

***Residual Neuromuscular
Blockade and Adverse
Respiratory Outcomes***

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Disclosure Information

- I have the following financial relationship to disclose:

Consultant for: Merck & Co., Inc

- I will not discuss off-label use and / or investigational use in my presentation

Is residual neuromuscular blockade associated with adverse respiratory outcomes during the early recovery period from anesthesia and surgery?





TOP-Watch[®] 5X

TOF

100%

°C
mA (µC)
TOF
PTC
1Hz

Power button and logo

How Is Residual Neuromuscular Blockade Defined

- With quantitative neuromuscular monitoring
 - MMG, EMG, AMG
 - Traditional definition: TOF ratio < 0.7
 - Based on several studies from 1970's
 - Current "gold standard": TOF ratio < 0.9
 - Based on several studies from 1990-Present
- Presence of signs or symptoms of muscle weakness in the postoperative period in patients who received NMBA's

REVIEW ARTICLE



Neuromuscular monitoring and postoperative residual curarization: a meta-analysis

M. Naguib¹ * †, A. F. Kopman³ † and J. E. Ensor²

Sub-population	Pooled Rate of PORC [§]	Confidence Interval	Heterogeneity	
			P-value	Inconsistency [†] (%)
Long-acting (TOF<0.7)	0.351	(0.25-0.46)	<0.001	86.7
Intermediate-acting (TOF<0.7)	0.115	(0.07-0.17)	<0.001	85.9
Long-acting (TOF<0.9)	0.721	(0.59-0.84)	<0.001	88.1
Intermediate-acting (TOF<0.9)	0.413	(0.25-0.58)	<0.001	97.2

The RECITE study: A Canadian prospective, multicenter study of the incidence and severity of residual neuromuscular blockade

Fortier LP, et al. *Anesth Analg* 2015;121:366-72

- Prospective observational study of the incidence of PRNB at 8 Canadian hospitals
- ASA I-III patients undergoing abdominal surgery were assessed
- TOF ratios measured immediately before extubation and on arrival to PACU

Results

- 302 patients enrolled
- Rocuronium used in 99% of cases
- Neostigmine reversal used in 73% of cases
- Incidence PRNB: 64% at extubation
57% at PACU arrival

Residual Neuromuscular Blockade and Adverse Respiratory Events

- Database Studies

- Large database or observational investigations examining the association between neuromuscular management characteristics and adverse respiratory outcomes

- Clinical Studies

- Prospective observational trials
 - Randomized clinical trials

Database Studies

● Advantages

- Large size
- Determine incidence of less common outcomes
- Frequently multi-institutional

● Disadvantages

- Uncontrolled and not randomized
- Observational and retrospective studies can only demonstrate *associations*, not causality
- The presence or absence of residual block was not definitively established using quantitative monitoring



A Study of the Deaths Associated with Anesthesia and Surgery

Beecher HK, Todd DP *Ann Surg* 1954; 104: 2-35

■ Methods

- Data collected by 10 teams at 10 hospitals over a 5-year period in the United States
- All cases of deaths on the surgical services were examined
- Causes of death were determined by the team at each hospital

■ Results

- Data collected on 599,548 anesthetics
- Mortality rates when NMBA's were used (1:370) were 6x higher than when NMBA's were avoided (1:2100)
- 63% of the deaths involving NMBA's were caused by respiratory failure

Death Attributable to Anaesthesia: A 10-Year Survey (1967-1976)

Harrison GG. Br J Anaesthesiol 1978; 50: 1041-46

■ Methods

- Mortality data collected over 10 years at Groote Schuur Hospital, Cape Town
- Examined data from 240,483 anesthetics

■ Results

- Frequency of death to which anesthesia contributed was 0.22 per 1000 anesthetics
- Anesthetic deaths were attributed to:
 1. Hypovolemia
 2. Respiratory inadequacy following myoneural block
 3. Complications of tracheal extubation
 4. Inadequate postoperative care and supervision



Anaesthesia-Related Surgical Mortality

Lunn JN, et al.

Anaesthesia 1983; 38: 1090-6

- Study conducted by the Association of Anaesthetists of Great Britain and Ireland
- Detailed data collected on all deaths that occurred within 6 days of surgery in 1981
- 2 assessors determined the role of anesthetic management in mortality (entirely, partially, or not all)

Results

- 32 of 197 (16%) of deaths were judged to be totally due to anaesthesia
- Single largest clinical cause of anaesthesia-related death in the series was:

“postoperative respiratory failure due to neuromuscular management”



Anaesthetic Practice and Postoperative Pulmonary Complications

Pedersen T, et al.

