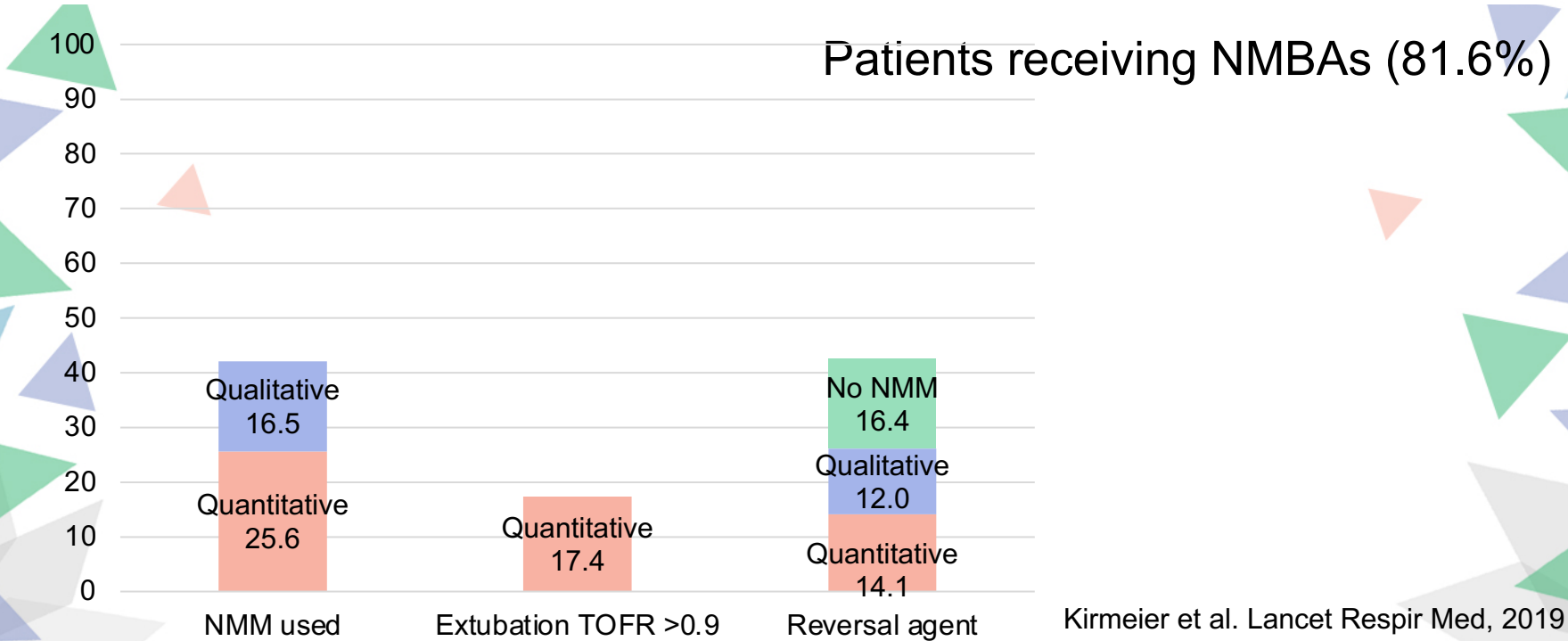
- NMBAAs, compared with No NMBAAs:
 - Increased respiratory complication (AOR 2.00, $p = 0.007$)
- NMBAAs without neostigmine, compared with NMBAAs with neostigmine:
 - Increased respiratory complication (AOR 1.71, $p < 0.0001$)

Bronsert et al. Anesth Analg, 2017

Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study

Postoperative Pulmonary Complications	Incidence	Adjusted OR (95%CI)	P-value
GA	7.6%		
Neuromuscular blocking agents	8.4%	1.86 (1.53-2.26)	< 0.0001
NMM used	10.6%	1.31 (1.15-1.49)	< 0.0001
Quantitative NMM (vs qualitative)	10.5%	1.07 (0.90-1.29)	0.44
Reversal agent given	8.9%	1.23 (1.07-1.41)	0.0028
Extubation at TOF ratio ≥ 0.9	10.0%	1.03 (0.82-1.31)	0.78
Sugammadex (vs neostigmine)	10.7%	1.03 (0.85-1.25)	0.74

