Postoperative Residual Neuromuscular Block: New Aspects of Detection and Management

Essay

Submitted for Partial Fulfillment of
Master Degree in Anesthesiology

By

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2010

Acknowledgement

First of all, thanks to ALLAH*, to whom I owe any success in achieving any work in my life.*

Words can never express my gratitude and thanks to **Professor Gihan Seif El Nasr Mohamed,** *Professor of Anesthesiology and intensive care, Faculty of Medicine, Ain Shams University. I owe her very much for her encouragement, support, and valuable advices throughout the whole work.*

Also I would like to express my gratitude and thanks to doctor, **Assistant Professor Osama Ahmad Galal El-Masry** *of Anesthesiology and Intensive Care, Faculty of Medicine, Ain Shams University, for his kind help meticulous supervision, continuous support and guidance throughout this work.*

Also I am deeply grateful to **Doctor Tarek Mohamed Ashoor** *Lecturer of Anesthesiology and Intensive Care, Faculty of Medicine, Ain Shams University, for his great support, valuable time, careful supervision and continuous advice throughout the whole work.*

Finally I wish to thank all members of my family, my colleagues, and any member who shared in this modest piece of work for their cooperation.

Shaimaa

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List of Abbreviations

ACh	*Acetylcholine.*
AChRs	*Acetylcholine receptors.*
AMG	*Acceleromyography.*
ANH	*Acute normovolaemic haemodilution.*
AP	*Adductor pollicis muscle.*
CMG	*Compressomyography.*
DBS	*Double burst stimulation.*
DMD	*Duchenne muscular dystrophy.*
EMG	*Electromyography.*
KMG	*Kinomyography.*
LEMS	*Lambert Eaton myasthenic syndrome.*
MEP	*Motor end plate.*
MG	*Myasthenia gravis.*
MH	*Malignant hyperthermia.*
MMG	*Mechanomyography.*
nAChRs	*Nicotinic acetylcholine receptors.*
NMB	*Neuromuscular block.*
NMBAs	*Neuromuscular blocking agents.*
NMJ	*Neuromuscular junction.*
PACU	*Post-operative care unit.*
PChE	*Plasma cholinesterase.*
PMG	*Phonomyography.*
PTC	*Post-tetanic count.*
TOF	*Train of four.*

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Introduction

Post-operative residual neuromuscular block is still a clinical problem despite the use of intermediate duration neuromuscular blocking drugs and their routine antagonism. Suboptimal antagonism, relatively short procedures and a short interval between antagonism of neuromuscular block and extubation need to be reinforced during postgraduate training and departmental quality assurance ***(Mc Caul et al., 2002)*.**

After a single intubating dose of intermediate-duration muscle relaxant with no reversal, residual paralysis is common, even more than two hours after the administration of muscle relaxant. Quantitative measurement of neuromuscular transmission is the only recommended method to diagnose residual neuromuscular block ***(Dabaene et al., 2003)***.

When neuromuscular blocking agents are monitored in the operating room, the dose of the neuromuscular agents and the incidence of residual neuromuscular block decrease. In addition, reversal of neuromuscular blocking agents was best used when combined with neuromuscular monitoring ***(Billard et al., 2005)***.

It is time to move from discussion to action and introduce objective neuromuscular monitoring in all operating rooms, not just those occupied by researchers of muscle relaxants. It is believed that objective neuromuscular monitoring is an evidence-based practice and should consequently be used whenever a non-depolarizing neuromuscular blocking agent is used, such

monitoring is non invasive and has little risk and there are strong reasons to believe that its use can improve patient outcome ***(Eriksson, 2003).***

Impaired inspiratory flow and upper air way obstruction occur at train of four ratio 0.83 ***(Eikermann et al., 2003)***, pharyngeal function and air way protection are impaired at train of four 0.9 in awake volunteers ***(Sundman et al., 2000)***, furthermore, hypoxic ventilatory response is reduced by approximately 30% in awake volunteers with a train of four ratio 0.7 ***(Eriksson et al., 1993).*** These findings suggest that removal of an endotracheal tube in the presence of minimal levels of residual neuromuscular block can potentially contribute to adverse pulmonary outcome ***(Murphys et al., 2005).***