Acta Anaesthesiol Scand 1992; 36: 812-8

- 7,029 surgical patients prospectively examined to determine risk factors for postoperative pulmonary complications
- Preoperative and intraoperative factors examined

Results

- 290 (4.1%) patients developed a POPC (atelectasis/pneumonia most common)
- Multiple logistic regression analysis revealed that the primary intraoperative risk factor was GA involving pancuronium for procedures ≥ 180 min (OR 2.64)

Critical Respiratory Events in the Postanesthesia Care Unit

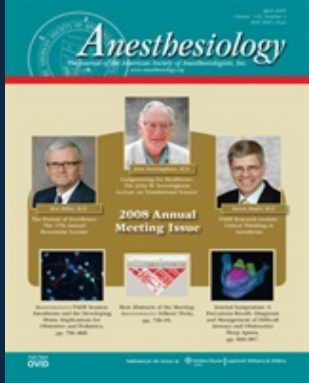
Patient, Surgical, and Anesthetic Factors

D. Keith Rose, M.D., F.R.C.P.C., Marsha M. Cohen, M.D., F.R.C.P.C.,†‡§ Dan F. Wigglesworth, B.Sc.,*
Don P. DeBoer, M.Math.†*

■ **Methods**

- **Prospectively collected data on 24,157 PACU patients who received a GA over a 33-month period**
- **A critical respiratory event (CRE) defined as unanticipated**
 - **Hypoxemia**
 - **Hypoventilation**
 - **Airway obstruction requiring an intervention**
- **Patient, surgical, and anesthetic risk factors identified**

Management	n*	Rate of Critical Respiratory Events	Relative Risk	95% Confidence Interval	Adjusted Relative Odds†	95% Confidence Interval
Premedication						
Sedative	2,611	2.0	1.87	(1.37–2.55)	2.00	(1.49–2.69)
Opioid ± sedative	3,432	2.6	2.51	(1.95–3.23)	1.76	(1.24–2.49)
No premedication§	17,631	1.0	1.00	—	1.00	—
Induction Agent						
Thiopental	18,230	1.6	3.86	(2.5–5.9)	2.46	(1.56–3.89)
Propofol§	5,158	0.4	1.00	—	1.00	—
Sedative						
Any benzodiazepine	13,634	1.5	1.26	(1.02–1.60)	1.28	(0.99–1.64)
Inhalational Agent						
Enflurane	12,682	1.4	1.09	(0.88–1.36)	‡	‡
Isoflurane§	9,765	1.4	1.00	—	‡	‡
Antiemetic						
Droperidol ≥ 0.01 mg · kg	6,089	1.8	1.36	(1.06–1.73)	1.05	(0.76–1.45)
Droperidol < 0.01 mg · kg	5,433	1.1	0.87	(0.64–1.16)	1.29	(0.97–1.71)
No droperidol§	12,120	1.3	1.00	—	1.00	—
Opioid						
Only fentanyl, >1–≤ 2 μg · kg ⁻¹ · h ⁻¹	8,595	1.1	0.76	(0.58–0.99)	1.07	(0.79–1.43)
Only fentanyl, >2 μg · kg ⁻¹ · h ⁻¹	3,529	1.3	0.91	(0.65–1.28)	1.87	(1.26–2.79)
Fentanyl, morphine combination	1,689	2.8	1.95	(1.40–2.73)	1.56	(1.06–2.29)
Alternate narcotic choices	1,167	1.3	0.90	(0.53–1.53)	0.98	(0.54–1.77)
Fentanyl, ≤1 μg · kg ⁻¹ · h ⁻¹ or nil§	8,694	1.4	1.00	—	1.00	—
Ventilation/muscle Relaxant						
Spontaneous—mask	4,620	0.3	0.21	(0.12–0.36)	0.68	(0.34–1.31)
Spontaneous—tracheal intubation	380	1.8	1.26	(0.60–2.67)	2.21	(0.95–5.13)
Controlled with						
Atracurium, ≥0.25 mg · kg ⁻¹ · h ⁻¹	1,252	3.4	2.30	(1.61–3.29)	2.17	(1.40–3.34)
Vecuronium, ≥0.04 mg · kg ⁻¹ · h ⁻¹	7,844	1.4	0.95	(0.73–1.25)	1.19	(0.87–1.62)
Pancuronium, ≥0.02 mg · kg ⁻¹ · h ⁻¹	1,399	2.2	1.52	(0.74–2.01)	1.45	(0.91–2.33)
Any combination	1,010	1.8	1.22	(1.02–2.26)	1.28	(0.81–2.00)
Controlled with low-dose§						
Atracurium, <0.25 mg · kg ⁻¹ · h ⁻¹ or Vecuronium, <0.04 mg · kg ⁻¹ · h ⁻¹ or Pancuronium, <0.02 mg · kg ⁻¹ · h ⁻¹	7,074	1.5	1.00	—	1.00	—



Predictors of Survival Following Cardiac Arrest in Patients Undergoing Noncardiac Surgery

Sprung J, et al.