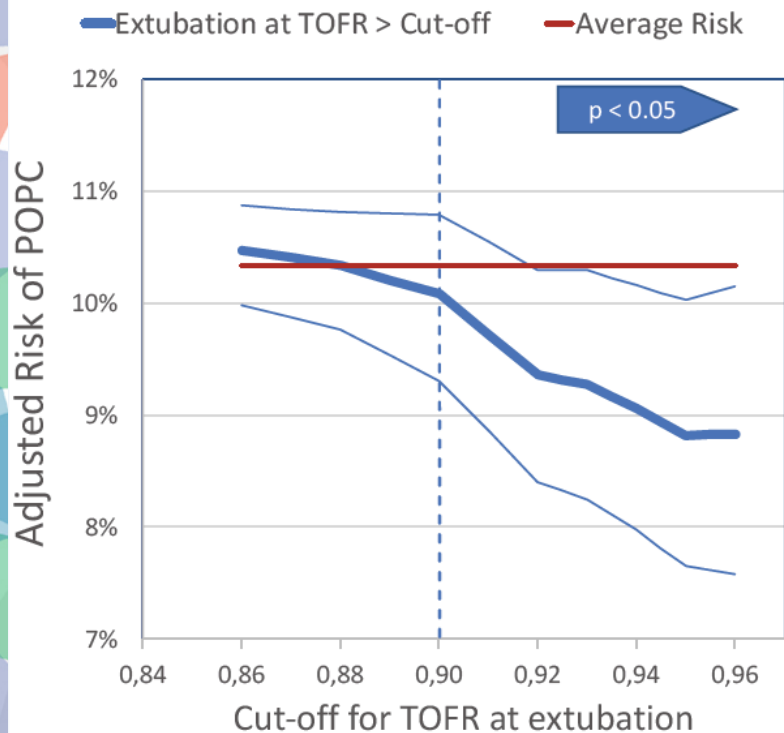
Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study



Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study

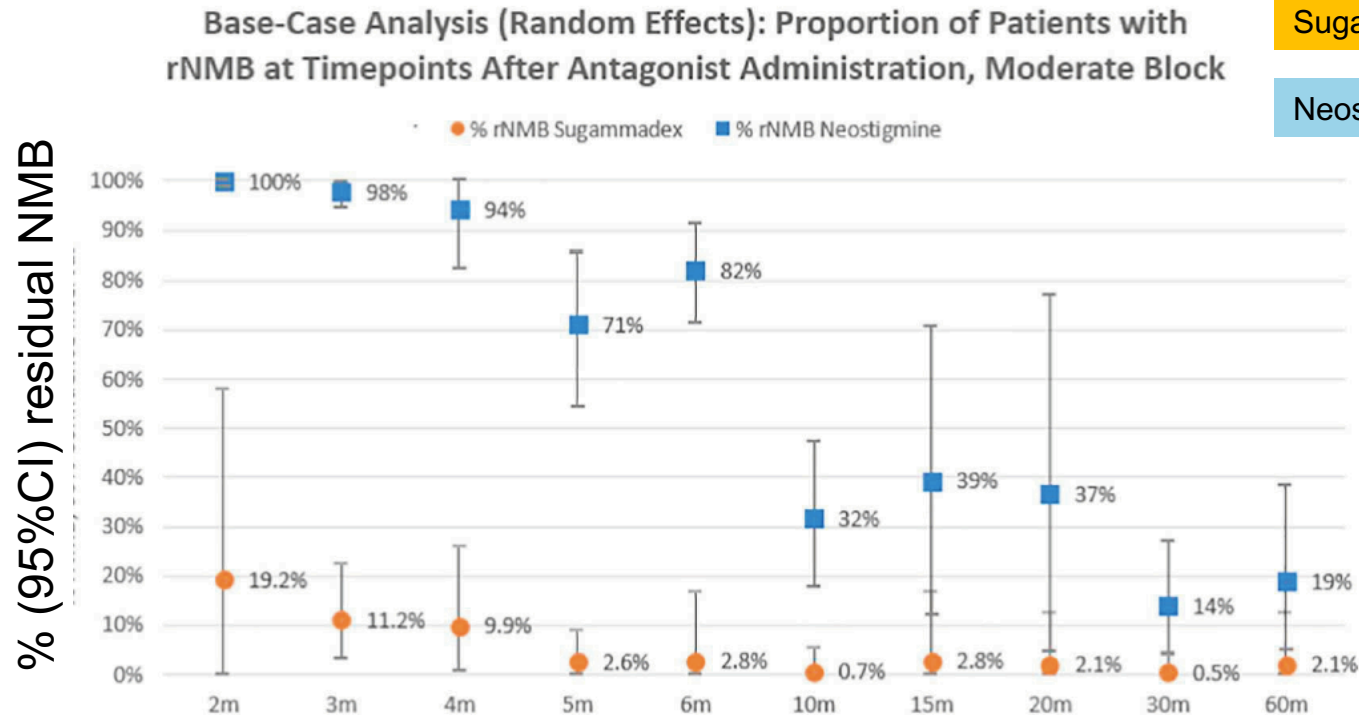
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Use of a train-of-four ratio of 0.95 versus 0.9 for tracheal extubation: an exploratory analysis of POPULAR data



