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Post-Extubation Residual Neuromuscular Blockade

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POST-EXTUBATION RESIDUAL NEUROMUSCULAR BLOCKADE

by

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Part I:

Post-extubation Residual Neuromuscular Blockade

Introduction

The bilateral lumbar laminectomy on the 77 year-old male was complete, the incision was sutured closed, and it was now time to wake the patient up and remove the endotracheal tube that had been supporting his breathing during the procedure. He appeared to be ready for the removal of the breathing tube. The patient exhibited a normal, relaxed breathing pattern at an appropriate rate. His tidal volumes were a little on the low side for his body size but were adequate enough for the removal of the tube. His spontaneous respirations were maintaining appropriate levels of oxygen and carbon dioxide in the blood. The endotracheal tube was removed without incident and the patient maintained good air exchange and oxygen saturation levels while in transit to the post-anesthesia care unit (PACU).

Shortly after arrival to the PACU, after awaking more thoroughly from the anesthetic, the patient exclaimed, "I can't breathe!" His chest and abdomen rocked paradoxically back and forth as he struggled to get an adequate breath.

"I can't breathe!" he again uttered between breaths. A high-pitched stridorous sound from his upper airway could be heard with each inspiration.

It was quickly determined that the patient was still partially blocked from the paralytic agent that he had been given at the beginning of the surgery to keep his muscles relaxed. Following the prompt intravenous administration of a paralytic reversal agent the patient's breathing became more relaxed, the paradoxical rocking of his abdomen and chest wall subsided, the high-pitched stridor in his upper airway ceased, and his anxiety fled as he was again able to take a deep breath.

Problem and Purpose

The above account describes an actual incident of post-extubation residual neuromuscular blockade (RNMB) that occurred recently in the PACU at Altru Hospital. RNMB can have serious, life-threatening consequences. Multiple studies have associated RNMB with various postoperative complications that have potential consequences ranging from muscle weakness and dyspnea to complete cardiopulmonary arrest (Bissinger et al., 2000; Eikermann et al., 2003; Erisksson et al., 2006; Sundman et al., 2000).

The purpose of this study is to: (a) explore a clinical problem with potentially serious adverse patient outcomes, (b) investigate key, problem-specific research questions, (c) acquire useful and practical knowledge to be applied in personal practice to avoid this post-operative complication, and (d) articulate research findings to fellow colleagues/classmates in anesthesia.

The seven key research questions addressed in this study will be as follows:

1. Why does post-extubation residual neuromuscular blockade (RNMB) occur?
2. What is the reported incidence of RNMB?
3. What are the potential consequences and clinical signs and symptoms of RNMB?
4. What are the differences between the various modalities of neuromuscular blockade monitoring used to detect RNMB?
5. Is any neuromuscular blockade monitoring modality the best at detecting RNMB?
6. How is RNMB best avoided?
7. How is RNMB treated when it does occur?

Theoretical Framework

Betty Neuman's Health Care Systems Model underscores the motivation for this clinical study. Neuman describes patients/individuals as open systems within their environment. As open systems, patients respond to and interact with various variables ("stressors") that cause system instability. Neuman asserts that an important role of nursing is to help the patient achieve optimal wellness, which she describes as, "the greater possible degree of system stability at a given point in time" (Neuman, 2005). RNMB is an example of a stressor that, when applied to individuals, causes acute system instability. The aim of this study is to better understand this clinical stressor—to explore what factors lead to its development, to learn how it is best detected, to determine how it can best be avoided, and finally, to review what immediate steps should be taken in order to achieve the "greater possible degree of system stability" should RNMB occur.

Definitions

After inducing a state of general anesthesia it is often necessary to place an endotracheal tube into the trachea to allow for the controlled ventilation of a patient's lungs during surgery. In order to place this tube, the patient must first be given a neuromuscular blocking agent (i.e. paralytic agent) to completely relax the muscles of the body. There are several types of surgeries that require further doses of neuromuscular blocker to be given during the surgery—in order to keep the muscles relaxed. When this is the case, it often becomes necessary to administer a paralytic reversal agent at the end of the surgery—in order to reverse the paralysis and to get the patient back breathing on his/her own. This must be done before the endotracheal tube can be removed (i.e. before the patient can be "extubated"). When the patient has been extubated but still exhibits

some degree of residual paralysis this is referred to as post-extubation RNMB. The potential consequences of RNMB, along with its associated clinical signs and symptoms, will be described later.

It is helpful to briefly review the normal physiology of the initiation of muscle contraction at the neuromuscular junction in order to better understand the pharmacology of neuromuscular blockade and the pathophysiology of RNMB. After this review, the above-mentioned key research questions will be addressed.

Physiology of Normal Neuromuscular Junction Function

The neuromuscular junction consists of three primary components: (a) the presynaptic nerve terminal, (b) the motor endplate of the muscle fiber, and (c) the synaptic cleft (i.e. the space between the presynaptic nerve terminal and the motor endplate). Acetylcholine (Ach), the neurotransmitter responsible for triggering the beginning of muscle contraction, is synthesized and stored in the presynaptic nerve. As an action potential travels down the presynaptic nerve and reaches the end of its axon (i.e. the nerve terminal) Ach is released by the presynaptic nerve into the synaptic cleft. Ach then diffuses across the synaptic cleft and binds to Ach receptors embedded in the cell membrane (i.e. the motor endplate) of the muscle fiber. Binding of Ach to its receptor causes a conformational change in the receptor resulting in the opening of sodium ion channels. When enough Ach receptors have been stimulated (i.e. when enough sodium ion channels have been opened) the resulting massive influx of sodium ions into the muscle fiber triggers depolarization of the muscle cell and ultimately leads to muscle contraction. The signal for muscle contraction is terminated primarily by the enzymatic breakdown of Ach by the enzyme acetylcholinesterase (Porth, 2005, p. 1200).

Pharmacology of Neuromuscular Blockade

Neuromuscular blocking agents exert their paralytic effects by competitively binding to Ach receptors, preventing Ach from binding to the receptor. As Ach is unable to bind to its receptor the muscle cell cannot depolarize and, therefore, muscle contraction cannot be initiated.

Paralytic reversal agents exert their effects by binding to the enzyme acetylcholinesterase, preventing the enzymatic breakdown of Ach. This results in a higher concentration of Ach within the synaptic cleft. A higher concentration of Ach results in a greater proportion of Ach receptors being bound to Ach than to the neuromuscular blocking agent and depolarization of the muscle fiber then becomes possible (Katzung, 2004, p. 440).