Anesthesiology 2003; 99: 259-69

- Medical records reviewed on all cardiac arrests that occurred at the Mayo Clinic over a 10-year period (1990-2000)
- Data collected on cardiac arrest that occurred after anesthesia initiated in the OR until discharge from the PACU or admission to the ICU
- Patient, anesthetic, and surgical factors analyzed

Results

- Cardiac arrest occurred in 223 of 518,294 anesthetics
- 24 patients had arrest primarily related to anesthesia
 - 13 medication-related
 - 11 airway/ventilation-related
 - 9 of the 24 “related to the use of NMBAs or RNMB”

Impact of Anesthesia Management Characteristics on Severe Morbidity and Mortality

M. Sesmu Arbous, M.D., Ph.D.,* Anneke E. E. Meursing, M.D., Ph.D.,† Jack W. van Kleef, M.D., Ph.D.,‡
Jaap J. de Lange, M.D., Ph.D.,§ Huub H. A. J. M. Spoomans, M.D.,|| Paul Touw, M.D., Ph.D.,#
Frans M. Werner, M.D., Ph.D.,** Diederick E. Grobbee, M.D., Ph.D.††


● **Methods**

- **Case-control study → identify risk factors related to anesthesia management for mortality or coma within 24 hours of surgery**
- **Data were collected (1995-1997) on all patients undergoing GA (869,483 patients) in 3 of 12 provinces in The Netherlands**
- **Cases: Patients who remained comatose or died**

● **Results**

- **807 “cases” and 883 matched “controls” were analyzed.**
- **The most significant risk factor identified in the analysis was related to neuromuscular management**
- **Reversal of the effects of muscle relaxants was associated with a marked reduction (odds ratio, 0.10; 95% CI, 0.03-0.31) in mortality and coma**

RESEARCH

Intermediate acting non-depolarizing neuromuscular blocking agents and risk of postoperative respiratory complications: prospective propensity score matched cohort study OPEN ACCESS

- Objective: To determine if NMBAs associated with an increased incidence of postop respiratory complications (O₂ saturation < 90% or reintubation requiring unplanned admission to the ICU)
- Prospective, propensity score matched cohort study (18,579 patients receiving NMBAs matched with 18,579 patients not administered NMBAs) conducted between 2006-2010

Neuromuscular blocking agents

Outcomes	Not received (n=18 579)	Received (n=18 579)	Odds ratio (95% CI)
Desaturation <90%	689	925	1.36 (1.23 to 1.51)
Desaturation <80%	128	212	1.66 (1.34 to 2.07)
Reintubation	108	151	1.40 (1.09 to 1.80)
In-hospital death	48	55	1.15 (0.78 to 1.69)