- Higher cut-off TOFR levels:
 - reduced POPC ($p < 0.05$)
- The lowest p-value:
 - TOFR 0.95 ($p=0.01$)
- POPC in TOFR 0.9 - 0.95: 11.3%
- TOFR > 0.95, compared with > 0.9:
 - Adjusted ARR of POPC 4.9% (1.2-8.5%)

Incidence of residual neuromuscular blockade and use of neuromuscular blocking agents with or without antagonists: A systematic review and meta-analysis of randomized controlled trials



Sugammadex 2mg/kg

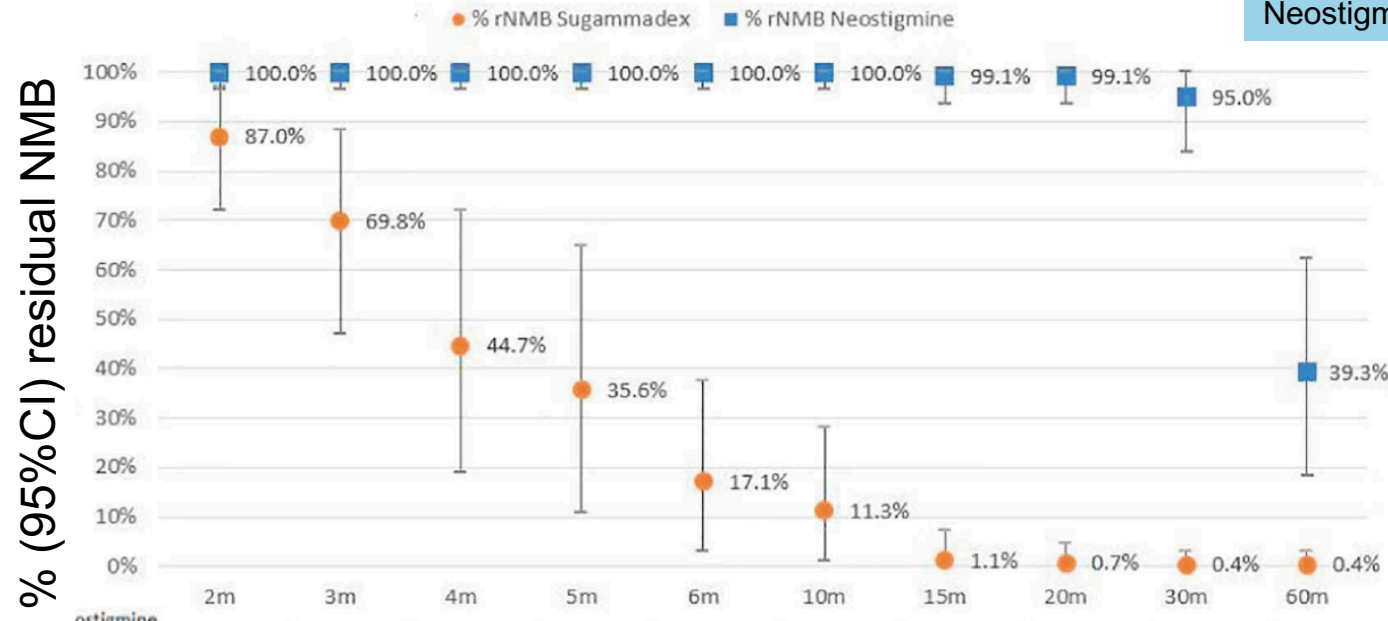
Neostigmine 0.05-0.07 mg/kg

Incidence of residual neuromuscular blockade and use of neuromuscular blocking agents with or without antagonists: A systematic review and meta-analysis of randomized controlled trials