Review of Literature

Now, to address the seven key research questions:

1. Why does RNMB occur?

Most of the neuromuscular blocking agents that are used to paralyze patients for the insertion of the endotracheal tube have a relatively short duration of action so that patients will be fully recovered and will regain full muscle activity by the time most surgeries are over. Often times, if continued paralysis is needed throughout the surgical procedure, additional paralytic agent will have to be administered. The inadequate reversal of these additional boluses of paralytic agent is usually what leads to RNMB (i.e. inadequate doses of reversal agent are given and so the concentration of Ach within the synaptic cleft does not reach high enough levels to maintain consistent depolarization/contraction of the muscle fiber).

One may wonder why RNMB still occurs when anesthesia providers have been trained in methods of RNMB detection and in the appropriate administration of reversal agents. The answer to the above question has to do with: (a) the *inadequate dosage* of paralytic-reversal agent, (b) the *timing* of the administration of the reversal agent, and/or (c) other possible miscellaneous contributing factors that will be discussed below.

So, how is it possible for an *inadequate dose* of reversal agent to be given? The first thing to understand is that there is not a *set dose* of reversal agent that is given to each patient, but rather a *dosage range* that the clinician uses as a guide to decide what dose to give the patient—based on what he/she needs (i.e. based on the degree of paralysis that still exists). There is a saying in anesthesia that certainly applies to this situation; it goes something like this: "Give the patient only what he/she needs; you can always give more, but you can't take back what you've already given."

There are undesirable side effects of paralytic reversal agents that duly justify limiting the amount of drug that is given to only that amount which is needed. Reversal agents have a wide array of effects on multiple body systems, to include: the central nervous system (increased alertness to generalized convulsions, coma, respiratory arrest), the cardiovascular system (bradycardia, ↓ cardiac output, ↓ cardiac contractility), the eye (pupillary constriction), the respiratory tract (bronchoconstriction, ↑ mucous secretions), and the gastrointestinal tract (↑ GI motility, ↑ salivary secretions) (Katzung, 2004, p. 103). Anticholinergic agents are, of course, administered to counteract these effects and minimize any undesired side effects of reversal agents, but it still stands within reason to only give that which is required by the patient's current level of paralysis.

A clinical practice that may contribute to the administration of an inadequate dose of reversal agent (and the occurrence of RNMB) is failing to test the patient with a peripheral nerve stimulator *before* and *after* the reversal agent has been given. A standard that is commonly taught in the clinical setting is to not administer any reversal agent until the patient exhibits at least one, preferably two, twitches to train-of-four (TOF) stimulation. If the anesthesia provider does not ensure that this partial recovery from paralysis has occurred, and just goes ahead and administers the reversal agent (when the patient has not gained any twitches back), the clinician has no idea how dense the original paralysis was and he/she then runs the risk of the reversal agent wearing off and the patient then developing RNMB later in the recovery unit. It is always important to also check the patient's response to TOF stimulation *after* the administration of the reversal agent in order to best evaluate the adequacy of the reversal from paralysis.

There are times when the anesthesia provider may assume (based on his/her clinical judgment & experience) that the amount of reversal agent is sufficient and goes ahead with extubation of the patient after the patient meets clinical extubation criteria—without double checking with a peripheral nerve stimulator to ensure that the patient is adequately reversed. Failing to check for adequate paralytic reversal, as described above, is not a wise practice to fall into; for, as illustrated in the clinical scenario described at the beginning of this paper, it is possible for a patient to exhibit general clinical readiness for extubation (e.g. adequate tidal volumes, appropriate respiratory rate, and good oxygen levels) but for increased respiratory difficulties to quickly ensue after extubation, while in the PACU.

Now, regarding the *timing* of the administration of reversal agents: The timing of the reversal agent administration can directly contribute to the development of RNMB in the recovery unit. Just as described in the above paragraph, if the reversal agent is given too early (i.e. before the patient has exhibited one or two twitches to TOF stimulation) the anesthesia provider runs the risk of the patient experiencing RNMB. It is important to note the differing pharmacokinetics of paralytics compared to their corresponding reversal agents—particularly their differing durations of action. Depending on the doses of each agent and the individual clearance of the drugs by the patient, neuromuscular blocking agents tend to have longer durations of action than their reversal agents. As an example: Neostigmine (a commonly used reversal agent) has a reported duration of action of 40 to 60 minutes; whereas Rocuronium (a commonly used nondepolarizing neuromuscular blocker), depending on the dosage, has a wide reported duration of action—ranging from 15 to 150 minutes (Omoigui, 2001). This makes it easy to see how potential for the development of RNMB in the recovery unit is possible.

There are a few other miscellaneous factors that may interfere with the adequate reversal of paralytic agents; these include: (a) the acid-base status of the patient (i.e. respiratory acidosis), (b) the presence of an electrolyte imbalance (hypokalemia and hypermagnesemia may produce interference with reversal of paralytics), (c) various drug interactions (calcium-channel blockers and aminoglycoside antibiotics), and (d) the temperature of the patient (i.e. states of hypothermia) (Miller, 2005, pp. 522-23).

2. What is the reported incidence of RNMB?

Residual paralysis following the administration of paralytic agents may occur more often than one might suspect. Studies have been conducted to describe its incidence

which have yielded interesting results (Baillard et al., 2000; Debaene, Plaud, Dilly, & Donati, 2003; Kim, Lew, Cho, & Cheong, 2002; Murphy et al., 2005). The incidence of RNMB in the recovery room varies significantly depending on whether or not a paralytic reversal agent has been administered in the operating room. Without the administration of a reversal agent, the incidence of RNMB in the recovery room has been reported to range from 16% (Debaene et al., 2003) to 42% (Baillard et al., 2000). Even with the administration of a paralytic reversal agent, the reported incidence of recovery room residual paralysis has ranged from 8% (Murphy et al., 2005) to as high as 20% (Kim et al., 2002).

Residual paralysis was determined to be present in the above mentioned studies when TOF-ratios were less than 0.7 (TOF-ratios were determined using acceleromyography). Studies have suggested that functional impairment of pharyngeal muscles may exist even with TOF-ratios less than 0.9. Such impairment places the patient at greater risk for aspiration should regurgitation occur. It has also been noted that the carotid body hypoxic ventilatory response can be impaired at a TOF-ratio of 0.7 or less (Eriksson).

