Residual Neuromuscular Blockade - An Opportunity to Provide Patient Care Following Surgery
Alyson Wilder, PharmD, BCPS

Home Study Webcast
4 Slides Per Page
Residual Neuromuscular Blockade –
An Opportunity to Provide Patient Care Following Surgery

ACTIVITY DESCRIPTION
Residual neuromuscular blockade has been a long standing problem for post-surgical patients. Residual blockade is one of the many factors that may delay recovery and cause additional complications post-surgery. Implementation of Enhanced Recovery After Surgery (ERAS) protocols has been shown to improve peri- and post-operative care of the surgical patient. This program will provide an overview of the risks associated with residual neuromuscular blockade and discuss pharmaceutical options for reversal. In addition, components of an ERAS protocol will be described and the potential role of reversal agents in ERAS protocols will be identified.

TARGET AUDIENCE
The target audience for this activity is pharmacists and nurses in hospital, community, and retail pharmacy settings.

LEARNING OBJECTIVES
After completing this activity, the pharmacist will be able to:

- Identify risk factors for residual neuromuscular blockade
- List adverse events that stem from residual neuromuscular blockade
- Describe elements of an Enhanced Recovery After Surgery (ERAS) protocol
- Identify role of reversal agents in enhanced recovery protocols

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ACTIVITY TYPE
Knowledge-Based Home Study Webcast

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Merck & Co., Inc..
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Assistant Professor, Presbyterian College School of Pharmacy

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Objectives

• Identify risk factors for residual neuromuscular blockade
• List adverse events that stem from residual neuromuscular blockade
• Describe elements of an Enhanced Recovery After Surgery (ERAS) protocol
• Identify the role of reversal agents in enhanced recovery protocols

Common Uses of Neuromuscular Blockers

• Facilitate emergency intubation
• Enhance mechanical ventilation for ARDS
• Prevent patient-ventilator dyssynchrony
• Manage elevated intracranial and intraabdominal pressure
• Maintain induced hypothermia after cardiac arrest

Neuromuscular Blockers (NMB)

<table>
<thead>
<tr>
<th>Depolarizing</th>
<th>Non-Depolarizing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Succinylcholine</td>
<td>Aminosteroidal</td>
</tr>
<tr>
<td></td>
<td>Benzyloisoquinolinium</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Atracurium</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Cisatracurium</td>
</tr>
<tr>
<td>Vecuronium</td>
<td></td>
</tr>
</tbody>
</table>
Acetylcholine Mechanism of Action

- Choline Acetate
- Choline
- ACh
- Na^+
- Channel closed
- Channel open normal

NMB Mechanism of Action

- Non-Depolarizing
- Depolarizing
- ACh
- Na^+
- Channel closed
- Channel open blocked

NMB Monitoring: Train of Four (TOF)

- Peripheral nerve stimulation
- Stimuli delivered every 0.5 sec
  - Total of 4 stimuli
- Twitches → level of block

<table>
<thead>
<tr>
<th>Number of Twitches</th>
<th>Receptors Blocked</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100%</td>
</tr>
<tr>
<td>1</td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td>75-80%</td>
</tr>
<tr>
<td>3</td>
<td>75%</td>
</tr>
<tr>
<td>4</td>
<td>0%</td>
</tr>
</tbody>
</table>

NMB Recovery Monitoring: TOF Ratio

- Train-of-Four (TOF)
Residual Neuromuscular Blockade

- Incomplete recovery from NMB
  - Presence of signs or symptoms of muscle weakness in the postoperative period after the intraoperative administration of an NMB
- Common complication in the post-anesthesia care unit (PACU)
- TOF ratio <0.9
- Patient safety issue

Complications of Residual NMB

Healthy Volunteers
- Swallowing dysfunction
- Decreased inspiration
- Profound muscle weakness

Surgical Patients
- ↑ risk of post-op hypoxemia
- ↑ risk of re-intubation
- Prolonged post-op ventilatory weaning
- Prolonged PACU stay

Risk Factors for RNMB

- Type and dose of NMB administered intraoperatively
- Degree of blockade maintained intraoperatively
- Use of interacting medications
- Patient specific factors
  - Electrolyte imbalances
  - Neurological and muscular diseases
  - Renal and hepatic function