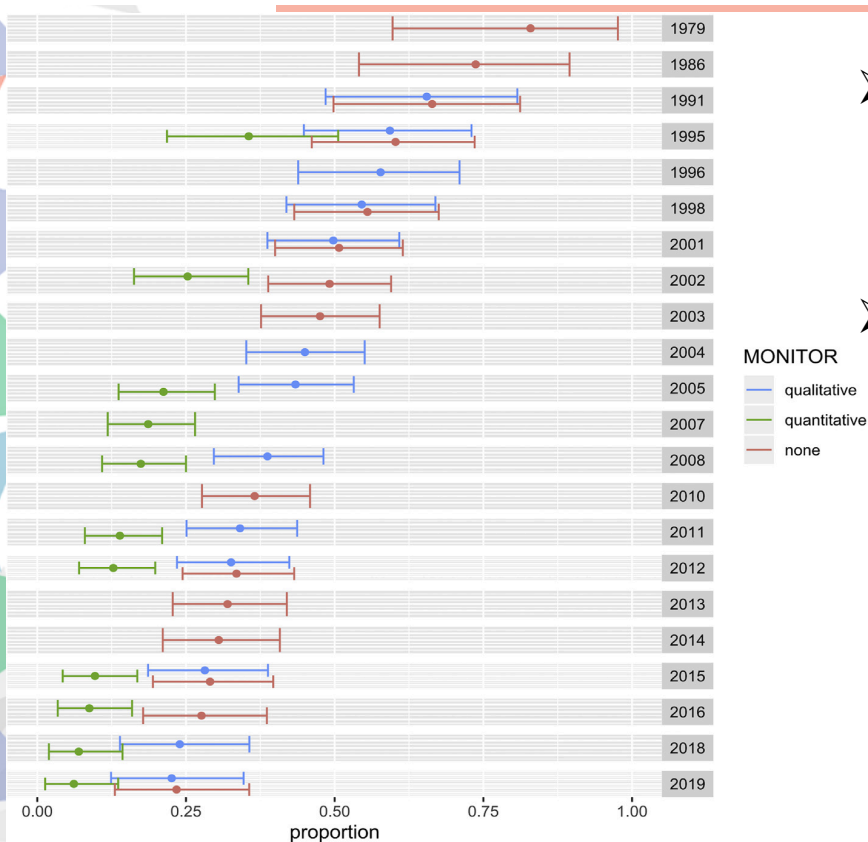
Base-Case Analysis (Random Effects): Proportion of Patients with rNMB at Timepoints After Antagonist Administration, Deep Block

Sugammadex 4 mg/kg

Neostigmine 0.05-0.07 mg/kg



Forty years of neuromuscular monitoring and postoperative residual curarisation: a meta-analysis and evaluation of confidence in network meta-analysis



- Global reduction in PORC with time, independently of the subtype of neuromuscular monitoring. ($p = 0.001$)
- Quantitative NMM, compared with qualitative and no NMM: lower PORC ($p < 0.001$)

Carvalho et al. BJA, 2020

Forty years of neuromuscular monitoring and postoperative residual curarisation: a meta-analysis and evaluation of confidence in network meta-analysis

Outcome	Absolute risk (95% CI)		
	Quantitative NMM	Qualitative NMM	No NMM
PORC (TOF ratio <0.9)	0.119 (0.061; 0.191)	0.311 (0.216; 0.415)	0.338 (0.243; 0.440)

- Quantitative NMM, compared with qualitative and no NMM:
 - lower PORC ($p < 0.001$, both)
- Qualitative NMM, compared with No NMM: no difference ($p = 0.92$)
- Sugammadex, compared with neostigmine: lower PORC ($P = 0.002$).

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Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults (Review)

- Recovery time from T2 to TOFR > 0.9 :
 - 10.22 min (95%CI 8.34-11.96) faster in Sugammadex (2 mg/kg), compared with Neostigmine (0.05 mg/kg).
- Recovery time from PTC 1-5 to TOFR >0.9 :
 - 45.78 min (95%CI 39.41-52.15) faster in Sugammadex (4 mg/kg), compared with Neostigmine (0.07 mg/kg).