3. What are the potential consequences and clinical signs and symptoms of RNMB?

Post-extubation RNMB can result in serious post-operative complications such as: obstruction of the upper airway (usually a result of poor muscle tone of the tongue—causing the tongue to drop into the back of the throat and obstruct air flow) (Eikermann, Groeben, Husing, & Peters, 2003), impaired airway reflexes (resulting in a four to five-fold increase in the incidence of misdirected swallowing—leading to the introduction of saliva directly into the trachea) (Sundman et al., 2000), a decreased hypoxic ventilatory response (Erisksson, Sato, & Severinghaus, 2006), and postoperative hypoxia (Bissinger,

Schimek, & Lenz, 2000); as such, the patient may exhibit the following signs and symptoms: Labored respirations with complaints of shortness of breath, use of accessory breathing muscles, little to no air exchange and/or paradoxical chest movement with upper airway obstruction, a weak, ineffective cough, and/or a decline in oxygen saturation levels.

4. What are the differences between the various modalities of neuromuscular blockade monitoring used to detect RNMB?

Detecting the presence and degree of neuromuscular blockade requires experience with the use of a peripheral nerve stimulator (PNS). A PNS applies electrical stimulation to a nerve that supplies a particular group of muscle fibers in the body. The mechanical response of the muscle to this stimulation can be monitored and evaluated in order to determine the degree of neuromuscular blockade that is present. Four main techniques used to detect RNMB will be discussed below. RNMB can be detected by the visual or tactile assessment of the mechanical response to: (a) train-of-four (TOF), (b) double-burst, or (c) tetanic stimulation. Finally, the mechanical response of the muscle to train-of-four stimulation and the determination of TOF-ratios can be determined using various, more sensitive neuromuscular monitoring techniques (i.e. mechanomyography (MMG), accelerography (ACG), electromyography (EMG), and Piezoeletric film) (Dorsch & Dorsch, 1999, pp. 850-59). TOF-ratios are determined simply by measuring the strength of the first and the last twitch of a train-of-four stimulation pattern and then determining the strength of the last twitch relative to the first (i.e. a TOF ratio of 0.9 means that the last twitch was 90% as strong as the first).

An understanding of how the above techniques differ from each other will help to better understand some of the research findings discussed below. All of the techniques listed above are similar to each other in that they all evaluate the response of the muscle to the applied electrical stimulus (i.e. they involve applying the electrical stimulus and then assessing the strength of muscle contraction either through visual or tactile assessment, or through the use of additional, more sensitive equipment). In general terms, these techniques differ from one another by the *frequency, duration*, and *pattern* of the applied electrical stimulus (Dorsch & Dorsch, 1999, pp. 850-59).

The TOF stimulation pattern consists of four impulses of equal intensity delivered over 2 seconds (2 Hertz) at 0.5 second intervals (the term Hertz (Hz) simply means the number of cycles/stimulations delivered per second).

With the double-burst stimulation pattern two short periods of 50 Hz tetanic stimulation are separated by 750 milliseconds. There are two main varieties of the double-burst stimulation pattern. These two varieties are $DBS_{3,3}$ and $DBS_{3,2}$. With $DBS_{3,3}$ three 0.2 millisecond, 50 Hz bursts are delivered, followed by three identical bursts 750 milliseconds later. $DBS_{3,2}$ involves the delivery of three 0.2 millisecond, 50 Hz bursts, followed by two such bursts 750 milliseconds later.

With tetanic stimulation, a rapidly repeated stimulation at 50 to 100 Hz (i.e. 50 to 100 stimulations per second) is applied to the nerve. This stimulus is commonly applied for a duration of 5 seconds (Dorsch & Dorsch, 1999, pp. 850-59).

Using the above described neuromuscular monitoring techniques, RNMB is detected by observing the contracting muscle for the presence of any "fade" or decline in the degree of muscle contraction over the period of the applied stimulus. If this "fade" or

decline in the strength of muscle contraction exists, then this is an indication that there is some degree of residual paralysis still present.

The last group of techniques mentioned above (MMG, ACG, EMG, and piezoelectric film) differ from TOF, double-burst, and tetanic stimulation primarily by the fact that they involve the assessment of the mechanical or electrical response of the muscle during contraction by using additional pieces of equipment that can easily detect even minor changes in the strength of contraction. These tests, therefore, are more sensitive for detecting RNMB (Dorsch & Dorsch, 1999, pp. 850-59).

5. Is any neuromuscular blockade monitoring modality the best at detecting RNMB?

Various studies have evaluated the efficacy of the different methodologies that are used to detect the presence of RNMB. Divatia, Kulkarni, Kerhalkar, and Kakodkar (1998) and Patil and Divatia (2005) found the visual assessment of the response to double burst stimulation to be a superior method for detecting RNMB over the visual assessment of the response to train-of-four stimulation. Ansermino, Sanderson, Bevan, and Bevan (1996) and Fuchs-Buder and Eikermann (2005) conducted studies to evaluate the efficacy of using acceleromyography (ACG) to detect RNMB—finding this modality to be superior to the visual assessment of the response to train-of-four stimulation. Samet, Capron, Alla, Meistelman, and Fuch-Buder (2005) found the ACG determination of train-of-four ratios to be superior to double-burst stimulation or tetanus in detecting RNMB. Researchers have found a close relationship between the TOF-ratios determined by ACG as compared to those determined by MMG or EMG (Dorsch & Dorsch, 1999, pp. 856).

In summary, it appears that the most superior method for detecting the presence of RNMB is by measuring TOF-ratios with the use of ACG (or other similar technology—

e.g. MMG or EMG). If this equipment is not available, and the clinician will be assessing the response to nerve stimulation via visual or tactile means, then double-burst or tetanic stimulation are superior methods (over TOF stimulation) for detecting RNMB. This is because "fade" is more obvious and more easily detected with these two stimulation patterns as compared to TOF stimulation (Morgan & Mikhail, 2002, p. 182).

6. How is RNMB best avoided?

When anesthesia providers become experienced with both the *routine use of neuromuscular blockade monitoring* techniques and the *routine administration of reversal agents*, the incidence of RNMB can be significantly reduced. Baillard et al. (2005) conducted a study that found that "between 1994 and 2005 quantitative measurement and reversal of neuromuscular block in the operating room increased from 2 to 60% and from 6 to 42% respectively ($p < 0.001$)." Over this same period of time, the incidence of RNMB in their institution decreased from 62 to 3% ($P < 0.001$).