Evidence of incomplete neuromuscular recovery in the post-anesthetic care unit was commonly detected in patient monitored with conventional peripheral nerve stimulator intra-operatively. In contrast, train of four ratio of 0.9 or less were rarely observed in subjects randomized to acceleromyographic monitoring. Furthermore, the risk of developing hypoxic episodes and air way obstruction during recovery from anesthesia were reduced significantly by the use of acceleromyography. To exclude with certainty the possibility of residual paresis and reduce associated adverse respiratory events, clinicians should use quantitative neuromuscular monitoring ***(Murphys et al., 2008).***

Post-operative residual paralysis is less frequent in outpatient than in inpatient probably because use of short acting neuromuscular blocking agents. Qualitative

neuromuscular transmission monitoring, pharmacological reversal and clinical tests did not adequately predict residual neuromuscular block, only quantitative neuromuscular transmission monitoring might prevent residual paralysis ***(Cammu et al., 2006).***

Minimal residual neuromuscular block in the awake state, in the absence of anesthesia, and to a degree insufficient to evoke respiratory symptoms markedly increase upper airway collapsibility and impaired genioglossus muscle compensatory response to pharyngeal negative pressure challenge. Increased upper airway collapsibility due to residual neuromuscular blockade is likely to put a patient at risk during recovery, particularly in the presence of airway challenge ***(Hebstreit et al., 2009).***

After repetitive administration of neuromuscular blocking agents, even with recovery of train of four ratio to 0.9 or more, the maximum skeletal muscle force can be reduced, and this may be explained by the persistence of neuromuscular transmission failure. The clinician should consider that the post-operative recovery of the train of four ratio to 0.9 does not exclude an impairment of neuromuscular transmission ***(Eikermann et al., 2007).***

The incidence of post-operative weakness is reduced if long acting relaxants are avoided. Several factors influence recovery of neuromuscular activity after the administration of reversal agents. The most important include depth of block at time of reversal, choice and method of administration of relaxant and the dose of reversal agent ***(Beven et al., 1992).***

Aim of Work

This review aims at focusing on the most updated methods of monitoring of neuromuscular transmission and highlighting the dreadful consequences of inadequate muscle relaxant reversal on the postoperative outcome.

Physiology of Neuromuscular Transmission

The neuromuscular junction (NMJ) has a complex cellular and molecular architecture that involves specialized regions to allow sustained release of neurotransmitters at various loads, allowing for safe neurotransmission. It consists of **(Figure 1):**

1- *Presynaptic zone:*

It is the distal part of the motor nerve axon. It is demylinated and more or less encapsulated by Schwann cells which support connection between the nerve and the muscle and promote the survival of the motor neuron ***(Rochen et al., 2001).***

2- *Synaptic cleft:*

It is nearly 50 nm from nerve ending to the muscle membrane. The nerve and muscle are held in tight alignment by protein filaments called basal lamina that span the cleft between the nerve and the plate ***(Fagerlund and Eriksson, 2009).***

3- *Postsynaptic zone:*

It consists of multiple folds located opposite the presynaptic nerve terminal. These primary (shallower) and secondary (deeper) folds of the postsynaptic membrane expand its surface many folds ***(Lichtman et al., 2005)***.

Perijunctional zone, in close proximity to the highly specialized postsynaptic membrane, has higher density of Na^+ channels than other parts of cell membrane making it

more capable of amplifying responses to depolarization. ***(Cohen Cory, 2002).***