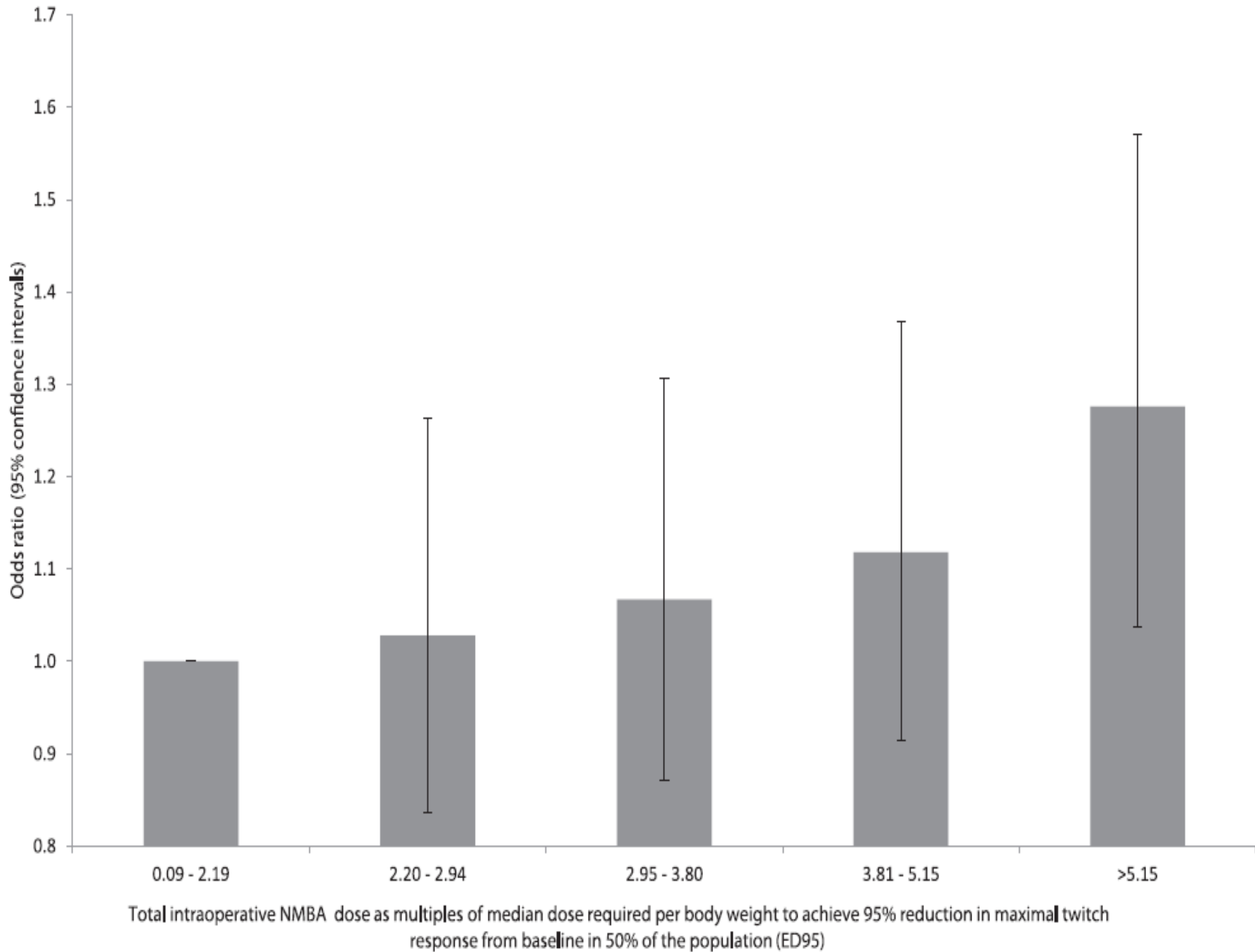
Dose-dependent Association between Intermediate-acting Neuromuscular-blocking Agents and Postoperative Respiratory Complications

Duncan J. McLean, M.B.Ch.B., Daniel Diaz-Gil, Cand.Med., Hassan N. Farhan, M.B.B.S., Karim S. Ladha, M.D., Tobias Kurth, M.D., Sc.D., Matthias Eikermann, M.D., Ph.D.

- Hospital-based registry of 48,499 patients who received NMBA at MGH between 2007-2012
- Hypothesis: Higher NMBA use associated with increased risk PoPC
- Data collected from AIMS, billing info, and Research Patient Data Registry
- PoPC= respiratory failure, PE, re-intubation, pneumonia

Results

- 1,812 patients (3.7% experienced PoPC)