In the clinical setting, some clinicians would argue that it is good practice to *routinely* administer reversal agents to any patient that has received a neuromuscular blocker—regardless of how much time has transpired since the administration of the paralytic. One could argue that the findings of the above-mentioned study support such a practice.

In the interest of preventing the development RNMB—in addition to the routine monitoring of neuromuscular function and administration of reversal agents—it also becomes of paramount importance to evaluate the patient's clinical readiness for extubation prior to removing the endotracheal tube. There are a number of clinical parameters that can be assessed by the anesthesia provider in order to make such a determination. Examples of such clinical parameters include: Tidal volume, response to

TOF stimulation, response to sustained tetany at 50 or 100 Hz for 5 seconds, vital capacity, response to double-burst stimulation, inspiratory force, head lift, sustained handgrip, and sustained bite (Miller, 2005, p. 487).

No one clinical test by itself ensures the absence of RNMB. There are some tests, however, that better indicate clinical readiness for extubation. It is important to note that the patient may pass several of the tests listed above, showing clinical readiness for extubation, and still have a significant amount of the acetylcholine receptors occupied by the neuromuscular blocker. Table 2 below shows the above listed clinical tests, along with their acceptable results and the approximate percentage of acetylcholine receptors that are still occupied by neuromuscular blockers at the time that the patient's response returns to normal values.

Table 2. Tests of Clinical Readiness for Extubation (adapted from Miller, 2005, p. 487).

Clinical Parameter	**Acceptable Results**	**Approximate percentage of Receptors Occupied When Response Returns to Normal**
Tidal volume	At least 5 ml/kg	80
Train-of-four (TOF)	No palpable fade	70-75
Sustained tetanus @ 50 Hz for 5 seconds	No palpable fade	70
Vital capacity	At least 20 ml/kg	70
Double burst	No palpable fade	60-70
Sustained tetanus @ 100 Hz for 5 seconds	No palpable fade	50
Inspiratory force	At least -40 cm H2O	50
Head lift	Sustained for 5 sec. while supine at 180 degrees.	50
Hand grip	Sustained at level qualitatively similar to preinduction baseline.	50
Sustained bite	Sustained jaw clench on tongue blade	50

As Miller (2005, p. 486) points out, "It is not known what proportion of receptors must be available or how sensitive a test must be to ensure adequate muscle strength to overcome airway obstruction and permit effective coughing and to be free of visual disturbances." It logically follows then, that it is in the best interest of the anesthesia provider to utilize as many clinical tests as practically possible to best ensure that the patient meets extubation criteria.

The take-home message of this section is this: Perhaps the best way to prevent the occurrence of RNMB is to *routinely* monitor the neuromuscular function and *routinely* administer reversal agents to all patients who have received a paralytic agent; also, as many clinical tests as practical and possible should be combined/utilized in order to ensure the patient's clinical readiness for extubation.

7. How is RNMB treated when it does occur?

The answer to the above question is intuitively obvious; give more reversal agent! However, to more completely answer how to best treat RNMB, this section will review the appropriate dosing and pharmacokinetic properties of the commonly administered reversal agents (neostigmine, edrophonium, and pyridostigmine) along with their corresponding anticholinergic agents (glycopyrrolate and atropine).

The appropriate doses for reversal agents and their corresponding anticholinergic agents are listed in Table 1 below. Anticholinergic agents (i.e. atropine and glycopyrrolate) are always administered in conjunction with reversal agents in order to minimize/blunt the undesired cholinergic effects of reversal agents (of primary concern is the bradycardia that can result from the administration of reversal agents). The first

important thing to note is the maximum doses listed for neostigmine, edrophonium, and pyridostigmine—these maximum doses are 5 mg, 40 mg, and 30 mg respectively.

The drugs in the table below have been color coded to highlight the differences and similarities in their pharmacokinetic properties. The anticholinergic agents that have the most similar onsets, peaks, and durations as their corresponding reversal agents have been assigned the same color—atropine with edrophonium, and glycopyrrolate with neostigmine and pyridostigmine. You'll notice that edrophonium has the quickest onset, the shortest time to peak effect, and the shortest duration—making this drug a good choice for reversing patients who are exhibiting RNMB and who are in acute distress. It is important to keep in mind, however, that this is the reversal agent with the shortest duration of action; therefore, the patient will need to be closely observed in recovery. It has been observed in the clinical setting to dose such a patient with reduced doses of both edrophonium (10-20 mg) *and* neostigmine (to a cumulative dose of 5 mg)—always remembering, of course, to coadminister the appropriate anticholinergic agent. Edrophonium may not be as effective as neostigmine for reversing a dense neuromuscular block. It is also worth noting that edrophonium's muscarinic effects (i.e. its tendency to cause bradycardia) are not as pronounced as neostigmine's (Morgan & Mikhail, 2002, p. 205)

Neostigmine, the most commonly administered reversal agent, has an intermediate onset, peak, and duration of action. Patients that are of extremes of age are prone to be more sensitive to its effects—resulting in a faster onset and a need for a reduction in the dose. Neostigmine has a longer duration of action in the geriatric patient. Though neostigmine is a polar molecule that does not easily cross lipid membranes it has been

known to cross the placenta, causing fetal bradycardia; therefore, atropine may be a more appropriate choice as an anticholinergic agent when giving neostigmine to the pregnant patient (atropine readily crosses lipid membranes and could therefore aid in minimizing undesired fetal heart rate declines) (Morgan & Mikhail, 2002, p. 204).

Pyridostigmine has the most delayed onset of action, the longest time to peak effect, and the longest duration of action. It is one-fifth as potent as neostigmine and therefore requires higher doses. This agent is a good choice for the patient who still has a significant degree of paralytic on board at the time of reversal—ensuring better postoperative coverage and minimizing the chances of RNMB later in recovery.

Table 1. Dosing & Pharmacokinetics of Reversal Agents & Their Corresponding Anticholinergics (Morgan & Mikhail, 2002, p. 204; Omoigui, 2001).