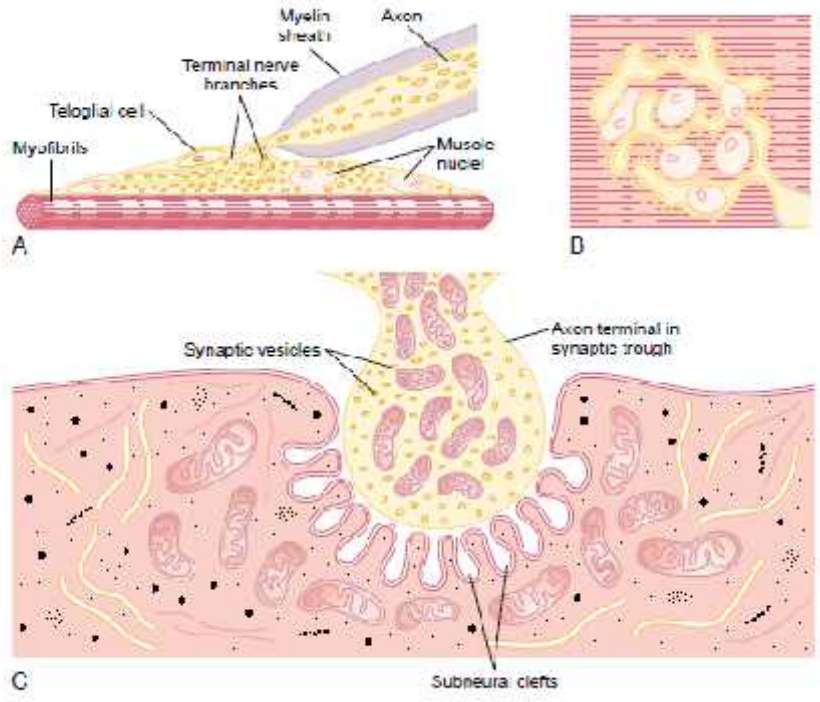

Figure (1): Shows different views of the motor end plate (MEP) A: Longitudinal section of MEP. B: Surface view of MEP. C: Electron micrographic appearance of the contact between a single axon terminal and the muscle fiber membrane ***(Guyton and Hall, 2006).***

Although most adult human muscles, have only one neuromuscular junction per cell, an important exception is some of the cells in extraocular muscles, which are multiply innervated with several NMJs ***(Fraterman et al., 2006).***

● Formation and storage of acetylcholine:

Acetylcholine (ACh) is the primary neurotransmitter in neuromuscular junction. All the ion channels, enzymes, other proteins, molecules, and membrane components, needed by the nerve ending to synthesize, store, and release acetylcholine are made in the cell body and transmitted to the nerve ending by axonal transport ***(Songy et al., 2006).***

Synthesis and release of ACh involves a cycle of events **(Figure 2)**, it is formed in the cytoplasm of the nerve terminal from acetyl coenzyme A and choline in a reaction catalyzed by the soluble enzyme choline acetyltransferase ***(Naguib et al., 2002).***

An energy dependent "transporter" accumulates ACh within vesicles in the terminal button of the nerve axon. Each vesicle contains 5000-10,000 molecules of ACh, together with adenosine triphosphate (ATP), proteoglycan, H^{+}, Mg^{++}, and Ca^{++} ions. The ACh molecules contained in a single vesicle is referred to as a "quantum" of transmitter ***(Naguib et al., 2002).***

● Nerve action potential:

During a nerve action potential, Na^{+} from outside flows across the membrane, and the resulting depolarizing voltage opens Ca^{++} channels, which allows entry of Ca^{++} ions into the nerve terminal and causes Acetylcholine to be released ***(Wang et al., 2004).***

Number of quanta released by stimulated nerve is greatly influenced by the concentration of ionized calcium in extracellular fluid ***(Wang et al., 2004).***

The calcium current persists until the membrane potential is returned to normal by outward fluxes of K^+ from inside the nerve cell. Along with Ca^{++} channels on the nerve terminals are K^+ channels, whose function is to limit the duration of the nerve terminal depolarization by limiting Ca^{++} entry ***(Ryan et al., 2007).***