Reversal Agents

Neostigmine
Sugammadex
NMB Reversal Agents

<table>
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<td></td>
<td>Atracurium</td>
</tr>
<tr>
<td>Sugammadex</td>
<td>Benzylishoquinolinium</td>
</tr>
<tr>
<td></td>
<td>Rocuronium</td>
</tr>
<tr>
<td></td>
<td>Cisatracurium</td>
</tr>
<tr>
<td></td>
<td>Vecuronium</td>
</tr>
</tbody>
</table>

Neostigmine (Bloxiverz™)

- Approved* May 2013
- Reversal of non-depolarizing NMB after surgery
- Single bolus injection over at least a minute
- Must be given with anticholinergic agent

<table>
<thead>
<tr>
<th>Dose</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.03mg/kg</td>
<td>NMB with shorter half-lives; 1st twitch &gt;10% of baseline or 2nd twitch present</td>
</tr>
<tr>
<td>0.07mg/kg</td>
<td>NMB with longer half-lives; weak first twitch response; rapid recovery</td>
</tr>
<tr>
<td>Max dose: 0.07mg/kg or 5mg (whichever is less)</td>
<td></td>
</tr>
</tbody>
</table>

Mechanism of Action

- Inhibits destruction of acetylcholine

Neostigmine (Bloxiverz™)

Contraindications
- Peritonitis
- Mechanical obstruction of GI/GU tract

Warnings
- Bradycardia
- Neuromuscular dysfunction with overdose
Neostigmine (Bloxiverz™)

- Hypotension
- Nausea/vomiting
- Dizziness

Special Populations
- Approved for pediatric use
- Adjust dose in renal impairment
- Not studied in hepatic impairment

Adverse Effects

Neostigmine and PACU Complications

- Retrospective cohort
- April 2005 – December 2013
- Adults having non-cardiac surgery + received NMB
- Incidence of major and minor PACU complications
  - Reversal agent vs. without

Major PACU Complications

<table>
<thead>
<tr>
<th>Major complication</th>
<th>Absolute numbers of complications</th>
<th>Incidence per 10,000 surgeries (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any major</td>
<td>2701</td>
<td>210 (202, 218)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>61</td>
<td>4.73 (3.68, 6.09)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>83</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Pulmonary aspiration</td>
<td>11</td>
<td>0.85 (0.46, 1.55)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4</td>
<td>0.31 (0.09, 0.83)</td>
</tr>
<tr>
<td>Unplanned admission to ICU</td>
<td>1357</td>
<td>105 (100, 111)</td>
</tr>
<tr>
<td>Return to OR</td>
<td>711</td>
<td>16 (14, 18)</td>
</tr>
<tr>
<td>Re-intubation</td>
<td>1522</td>
<td>118 (112, 124)</td>
</tr>
</tbody>
</table>

| * Exact binomial method for confidence intervals. |

Minor PACU Complications

<table>
<thead>
<tr>
<th>Minor complication</th>
<th>Absolute number of complications</th>
<th>Incidence per 10,000 surgeries (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any minor</td>
<td>45,375</td>
<td>3521 (3495, 3547)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5498</td>
<td>427 (418, 438)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18,677</td>
<td>1449 (1430, 1468)</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>5857</td>
<td>765 (750, 779)</td>
</tr>
<tr>
<td>Bronchoscopy</td>
<td>3254</td>
<td>252 (244, 261)</td>
</tr>
<tr>
<td>Prolonged NMB</td>
<td>89</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Nausea &amp; vomiting</td>
<td>18,604</td>
<td>1443 (1424, 1463)</td>
</tr>
<tr>
<td>Hypo/hyperglycaemia</td>
<td>3010</td>
<td>234 (225, 242)</td>
</tr>
<tr>
<td>Hypo/hyperkalemia</td>
<td>293</td>
<td>23 (20, 25)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>6</td>
<td>0.5 (0.01, 3.4)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>271</td>
<td>21 (19, 24)</td>
</tr>
</tbody>
</table>

| * Exact binomial method for confidence intervals. |
Major Complications: Incidence/10,000 surgeries

<table>
<thead>
<tr>
<th>Major Event</th>
<th>Neostigmine</th>
<th>No reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any major</td>
<td>170</td>
<td>605</td>
</tr>
<tr>
<td>MI</td>
<td>4.5</td>
<td>6.9</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>5.6</td>
<td>14.6</td>
</tr>
<tr>
<td>Pulmonary aspiration</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Unplanned ICU admission</td>
<td>84</td>
<td>319</td>
</tr>
<tr>
<td>Return to the OR</td>
<td>16.4</td>
<td>16.3</td>
</tr>
<tr>
<td>Reintubation</td>
<td>83.5</td>
<td>465</td>
</tr>
</tbody>
</table>