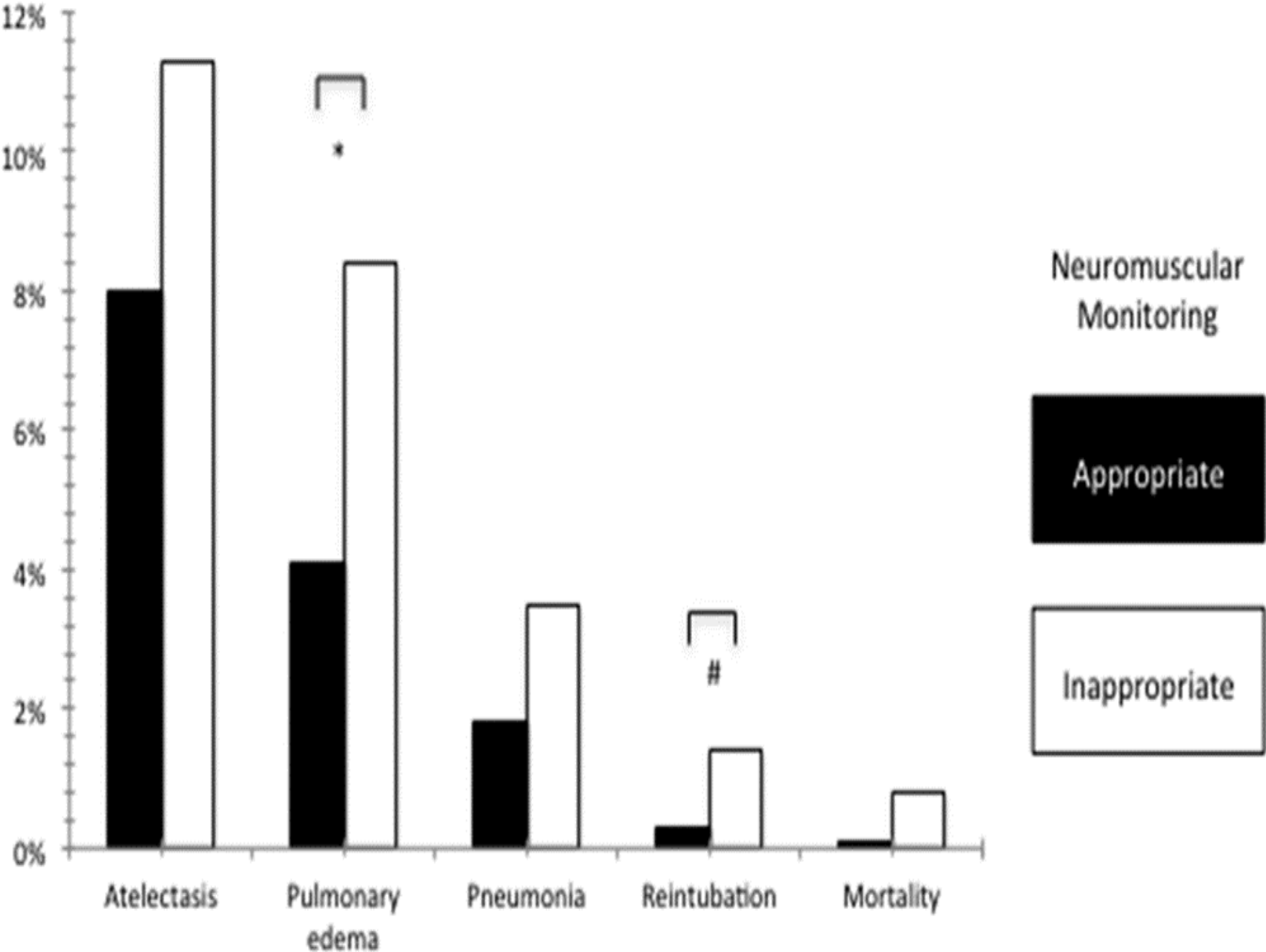


Effects of Neostigmine Reversal of Nondepolarizing Neuromuscular Blocking Agents on Postoperative Respiratory Outcomes

A Prospective Study

Nobuo Sasaki, M.D., Matthew J. Meyer, M.D., Sanjana A. Malviya, B.S., Anne B. Stanislaus, M.S., Teresa MacDonald, R.N., Mary E. Doran, R.N., Arina Igumenshcheva, B.A., B.S., Alan H. Hoang, M.D., Matthias Eikermann, M.D., Ph.D.

- Prospective observational study
- 3000 patients enrolled
- Unwarranted use of neostigmine:
 - Neostigmine used in the absence of NM monitoring
 - Neostigmine administered at a TOF count of 0



Retrospective investigation of postoperative outcome after reversal of residual neuromuscular blockade: Sugammadex, neostigmine, or no reversal

Ledowski T, et al. Eur J Anaesthesiol 2014;31:423-9

- Data collected from 1,444 patients from a single hospital in Australia in 2011
- Primary endpoint: Pulmonary complications within 7 days of surgery (scoring system from 0 to 100)

Results

- 722 sugammadex, 212 neostigmine, 510 no reversal
- Pulmonary outcome scores worsened in ASA 3 and 4 patients > 60 years old reversed with neostigmine or given no reversal; no detrimental effect of age on pulmonary outcome scores in patients in sugammadex group ($P < 0.05$)

Conclusions: Neuromuscular Management and Adverse Respiratory Events-Database Studies

- Several large database studies have examined anesthetic-related causes of major morbidity and mortality. Postoperative respiratory failure due to neuromuscular management was the primary cause of adverse outcomes in many of these investigations
- Limitation: The presence or absence of residual blockade not determined in these investigations
- Data is suggestive, not conclusive

Residual Neuromuscular Blockade and Adverse Respiratory Outcomes

Clinical Studies

Residual block measured in PACU →
adverse postoperative respiratory
events

- Hypoxemia
- Airway obstruction
- PoPC



Postoperative Residual Paralysis and Respiratory Status: A Comparative Study of Pancuronium and Vecuronium

Bissinger U, et al.