Drug	Dose	Onset	Peak	Duration
Edrophonium	0.5-1.0 mg/kg **(Max. 40 mg)**	30-60 sec.	1-5 min.	5-20 min.
Atropine	0.014 mg/mg Edro.	45-60 sec.	2 min.	1-2 hrs.
Neostigmine	0.04-0.08 mg/kg **(Max. 5 mg)**	< 3 min.	3-14 min.	40-60 min.
Glycopyrrolate	0.2 mg/mg of Neo.	< 1 min.	5 min.	2-3 hrs.
Pyridostimine	0.1-0.4 mg/kg **(Max. 30 mg)**	2-5 min.	< 15 min.	90 min.
Glycopyrrolate	0.05mg/mg Pyrido.	< 1 min.	5 min.	2-3 hrs.

Recommendations for Further Studies

Various studies have evaluated the different methodologies used to detect RNMB (Divatia et al., 1998; Patil et al., 2005; Ansermino et al., 1996; Fuchs-Buder et al., 2005; Samet et al., 2005). Other studies have described the incidence of RNMB according to which paralytic agents were used and according to whether or not a paralytic reversal agent was given (Baillard et al., 2000; Debaene et al., 2003; Kim et al., 2002; Murphy et al., 2005). Multiple studies have clearly identified clinician inexperience as a contributing factor to various perioperative anesthesia complications (Chinachoti et al., 2005; Kluger

& Bullock, 2002; Marcus, 2006; Paix et al., 2005; Rungreungvanich et al., 2005); however, it appears that no studies, as of yet, have attempted to directly relate the incidence of post-extubation RNMB with the experience level of the anesthesia provider. Perhaps a descriptive, correlational study could be conducted to examine the extent of a relationship between the incidence of post-extubation RNMB and the reporting anesthetist's number of years of experience.

Determining whether or not the experience level of the anesthetist is a factor in the development of RNMB, in any given institution, could help identify further continuing education/training needs and aid in the development of a targeted teaching module for nurse anesthetists. Such concentrated education efforts could help to reduce the incidence of this potentially serious postoperative complication.

Implications for Nurse Anesthesia Practice, Research, and Education

The findings of this study suggest that RNMB is a real potential problem with possible serious adverse patient outcomes. As described earlier, there are specific preventative measures that can be implemented into practice to greatly reduce its occurrence. It, therefore, stands within reason that each anesthesia provider or student of anesthesia should evaluate his/her own practice and develop a *consistent, systematic* routine that employs as many of these preventative measures as practical and possible.

The anesthetist's daily practice may be limited by institutional financial constraints; for example, the more sensitive neuromuscular monitoring equipment (such as ACG equipment) is more expensive than the standard train-of-four nerve stimulators and therefore is usually not available for use. In such instances the provider must utilize the resources that are available.

It is conceivable that, for some practitioners, the problem of RNMB could be deemed as clinically insignificant. It is possible for patients to have some degree of residual blockade, and to exhibit TOF-ratios that place them at increased risk for aspiration, and yet for them to breathe adequately—maintaining adequate gas exchange in transit to the PACU and while in the PACU. Thus, for some patients, the presence of a *small* degree of residual blockade may have no real clinical consequence. They're taken to the PACU and dropped off without incident. However, for some patients—particularly those with active gastroesophageal reflux disease (GERD) or patients who have had procedures done that place them at a higher risk for the development of postoperative nausea and vomiting—such residual blockade places them at an unacceptable risk for aspiration.

It would be very simple to formulate and conduct research to determine the incidence of RNMB within individual institutions. It could only entail the purchase of one or two ACG units and the brief testing of patients immediately upon arrival to the PACU. If practitioners could see that they are bringing their patients to the recovery room with TOF-ratios that have been associated with a higher risk of aspiration, this could help to promote a more aggressive integration of preventative measures into their daily practice.

The findings of this study help to emphasize the importance of educating student anesthetists regarding the measures that need to be taken to best detect and prevent the occurrence of RNMB. Student anesthetists should acquire a general understanding of how to use the various neuromuscular monitoring modalities and should be educated on how to use the neuromuscular monitoring equipment that is available to them at each clinical site. It is imperative that the association between even minor levels of residual blockade and increased risk for aspiration be understood.

Summary/Conclusions

Post-extubation RNMB can result in potentially life-threatening postoperative complications (Bissinger et al., 2000; Eikermann et al., 2003; Eriksson et al., 2006; Sundman et al., 2000). RNMB occurs when the patient has been extubated but still exhibits some degree of residual paralysis from the previously administered paralytic agent; this can happen as a result of an *inadequate dosage* of paralytic-reversal agent, the *timing* of the administration of the reversal agent, and/or because of other possible miscellaneous contributing factors.

Residual paralysis following the administration of paralytic agents may occur more often than one might suspect. Even with the administration of a paralytic reversal agent, the reported incidence of recovery room residual paralysis has ranged from 8% (Murphy et al., 2005) to as high as 20% (Kim et al., 2002).

It appears that the most superior method for detecting the presence of RNMB is by measuring TOF-ratios with the use of ACG (or other similar technology). If the clinician will be assessing the response to nerve stimulation via visual or tactile means, then double-burst or tetanic stimulation are superior methods (over TOF stimulation) for detecting RNMB.

Perhaps the best way to prevent the occurrence of RNMB is by the *routine* monitoring of neuromuscular function and *routine* administration of reversal agents to all patients who have received a paralytic agent—in conjunction with as many clinical tests as possible in order to ensure the patient's clinical readiness for extubation.

The optimal prevention and/or treatment of RNMB requires a thorough understanding of its pathophysiologic mechanisms, a solid working knowledge of the various

neuromuscular monitoring techniques, the consistent application of principles of clinical detection, and a complete familiarization with the various pharmacodynamic and pharmacokinetic properties of neuromuscular blocking agents, reversal agents, and their corresponding anticholinergics. The findings of this study have been shared with the intention of assisting the student of anesthesia in his/her pursuit of such knowledge.

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Part II:

Post-extubation Residual Neuromuscular Blockade: Presentation of Independent Study Research Findings to First-Year Student Anesthetists

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University of North Dakota

Graduate School of Nursing

Grand Forks, North Dakota

May
2007

Introduction

The research findings of my Post-extubation Residual Neuromuscular Blockade independent study were shared with first-year student anesthetists at the University of North Dakota's Nurse Anesthesia Program via oral/powerpoint presentation. In order to evaluate the efficacy of my teaching of certain key principles, pre-tests and post-tests were administered to each student. This packet contains the following:

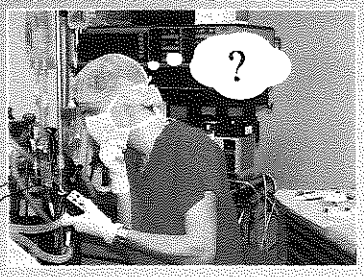
1. Print-out of the powerpoint presentation given to students.
2. Answer key for the pre/post-test that was administered.
3. Analysis/Discussion of the students' pre & post-test scores.