Minor Complications: Incidence/10,000 surgeries

<table>
<thead>
<tr>
<th>Minor Event</th>
<th>Neostigmine</th>
<th>No reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>423</td>
<td>462</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1450</td>
<td>1438</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>747</td>
<td>945</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>253</td>
<td>246</td>
</tr>
<tr>
<td>Pulmonary aspiration</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>Unplanned ICU admission</td>
<td>16.6</td>
<td>65.2</td>
</tr>
<tr>
<td>Return to the OR</td>
<td>1445</td>
<td>1429</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>236</td>
<td>211</td>
</tr>
<tr>
<td>Hypo/Hyperkalemia</td>
<td>23</td>
<td>19.7</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>16.6</td>
<td>65.2</td>
</tr>
</tbody>
</table>

Sugammadex (Bridion®)

- Approved December 2015
- Reversal of rocuronium and vecuronium in adults surgical pts
- Single bolus injection over 10 seconds

<table>
<thead>
<tr>
<th>Indication</th>
<th>Rocuronium</th>
<th>Vecuronium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate block</td>
<td>2mg/kg</td>
<td>2mg/kg</td>
</tr>
<tr>
<td>Deep block</td>
<td>4mg/kg</td>
<td>4mg/kg</td>
</tr>
<tr>
<td>Immediate reversal</td>
<td>16mg/kg</td>
<td>Not studied</td>
</tr>
</tbody>
</table>

Mechanism of Action

- Forms a complex with the NMB in the plasma
- Amount of available NMB to bind to nicotinic receptors is reduced
Sugammadex (Bridion®)

**Warnings**
- Increased aPTT and PT/INR
- Marked bradycardia

**Adverse Effects**
- Nausea/vomiting
- Hypotension and headache

**Special Populations**
- Contraindicated in CrCl <30 and dialysis
- Caution in hepatic impairment

**Sugammadex and Residual NMB**

- Randomized, parallel group, assessor-blinded
- December 2011 – November 2012
- Elective laparoscopic or open abdominal surgery + rocuronium
- Sugammadex vs. usual care (neostigmine/glycopyrrolate)
- Reduction in incidence of residual blockade

**Sugammadex and Reversal Efficacy**

- Reduction in incidence of residual blockade

**Impact on Extubation and Discharge**

<table>
<thead>
<tr>
<th></th>
<th>Sugammadex (n=74)</th>
<th>Usual Care (n=77)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Last NMB dose to last stitch</td>
<td>39 min</td>
<td>49 min</td>
<td>0.063</td>
</tr>
<tr>
<td>Reversal administration to extubation</td>
<td>11 min</td>
<td>15.2 min</td>
<td>0.014</td>
</tr>
<tr>
<td>Reversal administration to OR discharge ready</td>
<td>14.7 min</td>
<td>18.6 min</td>
<td>0.021</td>
</tr>
<tr>
<td>Reversal administration to OR discharge</td>
<td>19.9 min</td>
<td>24.1 min</td>
<td>0.020</td>
</tr>
<tr>
<td>PACU admission to PACU discharge ready</td>
<td>135 min</td>
<td>132 min</td>
<td>0.63</td>
</tr>
<tr>
<td>PACU admission to PACU discharge</td>
<td>209 min</td>
<td>235 min</td>
<td>0.22</td>
</tr>
</tbody>
</table>
The Surgical Patient

Goals for discharge
- Sufficient oral intake
- Return of bowel function
- Oral pain control
- Sufficient mobility
- No complications requiring hospital care

Challenges
- Stress of surgery
- Delayed gut function
- Multiple transitions of care

Enhanced Recovery After Surgery (ERAS)

- Multimodal, multidisciplinary approach to care of the surgical patient
  - Multidisciplinary team
  - Multimodal approach to complications that delay recovery
  - Evidence-based care protocols
- Key surgical endpoint is quality of recovery
- Consists of 24 core elements
  - Supported by scientific evidence

ERAS Society Guidelines
- Began as published protocol for colonic resections
- ERAS Society formed in 2010
- Guidelines incorporate core elements in for specific procedures
- www.erassociety.org

ERAS Protocol Implementation
- Decreased length of stay
  - Consistent results
  - Multiple surgery types and complex patients
- Reduction in rates of complications
  - Up to 50% demonstrated in colorectal surgery
  - Decrease in severe complications and mortality in colorectal cancer
- Compliance with protocol produced better outcomes
  - Complications, length of primary and total stay, and readmissions
**ERAS Flowchart Example**