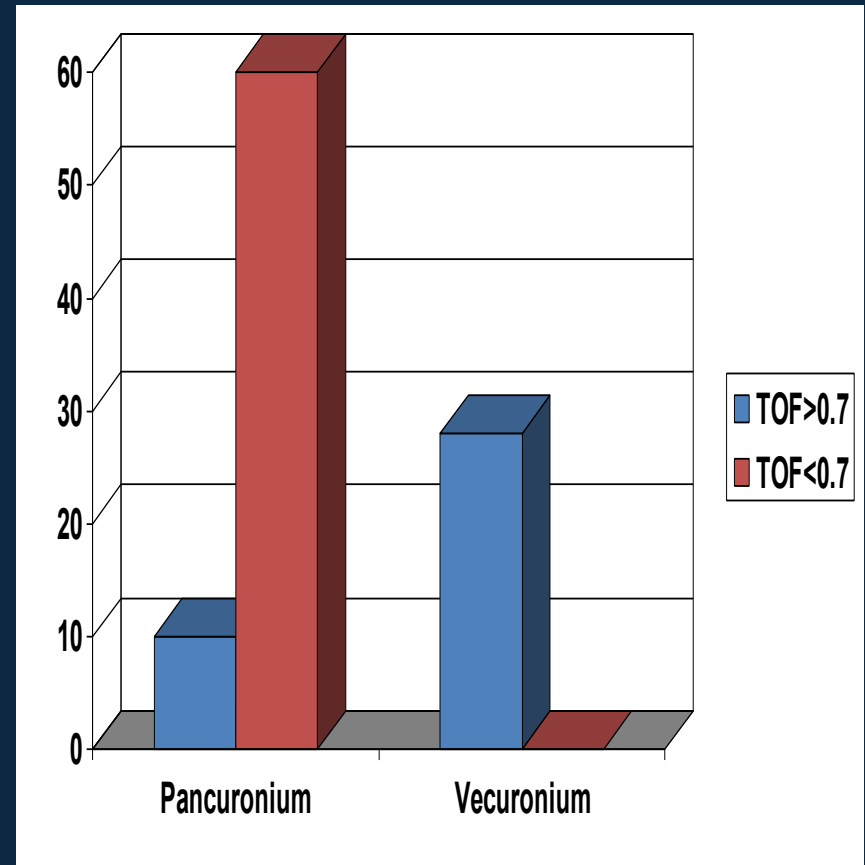
Physiological Research 2000; 49: 455-62

- Objective: To determine whether RNMB after pancuronium or vecuronium results in hypoxemia or hypercarbia in the PACU
- 76 consecutive surgical patients enrolled
- On arrival to PACU, TOF ratios quantified with AMG
- RNMB defined as a TOF ratio < 0.7

Bissinger et al.-Results

- TOF ratio < 0.7:
 - Pancuronium 20%
 - Vecuronium 7%
- No differences between groups in incidence of hypercapnia

Incidence of Hypoxemic events



Postanesthesia Care Unit Recovery Times and Neuromuscular Blocking Drugs: A Prospective Study of Orthopedic Surgical Patients Randomized to Receive Pancuronium or Rocuronium

Glenn S. Murphy, MD*, Joseph W. Szokol, MD*, Mark Franklin, MD*, Jesse H. Marymont, MD*, Michael J. Avram, PhD†, and Jeffery S. Vender, MD*

- **Objective:** to assess the effect of choice of NMBA (long-or intermediate-acting) on postoperative recovery and respiratory status
- **Methods**
 - 70 patients undergoing orthopedic surgical procedures randomized to receive pancuronium or rocuronium
 - NM monitoring and reversal used in all subjects
 - TOF ratios quantified with acceleromyography (AMG) on arrival to PACU and at + 30 minutes
 - Episodes of hypoxemia measured ($SpO_2 < 93$ or 90%)

Murphy et al.-Results

Variable	Rocuronium group	Pancuronium group	P value
Train-of-four ratio <0.9 at:			
PACU arrival	10	29	<0.001
30 min after PACU arrival	1	11	0.003
Patients having episodes of			
SpO ₂ <93%	10	21	0.015
SpO ₂ <90%	7	15	NS
Need for oxygen therapy	4	10	NS

Residual Neuromuscular Blockade and Critical Respiratory Events in the Postanesthesia Care Unit

Glenn S. Murphy, MD

Joseph W. Szokol, MD

Jesse H. Marymont, MD

Steven B. Greenberg, MD

Michael J. Avram, PhD

Jeffery S. Vender, MD

Hypothesis: Patients with evidence of severe respiratory impairment in the PACU would have a higher incidence of residual block compared to matched controls without CREs

Methods

- Design: Case-control study
- All cases during the 1-year study period with the outcome of interest in the PACU (CRE) were identified
 - CRE:
 - 1) Upper airway obstruction requiring intervention
 - 2) Mild-mod (90-93% SpO₂) or severe (<90% SpO₂) hypoxemia on >3L NC/min not responsive to intervention
 - 3) Signs respiratory distress/impending ventilatory failure
 - 4) Patient requiring re-intubation
 - 5) Evidence of aspiration
- If CRE identified by PACU nursing, study investigator immediately contacted and TOF ratio quantified using acceleromyography

Murphy et al.-Results

- Data was collected on 7,459 patients undergoing GA during the 1-year period
- CREs identified in 61 patients (0.8%)
- Multiple logistic regression analysis revealed the only preoperative or intraoperative factor associated with CREs was residual block