1. Print-out of the Powerpoint Presentation:

(See following pages)

Post-extubation Residual Neuromuscular Blockade

Jacob J. Reinen, SRNA



UND UNIVERSITY OF NORTH DAKOTA

Problem Statement

Post-extubation residual neuromuscular blockade can result in serious post-operative complications:

- impaired airway reflexes
- upper airway obstruction
- decreased hypoxic ventilatory response
- postoperative hypoxia

(Murphy et al., 2005)

Purpose of Inquiry

- **Investigate a clinical problem** with potentially serious adverse patient outcomes.
- **Investigate problem-specific research questions.**
- **Acquire useful and practical knowledge** to be applied in personal practice to avoid this post-operative complication.

Research Questions

1. **Why** does post-extubation residual neuromuscular blockade (RNMB) occur?
2. What is the **reported incidence** of RNMB?
3. What are the **potential consequences** & clinical S&S of RNMB?
4. What are the differences between the various **modalities of neuromuscular blockade monitoring** used to detect RNMB?

Research Questions

5. Is any neuromuscular blockade monitoring **modality the best at preventing RNMB**?
6. **How** is RNMB best **avoided**?
7. **How** is RNMB best **treated** when it does occur?

1. Why does RNMB occur?

We've been trained in . . .

- methods of RNMB detection
- appropriate administration of reversal agents

Why does it still occur?

1. WHY DOES RNMB OCCUR?

- **Inadequate dosage** of reversal agent
- **Timing** of reversal agent administration
- Other **misc. factors**

1. WHY DOES RNMB OCCUR?

Inadequate dosage of reversal:

- **Conservative dosing** . . .
  - "Give only what's needed—you can always give more but you can't take back what's already been given."
  - **Undesirable side effects** of anticholinesterases:
    - CNS (increased alertness to generalized convulsions, coma, respiratory arrest)
    - CV (bradycardia, ↓ cardiac output, ↓ cardiac contractility)
    - EYE (pupillary constriction)
    - RESP (bronchoconstriction, ↑ mucous secretions)
    - GI (bronchoconstriction, ↑ mucous secretions)

(Katzung, 2004)

  - **Too much reversal agent** = potential for making patient **weaker**!
    - Excess Ach at receptor sites (similar to depolarizing block)

(Miller, 2005)

1. Why does RNMB occur?

Inadequate dosage of reversal:

- Less than vigilant neuromuscular monitoring
  - E.g. failing to check TOF *before* and *after* administering reversal.
    - If not checked *before* → have no idea how dense the initial blockade was.
    - If not checked *after* → have no idea if selected reversal dose was adequate.

Question: Can a patient with no response to TOF stimulation be reversed? Should they be?

1. Why does RNMB occur?

Inadequate dosage of reversal

Question: Can a patient with no response to TOF stimulation be reversed?

1-2 twitches with TOF = known level of blockade with predictable recovery

- E.g. 1 of 4 twitches =
  - approx. 30" recovery to TOFR 0.7 with intermediate acting NDNMB.
  - Approx. 60" recovery to TOFR 0.7 with long-acting NDNMB

(Miller, 2005, p.522)

1. Why does RNMB occur?

Timing of administration of reversal

- Reversal given before adequate spontaneous recovery is has been achieved.
- NDNMB can outlast reversal agents.

E.g.

- Neostigmine duration of action = **40-60 min.**
- Rocuronium duration of action = **15-150 min.** (Omoigui, 2001)

1. Why does RNMB occur?

Other misc. factors:

- **acid-base status** of the patient (i.e. both metabolic &respiratory acidosis augment neuromuscular blockade but *only resp. acidosis* prevents adequate antagonism)
- **electrolyte imbalance** (hypokalemia and hypermagnesemia may produce interference with reversal of paralytics)
- **Severe dehydration** (↑ plasma levels of paralytic)
- **various drug interactions** (calcium-channel blockers and aminoglycoside antibiotics)
- **temperature** of the patient (i.e. states of hypothermia) (Miller, pp. 522-23).

2. WHAT IS THE REPORTED INCIDENCE OF RNMB?

Without the administration of a reversal agent, the incidence of RNMB in the recovery room:

- **16%** (Debaene et al., 2003) to **42%** (Baillard et al., 2000)

2. WHAT IS THE REPORTED INCIDENCE OF RNMB?

Even with the administration of a paralytic reversal agent, the reported incidence of recovery room residual paralysis:

- **8%** (Murphy et al., 2005) to as high as **20%** (Kim et al., 2002).

2. What is the reported incidence of RNMB?

Residual paralysis = TOF-ratios < 0.7 (using acceleromyography).

TOF-ratio < 0.9 =

- **Impaired pharyngeal muscle** function
  - ↑ risk of aspiration

TOF-ration ≤ 0.7 =

- **Impairment of carotid body hypoxic ventilatory response**.

(Eriksson)

3. What are the potential consequences of RNMB?

- **Obstruction of the upper airway**
  - poor muscle tone (Eikermann, Groeben, Husing, & Peters, 2003)
- **Impaired airway reflexes**
  - four to five-fold increase in the incidence of misdirected swallowing (Sundman et al., 2000)
    - introduction of saliva directly into the trachea
- **Decreased hypoxic ventilatory response** (Eriksson, Sato, & Severinghaus, 2006)
- **Postoperative hypoxia** (Bissinger, Schimek, & Lenz, 2000)

3. WHAT ARE THE CLINICAL S&S OF RNMB?

- **Labored respirations**
- **SOB**
- Use of **accessory muscles** for breathing
- Little to **no audible air exchange** and/or
- **Paradoxical chest movement** with upper airway obstruction
- **Weak, ineffective cough**
- **Oxygen desaturation**

4. WHAT ARE THE DIFFERENCES BETWEEN THE VARIOUS MODALITIES OF NEUROMUSCULAR BLOCKADE MONITORING USED TO DETECT RNMB?

In general terms, these techniques differ from one another by . . .