**Impact of Surgical Insult**

- **Catabolism**
  - Loss of protein
  - Loss of muscle strength

- **Bowel dysfunction**
  - Delayed return to normal function
  - Post-op ileus

- **Fluid shifts**
  - Reduced perfusion
  - Salt and fluid overload

- **Metabolic stress**
  - Increased insulin resistance

**Achieving Goals of ERAS**

- Avoid factors known to worsen outcomes
- Maximize nutrition
- Minimize stress & improve response to stress
- Promote early return of bowel function

**Patient Case**

- SR is a 43 yo M scheduled for bariatric surgery
- PMH significant for HTN, DM, HLD and obesity
- Remote history of smoking and alcohol use
- Wife accompanies patient to all appointments
ERAS: Preadmission Core Elements

- Smoking cessation and limit alcohol intake
- Nutritional screening, assessment & support
- Medical optimization of chronic disease

ERAS: Preoperative Core Elements

- Structured information and patient engagement
- Preoperative carbohydrate treatment
- Thrombosis prophylaxis
- Infection prophylaxis
- Nausea & vomiting prophylaxis

Patient Case: Preadmission Core Elements

- Remind SR of importance of abstaining from smoking and alcohol
  - Use increases risk of complications
- Conduct nutritional assessment and provide nutrition support
  - Pre-op nutrition deficiency is a strong predictor poor overall survival
- Optimize medical management of his HTN, DM and HLD
  - Reduces post-operative complications

Patient Case: Preoperative Core Elements

- Thoroughly explain what to expect during hospital stay to SR and his wife
  - Patient must understand their role in the process
  - Reduce patient anxiety & improve compliance with protocol
- Provide clear carbohydrate drinks up to 2hr before surgery
  - Decreases protein losses & post-op insulin resistance
  - Facilitates early return of bowel function
  - 6hr fast of solids before surgery
**Patient Case: Preoperative Core Elements**

- SR will be started on mechanical and/or pharmacological thrombosis prophylaxis
  - Significant cause of morbidity and mortality in bariatric patients
- Pre-operative antibiotics likely not needed for bariatric surgery
- Orders will be written for anti-nausea medications
  - PONV delays gut function and can cause metabolic derangements

**ERAS: Intraoperative Core Elements**

- Minimize invasive techniques and surgical drains
- Avoid long-acting opioids
- Maintain fluid balance
- Use epidural anesthesia for open surgery
- Remove NG tubes before anesthesia reversal
- Control body temperature

**Patient Case: Intraoperative Core Elements**

- Invasive techniques and surgical drains will be minimized
  - Known to cause significant complications
  - Promote faster recovery and reduce pain
- Epidural anesthesia will be used
  - Reduces stress response
  - Decreases risk of post-op ileus
- Long-acting opioids will be avoided
  - Decreases risk of post-op ileus
  - Long-acting opioids known to prolong recovery

**Patient Case: Intraoperative Core Elements**

- Fluid balance will be maintained and may use vasopressors for BP control
  - Fluid overload associated with delayed gut function and increased post-operative complications
- Nasogastric (NG) tube will be removed intraoperatively
  - Impair gut function
  - Increase incidence of post-op fever, atelectasis and pneumonia
- Hypothermia will be avoided
  - Increased risk of infection and bleeding
  - Affects pharmacokinetics of NMBs
ERAS: Postoperative Core Elements

- Early mobilization and prepare for early discharge
- Early intake of oral fluids and solids
- Early removal of IV fluids and urinary catheters
- Use of protein and energy-rich supplements
- Opioid sparing pain control and use of laxatives
- Multimodal approach to N/V control
- Regular audit of process and outcomes

Patient Case: Postoperative Core Elements

- Goal for SR to be up to chair and walking the day of surgery
  - Bed rest increases insulin resistance, muscle loss and risk of thrombosis
- Will offer oral fluids and solids day of surgery
  - Facilitates early return of bowel function and decreases post-op morbidity
- Will give protein rich supplements in addition to oral diet
  - Decrease protein loss
  - Promote wound healing

Patient Case: Postoperative Core Elements

- IV fluids and urinary catheters will be removed as soon as possible
  - Removal of fluids promotes mobilization and supports oral intake
  - Removal of catheter supports mobilization and decreases infection risk
- Continue use of medications to avoid nausea and vomiting
- Pain will be managed with oral, non-opioid agents if possible
  - Pain control reduces insulin resistance
  - Opioids delay gut motility
  - Oral medications facilitate discharge