Efficacy and safety of sugammadex versus neostigmine in reversing neuromuscular blockade in adults (Review)

Outcomes	Neostigmine (any dose)	Sugammadex (any dose)	RR (95%CI)
Composite adverse events	28.3%	15.9%	0.60 (0.49-0.74)
Bradycardia	8.4%	1.3	0.16 (0.07-0.34)
PONV	13.1%	6.8%	0.52 (0.28-0.97)
Residual paralysis	13.1%	5.2%	0.40 (0.28-0.57)
Serious adverse events	1.0%	0.6%	0.54 (0.13-2.25)

Sugammadex vs Neostigmine for Reversal of Neuromuscular Blockade and Postoperative Pulmonary Complications (STRONGER)

A Multicenter Matched Cohort Analysis

Outcomes	Sugammadex, Adjusted OR (95%CI)
Pulmonary complications	0.70 (0.63 - 0.77)
Pneumonia	0.53 (0.44 - 0.62)
Respiratory failure	0.45 (0.37 - 0.56)

- 12 centers,
- 45,712 patient

- Hemodynamically significant anaphylaxis: None

Current Status of Neuromuscular Reversal and Monitoring

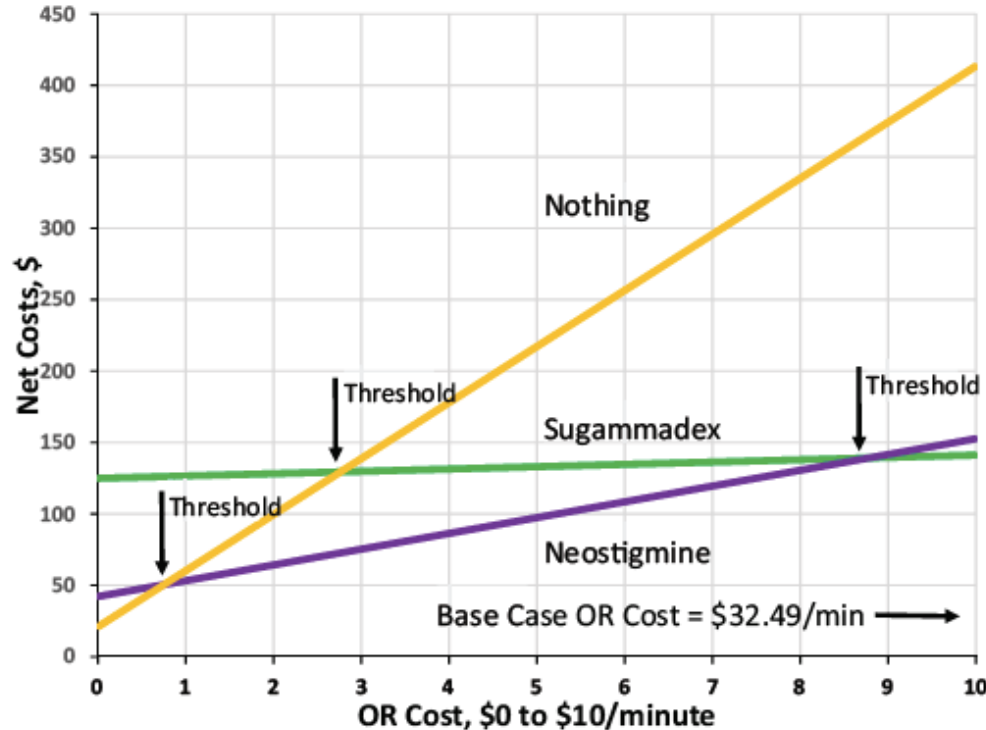
Challenges and Opportunities

Depth of Block	Neostigmine Dose (mg/kg)	Sugammadex Dose* (mg/kg)
Posttetanic count < 2	Delay reversal	4–16†
Posttetanic count ≥ 2	Delay reversal	2–4†
TOF count 0–1		
TOF count 2–4	0.05–0.07	1.0–2.0†
TOF with fade by tactile or visual means		
TOF < 0.40‡		
TOF count 4, no tactile or visual fade	0.02–0.03	0.25–0.5†
TOF = 0.40–0.90‡		
TOF ratio ≥ 0.90‡	Reversal unnecessary	Reversal unnecessary

*Dose ranges reported in the literature; cited doses may deviate from package insert recommendations. †When reversing vecuronium, use higher end of dosing range. ‡TOF ratio confirmed by quantitative monitoring.