	Critical respiratory event group	Control group	Difference (95% CI)	P Value
Train-of-four ratio	0.62±0.20	0.98±0.07	-0.36(-0.43 to -0.30)	<0.0001‡
Degree of NM Blockade ^b				
Acceptable	4(9.5%)	38(90.5%)	-81.0%(-90 to -66)	<0.0001*
Mild-to-moderate	7(9.5%)	4(9.5%)	7.1%(-9 to 24)	<0.366*
Severe	31(73.8%)	0(0%)	73.8%(59 to 85)	<0.0001*

Intraoperative Acceleromyographic Monitoring Reduces the Risk of Residual Neuromuscular Blockade and Adverse Respiratory Events in the Postanesthesia Care Unit

Glenn S. Murphy, M.D.,* Joseph W. Szokol, M.D.,* Jesse H. Marymont, M.D.,* Steven B. Greenberg, M.D.,†
Michael J. Avram, Ph.D.,‡ Jeffery S. Vender, M.D.,§ Margarita Nisman, B.A.||

- Hypothesis: If AMG reduces the frequency of residual NMB, it should also reduce the incidence of associated adverse respiratory events
 - 185 patients randomized to AMG group (quantitative monitor) or a control group (standard PNM-qualitative monitor)
 - TOF group: Extubation when standard criteria met + no fade TOF
 - AMG group: Extubation when standard criteria met + TOF ratio > 0.8
 - During transport to PACU and in PACU: Examined for hypoxemia + airway obstruction

Murphy et al.-Results

	Acceleromyography Group	Conventional TOF Group	Difference (99% CI)	P Value
Degree of neuromuscular blockade*				
Acceptable recovery	85 (95.5%)	63 (70%)	25.5% (12.0 to 39.7%)	<0.0001
Moderate	4 (4.5%)	15 (16.7%)	-12.2% (-25.2 to -0.4%)	0.014
Severe	0 (0%)	12 (13.3%)	-13.3% (-25.1 to -6.0%)	<0.001

	Acceleromyography Group	Conventional TOF Group
Number	89	90
No. with episodes of SpO ₂ 90-93% During Transport	9 (10.1%)	7 (18.9%)
No. with episodes of SpO ₂ <90% During Transport	0 (0%)	10 (21.1%)
Lowest SpO ₂ During Transport, %	96 (90-100)	94 (78-100)
No. requiring airway maneuver during transport	0 (0%)	10 (11.1%)



Residual Neuromuscular Blockade is a Risk Factor for Postoperative Pulmonary Complications

Berg H, et al. *Acta Anaesthesiol Scand* 1997; 41: 1095-1103

- **Objective:** To determine the incidence of **POPC** following the use of pancuronium, atracurium, and vecuronium and to examine the effect of **RNMB** in the **PACU** on the incidence of **POPC**
- **Methods**
 - 691 patients (abdominal, gynecologic, or orthopedic) randomized to receive pancuronium, atracurium, or vecuronium
 - NM management standardized; all patients reversed
 - TOF ratios measured in PACU with MMG and patients examined for signs of muscle weakness
 - Patients examined over post-operative day (POD) 1-6 for POPC
 - Pneumonic infiltrate or atelectasis on chest X-ray (CXR)