Role of NMB Reversal in ERAS Protocol

- Incorporate appropriate use of NMB and reversal agents into intraoperative core elements
  - Could also consider screening for risk factors during preadmission
- Risk of residual blockade and benefits of reversal agents well documented
- Verbiage in ERAS Society Guidelines for GI and bariatric surgery
  - Do not recommend one NMB or reversal agent over another
### ERAS in GI Surgery
- Avoid long-acting NMB
- Use minimum necessary NMB dose and level of block
- Maintain normothermia
- Use appropriate NMB monitoring techniques
- Avoid residual NMB with use of reversal agent

### ERAS in Bariatric Surgery
- Consider deep neuromuscular block
- Ensure full reversal of neuromuscular blockade
- Use appropriate monitoring of neuromuscular blockade

### Benefits of Inclusion in ERAS Protocols
- Early identification and correction of modifiable risk factors
- Reduced incidence of residual neuromuscular blockade
- Decrease in post-operative complications
- Improved patient outcomes

### Summary
- Residual neuromuscular blockade causes significant post-surgical complications
- Many risk factors of residual blockade are modifiable
- Available reversal agents shown to reduce complications of residual blockade
- Enhanced Recovery After Surgery (ERAS) protocols improve patient care
- Appropriate use of neuromuscular blockers and reversal agents play a role in ERAS protocols
Exam Questions

1. Choose the CORRECT statement regarding Train of Four (TOF) below:
   A. TOF of 0 is full, deep blockade
   B. TOF of 0 is full movement
   C. TOF of 5 is full, deep blockade
   D. TOF of 5 is full movement

2. The current definition of residual neuromuscular blockade is defined as:
   A. TOF ratio <0.3
   B. TOF ratio <0.5
   C. TOF ratio <0.7
   D. TOF ratio <0.9

Use the case below to answer questions 3 and 4.
LM is a 61yo F who underwent bariatric surgery. Her PMH includes HTN, DM and CKD. During surgery, LM received propofol, sevoflurane and pancuronium. She was maintained at a TOF of 0 during surgery. She arrived to the PACU with a TOF of 0.5 despite use of a reversal agent. Post-surgery, she became hypoxemic requiring re-intubation and was admitted to the ICU.

3. Which of the following is NOT a risk factor for LM’s residual neuromuscular blockade?
   A. A female undergoing bariatric surgery
   B. Use of pancuronium, a long acting neuromuscular blocker
   C. Use of deep blockade requiring large doses of pancuronium during surgery
   D. Use of sevoflurane, an inhaled anesthetic

4. LM arrived to the PACU with signs and symptoms of residual neuromuscular blockade. Which of the following is a complication of residual neuromuscular blockade?
   A. Early extubation
   B. Re-intubation
   C. Shortened hospital stay
   D. Increased inspiration

5. Sugammadex is approved for reversal of:
   A. All depolarizing neuromuscular blockers
   B. All non-depolarizing neuromuscular blockers
   C. Rocuronium and vecuronium only
   D. Atracurium and cisatracurium only
6. Choose the CORRECT statement regarding reversal agents below:
A. Sugammadex must be given with glycopyrrolate and atropine
B. Neostigmine is FDA approved to reverse succinylcholine only
C. Sugammadex has an approved dosing regimen for reversal of deep blockade.
D. Neostigmine has an approved dosing regimen for reversal of deep blockade.

7. The primary goal of Enhanced Recovery After Surgery (ERAS) is:
A. Decreased length of surgical procedure
B. Quality of surgical procedure
C. Increased time to recovery
D. Quality of recovery

8. Which of the following is NOT an ERAS preoperative core element?
A. Infection prophylaxis
B. Weight loss prophylaxis
C. Nausea and vomiting prophylaxis
D. Thrombosis prophylaxis

9. Choose the CORRECT statement regarding the role of reversal agents in ERAS protocols?
A. Reversal agents are included in ALL published ERAS Society Guidelines
B. Reversal agents are not addressed in ANY published ERAS Society Guidelines
C. Reversal agents may be addressed in the preadmission and intraoperative portions of ERAS protocols
D. Reversal agents have no role in ERAS protocols

10. Which of the following ERAS Postoperative elements helps to improve gut motility after surgery?
A. Opioid sparing pain control and use of laxatives
B. Early removal of IV fluids and urinary catheters
C. Preparation for early discharge
D. Regular audit of process and outcomes