- *Frequency*
- *Duration*
- *Pattern*

. . .of the applied electrical stimulus to the nerve (Dorsch & Dorsch, 1999, pp. 850-59).

4. What are the differences between the various modalities of neuromuscular blockade monitoring used to detect RNMB?

- **Visual/Tactile** Evaluation of fade
  - TOF
    - 4 impulses over 2 seconds (2 Hz)
  - Sustained tetanus
    - 50 Hz (i.e. 50 impulses/second)
    - 100 Hz
  - Double-burst
    - two short periods of 50 Hz tetanic stimulations are separated by 750 milliseconds
      - $DBS_{3,3}$
      - $DBS_{3,2}$
- **TOF-ratio determination** with additional equipment
  - mechanomyography (MMG)
  - accelerography (ACG)
  - Piezoeletric film
  - *electromyography (EMG)*

(Dorsch & Dorsch, 1999, pp. 850-59).

5. Is any neuromuscular blockade monitoring modality the best at preventing RNMB?

- **Double-burst** superior to **TOF**

(Divatia, Kulkarni, Kerhalkar, & Kakodkar,1998; Patil & Divatia, 2005).

- TOFR determination with **ACG** superior to **TOF**

(Ansermino, Sanderson, Bevan, & Bevan, 1996; Fuchs-Buder & Eikermann, 2005).

- TOFR determination with **ACG** superior to **Double-burst** or **Tetanus**

(Samet, Capron, Alla, Meistelman, & Fuch-Buder, 2005).

5. Is any neuromuscular blockade monitoring modality the best at preventing RNMB?

Take home message:

- TOFR determination with **ACG best** method.
  - Close relationship between the TOFR determined by ACG as compared to those determined by MMG or EMG (Dorsch & Dorsch, 1999, pp. 856)
- If ACG not available, then **Double-burst** best method.
  - fade is more obvious and more easily detected than with TOF (Morgan & Mikhail, 2002, p. 182).

6. How is RNMB best avoided?

1. ***Routine* monitoring of neuromuscular function** with all patients who have received a paralytic agent.
2. ***Routine* administration of reversal agent** to all patients who have received a paralytic agent.
3. **Combine/utilize as many clinical tests as practical and possible** in order to ensure clinical readiness for extubation.

6. How is RNMB best avoided?

Baillard et al. (2005) study:

- "Between 1994 and 2005 **quantitative measurement** and **reversal** of neuromuscular block in the operating room increased from 2 to 60% and from 6 to 42% respectively ($p < 0.001$)."
- Over this same period of time, the **incidence of RNMB** in their institution decreased from 62 to 3% ($P < 0.001$)

6. How is RNMB best avoided?

Combining multiple clinical tests

- No one clinical test by itself assures the absence of RNMB.
- There are some tests, however, that do better indicate clinical readiness for extubation.

Clinical Parameter	Acceptable Results	Approximate percentage of Receptors Occupied When Response Returns to Normal
Tidal volume	At least 5 ml/kg	80
Train-of-four (TOF)	No palpable fade	70-75
Sustained tetanus @ 50 Hz for 5 seconds	No palpable fade	70
Vital capacity	At least 20 ml/kg	70
Double burst	No palpable fade	60-70

(ADAPTED FROM MILLER, 2005, P. 487).

Clinical Parameter	Acceptable Results	Approximate percentage of Receptors Occupied When Response Returns to Normal
Sustained tetanus @ 100 Hz for 5 seconds	No palpable fade	50
Inspiratory force	At least -40 cm H2O	50
Head lift	Sustained for 5 sec. while supine at 180 degrees.	50
Hand grip	Sustained at level qualitatively similar to preinduction baseline.	50
Sustained bite	Sustained jaw clench on tongue blade	50

(ADAPTED FROM MILLER, 2005, P. 487).

6. How is RNMB best avoided?

According to Miller (2005, p. 486):

"It is **not known what proportion of receptors must be available** or how sensitive a test must be to ensure adequate muscle strength to overcome airway obstruction and permit effective coughing and to be free of visual disturbances."

It logically follows then . . .

Best to **use as many clinical tests as practically possible** to best ensure the patient meets extubation criteria.

6. How is RNMB best avoided?

TAKE HOME . . .

- ***Routine* monitoring of neuromuscular function** with all patients who have received a paralytic agent.
- ***Routine* administration of reversal agent** to all patients who have received a paralytic agent.
- **Combine/utilize as many clinical tests as practical and possible** in order to ensure clinical readiness for extubation.

7. How is RNMB best treated when it does occur?

Table 1. Dosing & Pharmacokinetics of Reversal Agents & Their Corresponding Anticholinergics (Morgan & Mikhail, 2002, p. 204; Omoigui, 2001)

Drug	Dose	Onset	Peak	Duration
Edrophonium	0.5-1.0 mg/kg (Max. 40 mg)	30-60 sec.	1-5 min.	5-20 min.
Atropine	0.014 mg/mg Edro.	45-60 sec.	2 min.	1-2 hrs.
Neostigmine	0.04-0.08 mg/kg **(Max. 5 mg)**	< 3 min.	3-14 min.	40-60 min.
Glycopyrrolate	0.2 mg/mg of Neo.	< 1 min.	5 min.	2-3 hrs.
Pyridostimine	0.1-0.4 mg/kg (Max. 30 mg)	2-5 min.	< 15 min.	90 min.
Glycopyrrolate	0.05mg/mg Pyrido.	< 1 min.	5 min.	2-3 hrs.

EDROPHONIUM

- QUICKEST ONSET, SHORTEST TIME TO PEAK EFFECT, AND THE SHORTEST DURATION.
- GOOD CHOICE FOR REVERSING PATIENTS IN ACUTE DISTRESS (REMEMBER—SHORTEST DURATION!)
- MAY NOT BE AS EFFECTIVE AS NEOSTIGMINE FOR REVERSING A DENSE NEUROMUSCULAR BLOCK.
- MUSCARINIC EFFECTS ARE NOT AS PRONOUNCED AS NEOSTIGMINE'S.

7. How is RNMB best treated when it does occur?

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Glycopyrrolate	0.05mg/mg Pyrido.	< 1 min.	5 min.	2-3 hrs.