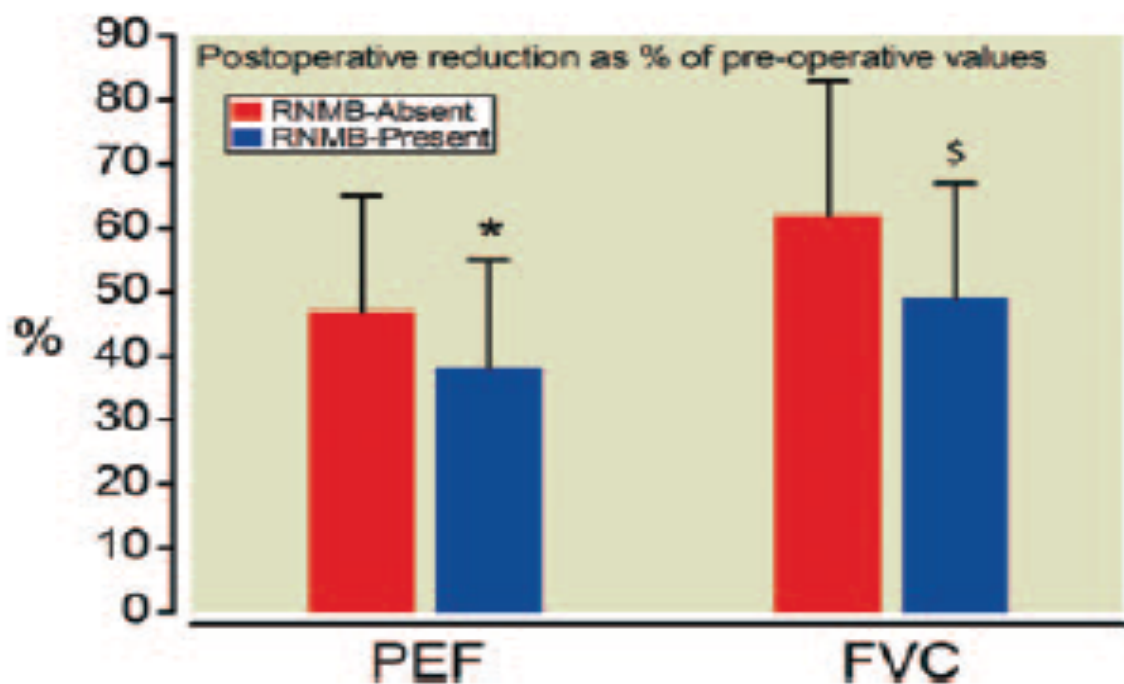
Berg et al-Results

Pancuronium (n=266)				Attracurium or Vecuronium (n=450)			
Number of Patients		Patients with POPC		Number of Patients		Patients with POPC	
		n	%			n	%
TOF \geq 0.7	167	8	4.8	TOF \geq 0.7	426	23	5.4
TOF<0.7	59	10	16.9*	TOF<0.7	74	1	4.2

* $P < 0.02$

Residual Neuromuscular Blockade Affects Postoperative Pulmonary Function

Gopalaiah Venkatesh Kumar, M.B.B.S., D.N.B.,* Anita Pramod Nair, M.B.B.S., D.N.B.,†
Hanuman Srinivasa Murthy, M.B.B.S., M.D.,‡ Koppa Ramegowda Jalaja, M.B.B.S., D.N.B.,‡
Karnate Ramachandra, M.B.B.S., M.D.,‡ Gundappa Parameshwara, M.B.B.S., M.D.‡



The influence of residual neuromuscular block on the incidence of critical respiratory events. A randomized, prospective, placebo-controlled trial

Sauer M, et al. Eur J Anaesthesiol 2011;28:842-8

- 114 patients undergoing orthopedic procedures under GA randomized to reversal (neostigmine) or placebo (saline)
- Neostigmine monitored with TOF-Watch
- Placebo group monitored with a standard PNS

Results

- Placebo group -TOF ratio 0.7 in PACU
- Neostigmine group -TOF ratio 1.0 in PACU
- 45 (40%) patients had hypoxemia ($SpO_2 < 93\%$)
 - 29 patients placebo group
 - 16 patients neostigmine group ($P=0.021$)

Residual neuromuscular block as a risk factor for critical respiratory events in the PACU

Norton M, et al. Rev Esp Anesthesiol Reanim 2013;60:190-6

- Prospective cohort study conducted over 3 weeks
- 202 patients arriving in PACU were examined for PRNB (TOF < 0.9)

Results

- Incidence of PRNB 30%
- Patients with PRNB had higher incidence of:
 - CRE (51 vs. 16%)
 - airway obstruction (10% vs. 2%)
 - mild-mod hypoxemia (23% vs. 4%)
 - severe hypoxemia (7% vs. 1%)
 - respiratory failure (8% vs. 1%)
 - inability to breathe deeply (38% vs. 12%)
 - muscular weakness (16% vs. 1%)

Residual Neuromuscular Block in the Elderly: Incidence and Clinical Implications

Murphy GS, et al. *Anesthesiology* 2015;123:1322-36

- Data prospectively collected on 150 younger (18-50) and 150 elderly (>70) patients
- TOF ratios measured on arrival to PACU
- Patients examined for adverse respiratory events from tracheal extubation until hospital discharge
- Postoperative muscle weakness quantified using a standardized exam, and PACU and hospital lengths of stay were determined

Results-continued

- Incidence of PRNB was 57.7% in elderly and 30.0% in younger patients ($P < 0.001$).
- Airway obstruction, hypoxemic events, signs and symptoms of muscle weakness, postoperative pulmonary complications, and increased PACU and hospital lengths of stay were observed more frequently in the elderly (all $P < 0.01$).
- In elderly cohort, no differences in preop or introp characteristics between those with and without PRNB
- However, the majority of adverse events were observed in patients with PRNB.

Conclusions: Residual Neuromuscular Blockade and Adverse Respiratory Outcomes

- Databased investigations suggest an association between residual blockade and major adverse respiratory morbidity and mortality.
- Clinical studies have demonstrated that incomplete neuromuscular recovery in the PACU results in adverse respiratory events
- Methods to reduce the risk of postoperative residual blockade are needed in order to optimize patient recovery and improve patient safety.