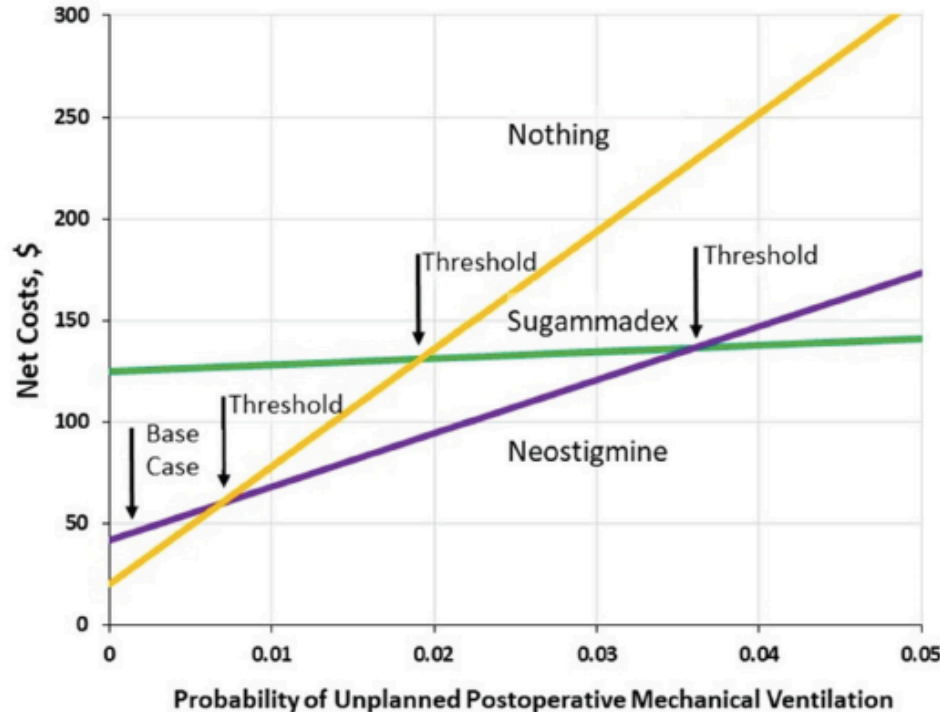
TOF = train-of-four.

Sugammadex versus neostigmine for routine reversal of rocuronium block in adult patients: A cost analysis



- Base-case OR cost:
 - Drug price
 - OR time cost
 - PONV cost
 - Unplanned postoperative mechanical ventilation
- Most of the cost savings with sugammadex:
 - reduced non-operative OR time
- Sugammadex If OR time cost \geq 8.60\$/min

Sugammadex versus neostigmine for routine reversal of rocuronium block in adult patients: A cost analysis



- Sugammadex if probability of unplanned postoperative mechanical ventilation > 0.036
- Neostigmine/Glycopyrrolate:
 - 21.21\$
- Sugammadex high dose:
 - 171.05\$
- Sugammadex low dose:
 - 93.40\$

Cost

- Sugammadex (200 mg) : 3560 บาท
- Glycopyrrolate (0.2 mg) : 36 บาท (เอกสารแจ้งปรับราคา ยา รพ.ศิริราช 2562)
- Atropine (0.6 mg): 3 บาท (รายการยาโรงพยาบาลศิริราช 2553)
- Neostigmine (2.5 mg): 25 บาท (รายการยาโรงพยาบาลศิริราช 2553)

Take Home Message

- NMBA increased PPCs: used when there are indications.
- Despite full reversal: impaired ventilatory response.
- Reversal agents decreased PPCs: right dose, right time.
- NMM: decreased risk of PPCs? Correct interpretation?
- Extubation at TOFR > 0.9 might not be appropriate, Consider TOFR > 0.95 ?
- Sugammadex: decreased residual NMB, decreased PPCs, faster recovery : Cost efficiency?



Thank you