NEOSTIGMINE

- INTERMEDIATE ONSET, PEAK, AND DURATION OF ACTION.
- PATIENTS AT EXTREMES OF AGE ARE PRONE TO BE MORE SENSITIVE TO ITS EFFECTS
  - FASTER ONSET, NEED FOR DOSE REDUCTION, PROLONGED DURATION OF ACTION IN GERIATRIC PTS.
- KNOWN TO CROSS PLACENTA AND CAUSE FETAL BRADYCARDIA.
  - ATROPINE BETTER CHOICE FOR ANTICHOLINERGIC.

7. How is RNMB best treated when it does occur?

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Glycopyrrolate	0.05mg/mg Pyrido.	< 1 min.	5 min.	2-3 hrs.

PYRIDOSTIGMINE

- MOST DELAYED ONSET OF ACTION, THE LONGEST TIME TO PEAK EFFECT, AND THE LONGEST DURATION OF ACTION.
- ONE-FIFTH AS POTENT AS NEOSTIGMINE → REQUIRES HIGHER DOSES.
- ENSURES BETTER POSTOPERATIVE COVERAGE--MINIMIZING THE CHANCES OF RNMB LATER IN RECOVERY.

(MORGAN & MIKHAIL, 2002, P. 205)

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2. Pre/Post-Test Answer Key:

(See following pages)

Residual Neuromuscular Blockade Post-Test

(Circle the one correct/best answer for each question)

1. **Administering excessive amounts of a paralytic reversal agent may have the opposite effect and may actually render the patient *weaker*. TRUE or FALSE?**

   A. True
   B. False

2. **All of the following factors may interfere with the reversal of neuromuscular blockers—contributing to a state of deepened paralysis—EXCEPT:**

   A. Respiratory acidosis.
   B. Hypermagnesemia.
   C. Concomitant administration of an aminoglycoside antibiotic (e.g. Gentamicin).
   D. Hyperthermia.

3. **Select the best answer to the following question: Can a patient with *no response* to train-of-four stimulation be reversed with an anticholinesterase?**

   A. No. Anticholinesterases will have no effect until the patient has at least partially recovered from the paralytic dose and exhibits at least one twitch to train-of-four stimulation.
   B. Yes, but only if both edrophonium (quick onset, short duration of action) and neostigmine (intermediate onset, intermediate duration of action) are co-administered at high doses.
   C. Yes, this is possible but not recommended. This is because you don't know how densely blocked the patient was to begin with; therefore, this places the patient at a higher risk for recurarization to occur later in the recovery unit as the reversal agent begins to wear off.
   D. None of the above.

4. **Once the patient's train-of-four-ratio (TOFR) exceeds 0.5, normal pharyngeal muscle tone has been restored. TRUE or FALSE?**

   A. True
   B. False

5. **All of the following are potential consequences of residual neuromuscular blockade (RNMB) EXCEPT:**

   A. Upper airway obstruction.
   B. Impaired airway reflexes.
   C. Decreased carotid body hypoxic ventilatory response.
   D. *All* of the above listed items are potential consequences of RNMB.

6. **All of the following methods of neuromuscular blockade monitoring can be used to determine train-of-four-ratios EXCEPT:**

   A. Mechanomyography (MMG).
   B. Accelerography (ACG).
   C. Double-burst$_{3,2}$ stimulation.
   D. Piezoelectric film.

7. **Place the following methods of neuromuscular blockade monitoring in the appropriate order—from the method that is the *most sensitive* at detecting residual paralysis to the method that is the *least sensitive*:**

   A. Train-of-four ratio (TOFR) determination with accelerography (ACG), Double-burst stimulation, Train-of-four (TOF) count.
   B. Double-burst stimulation, TOFR determination with ACG, TOF count.
   C. TOF count, Double-burst stimulation, TOFR determination with ACG.
   D. TOFR determination with ACG, TOF count, Double-burst stimulation.

8. **A patient can exhibit tidal volumes of 5 ml/kg, sustained tetanus at 50 Hz for 5 seconds, and a vital capacity of 20 ml/kg and yet still can have 70% of his/her acetylcholine receptors at the neuromuscular junction occupied/blocked by a paralytic agent. TRUE or FALSE?**

   A. True
   B. False

9. **The patient can exhibit a sustained head lift for 5 seconds and a sustained hand grip and yet still can have 70% of his/her acetylcholine receptors at the neuromuscular junction occupied/blocked by a paralytic agent. TRUE or FALSE?**

   A. True
   B. False

10. **Neostigmine has been known to cross the placenta and cause fetal bradycardia. Which anticholinergic agent would be best to co-administer with neostigmine to the pregnant patient and why?**

    A. Glycopyrrolate because of its high water-solubility.
    B. Glycopyrrolate because of its high lipid-solubility.
    C. Atropine because of its high water-solubility.
    D. Atropine because of its high lipid-solubility.

3. Analysis/Discussion of Pre & Post-Test Scores:

Scores

The first-year student anesthetists' pre- & post-test scores were as follows:

Table 1. Question-by-question Breakdown of Student Performance

Pre-test			Post-test		
Question	**# of students with correct answer**	**% students with correct answer**	**Question**	**# of students with correct answer**	**% students with correct answer**
1	10	91	**1**	11	100
2	4	36	**2**	9	82
3	4	36	**3**	10	91
4	10	91	**4**	11	100
5	10	91	**5**	11	100
6	2	18	**6**	11	100
7	6	55	**7**	9	82
8	10	91	**8**	11	100
9	3	27	**9**	8	73
10	4	36	**10**	11	100

Table 2. Overall Test Scores

Pre-test scores (%)		Post-test scores (%)	
60		60	
70		80	
50		80	
80		100	
60		100	
40		100	
50		100	
80		100	
40		100	
60		100	
40		100	
Overall Average	57.3%	**Overall Average**	92.7%

(Discussion on next page).

Discussion

As is the case with any *teaching* project, the goal, of course, is to cover material that is not already known by the majority of the students. Hence, the ideal set of pre-test scores should be low—indicating a general knowledge deficit. This certainly was the case with the pre-test that was given to the first-year anesthesia students; test scores were low. Students did very poorly on 6 out of the 10 questions with only 18 to 55 % of the students getting these questions correct. Test scores ranged from 40% to 80 % with an overall average of 57.3%.

There was a significant improvement in post-test scores. Test scores ranged from 60% to 100% with 8 of the 11 students scoring 100%. The overall post-test average was 92.7% (a 62 % improvement in the overall average test score). These scores certainly indicate a more solid understanding of the tested key concepts.