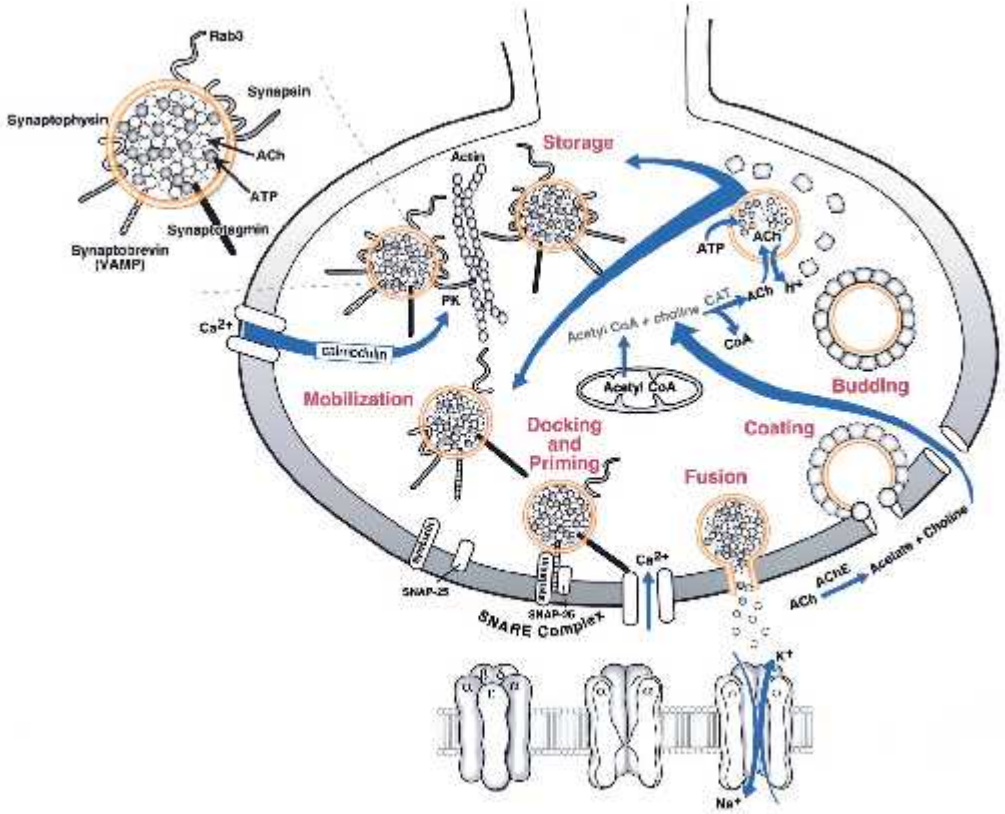

Figure (2): Formation, storage and release of acetylcholine ***(Naguib et al., 2002).***

● Release of Ach:

During an action potential and Ca^{++} influx, neurotransmitter is released, a process called exocytosis.

There are two pools of vesicles that release acetylcholine, readily releasable pool (VP2) which are very close to the nerve membrane, bound to active zones and ordinarily release transmitter. The others are the reserve vesicles (VP1) which are deeper from nerve membrane and firmly tethered to cytoskeleton by many proteins, including actin, synaptin, synaptotagamin, and spectin ***(Sudhof, 2006)***.

The SNARE proteins (soluble N-ethylmaleimide-sensitive attachment protein receptors) are involved in the release of acetylcholine from its vesicles at the active zones. SNAREs include the synaptic vesicle synaptobrevin and the plasmalemma-associated proteins sytaxin and synaptosome-associated protein of 25 kd(SNAP-25) ***(Lang, 2008).***

Syntaxin and SNAP-25 are complexes attached to plasma membrane. After initial contact, the synaptobrevin on the vesicle forms a complex with syntaxin and SNAP-25.Assembly of the complex forces the vesicles close to the underlying nerve terminal membrane (active zone), and the vesicles are then ready for release. Synaptotagmin is the protein on the vesicular membrane that acts as a calcium sensor, localizes the synaptic vesicles to synaptic zones rich in calcium channels, and stabilizes the vesicles in docked state ***(Heidelberger, 2007).***

An action potential in the nerve terminal allows entry of Ca^{++} that with the close proximity of release sites, Ca^{++} channels, and synaptic vesicles with Ca^{++} sensor lead to a