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A Comparative Study between Sugammadex versus Neostigmine as Regards Efficiency of Reversal of Rocuronium and Bleeding Tendency Effect after Septoplasty

Thesis
Submitted for Partial Fulfillment of M.D. Degree in Anesthesiology

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2018

Acknowledgement

First of all, all gratitude is due to ***GOD*** *almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

Really I can hardly find the words to express my gratitude to ***Prof. Dr. Gehan Fouad Kamel Youssef,*** *Professor of Anesthesiology, Intensive Care and pain management, Faculty of Medicine - Ain Shams University, for her supervision, continuous help, encouragement throughout this work and tremendous effort she has done in the meticulous revision of the whole work. It is a great honor to work under her guidance and supervision.*

I would like also to express my sincere appreciation and gratitude to ***Prof. Dr. Mohamed Anwar Abd Elaati Elshafay****, Professor of Anesthesiology, Intensive Care and pain management, Faculty of Medicine - Ain Shams University, for his continuous directions and support throughout the whole work.*

I cannot forget the great help of ***Dr. Amal Hamed Abd Elhamid Rabie****, Lecturer of Anesthesiology, Intensive Care and pain management, Faculty of Medicine - Ain Shams University, for her invaluable efforts , tireless guidance and for her patience and support to get this work into light.*

Words fail to express my love, respect and appreciation to ***my wife*** *for her unlimited help and support.*

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Ayman Gawargusse Awad

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List of Abbreviations

Ach	Acetylcholine
AMG	Acceleromyography
ASA	American society of anesthesiology
CBC	Complete blood count
DBS	Double-burst stimulation
ECG	Electrocardiogram
EMG	Electromyography
HR	Heart rate
Hz	Hertz
IGP	Increased intragastric pressure
IOP	Increased intraocular pressure
KFT	Kidney function tests
LFT	Liver function tests
MAP	Mean arterial pressure
MMG	Mechanomyography
msec	Millisecond
N	Fourth group
NMB	Neuromuscular blockade
NMBDs	Neuromuscular blocking drugs
NMJ	Neuromuscular junction
PACU	Post anesthesia care unit
PMG	Phonomyography
PONV	Post-operative nausea and vomiting
PT	Prothrombin time
PTC	Post-tetanic count
PTT	Partial thromboplastin time

List of Abbreviations (Cont.)

RBS	Random blood sugar
RSI	Rapid sequence induction
S1	First group
S2	Second group
S4	Third group
Sch	Succinylcholine
SD	Standard deviation
SpO2	Peripheral oxygen saturation
SpO2	Peripheral arterial oxygen saturation
SPSS	Statistical Program for Social Science
T1	First twitch
T2	Second twitch
T4	Forth twitch
TOF	Train-of-four
α	Alpha
β	Beta
δ	Delta
ε	Epsilon

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Introduction

Septoplasty is an operative procedure with expected early postoperative respiratory complications and bleeding. These complications can be decreased with appropriate anesthesia methods ***(Karaman et al., 2011).***

Sugammadex, a modified γ-cyclodextrin, has been recently introduced into clinical practice as a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block during general anesthesia ***(Gaszynski et al., 2012).***

Intraoperative deep neuromuscular blockade (NMB) can improve conditions for some surgical procedures. Sugammadex has already proven its reproducible efficacy to reverse NMB induced by rocuronium and vecuronium ***(Martini et al., 2014).***

In the case of neuromuscular blocking drugs and their reversal agents, dosing is of uppermost importance. Few studies addressed the optimal dose of sugammadex after continuous deep neuromuscular blockade. Under dosing sugammadex in this situation can be dangerous and may lead to residual or even re-curarization which will result in significant adverse events ***(Ingrande and Lemmens, 2010).***

Acetylcholinesterase inhibitors such as neostigmine are commonly administered to reverse NMB at the end of surgery and to reduce the risk of residual paralysis and associated adverse respiratory events. However, these agents may provide slow and unpredictable recovery, and are associated

with several unwanted side-effects, both alone and in combination with anticholinergic agents ***(Brull and Murphy, 2010).***

It has been known that with sugammadex some changes in coagulation parameters occurred without documented clinical consequences. There are still controversies about the relation between sugammadex and bleeding ***(Raft et al., 2011).***

Aim of The Study

The purpose of this study was to compare the efficacy of different doses of sugammadex versus neostigmine for rocuronium reversal and its effects on hemostasis and bleeding tendency in septoplasty surgery regarding the reversal time, occurrence of residual paralysis, incidence of adverse events, hemodynamic parameters and effect on coagulation profile.

Chapter One

Neuromuscular Blockers and Antagonists

Muscle relaxation can be achieved by direct central nervous system depression with volatile inhalation anesthetics or by neural blockade either at the peripheral nerve or with drugs that act at the neuromuscular junction. Neuromuscular blocking drugs (NMBDs) are essential in anesthetic practice to facilitate endotracheal intubation and provide optimum surgical conditions for a variety of procedures ***(Naguib et al., 2002).***

Although volatile anesthetic agents can be used for muscle relaxation, the addition of NMBD significantly reduces the concentration of volatile anesthetics required to provide adequate analgesia and amnesia with rapid postoperative recovery. Neuromuscular blocking drugs have no inherent analgesic or amnestic properties, and their use is contraindicated if artificial ventilation is not possible ***(Naguib et al., 2002).***

Physiology of neuromuscular transmission:

Acetylcholine (Ach), the neurotransmitter at the neuromuscular junction, is released from presynaptic nerve endings on passage of a nerve impulse (an action potential) down the axon to the nerve terminal. The neurotransmitter is synthesized from choline and acetyl coenzyme A by the enzyme choline acetyltransferase and stored in vesicles in the nerve terminal. The action potential depolarizes the nerve

terminal to release the neurotransmitter; entry of Ca^{2+} ions into the nerve terminal is a necessary part of this process, promoting further acetylcholine release. On the arrival of an action potential, the storage vesicles are transferred to the active zones on the edge of the axonal membrane, where they fuse with the terminal wall to release the acetylcholine ***(Willcockson et al., 2002).***

The active sites of release are aligned directly opposite the acetylcholine receptors on the junctional folds of the postsynaptic membrane, lying on the muscle surface. The junctional cleft, the gap between the nerve terminal and the muscle membrane, has a width of only 60 nm. It contains the enzyme acetylcholinesterase, which is responsible for the ultimate breakdown of acetylcholine ***(Paul et al., 2002).***

Each receptor consists of five subunits, two of which, the alpha (α), are identical. The other three, slightly larger subunits, are the beta (β), delta (δ) and epsilon (ε) (figure 3). Each of the α subunits carries a single acetylcholine binding region on its extracellular surface. Activation of the receptor requires both α sites to be occupied, producing a structural change in the receptor complex ***(Paul et al., 2002).***

After Ach binds to the active site of both α subunits, the receptor undergoes a conformational change, opening a central channel within the five subunits. The structure of this channel permits the transit of Na^{+}, K^{+}, and Ca^{2+} ions while blocking anions and larger cations. When non-depolarizing NMBDs bind to either α subunit, the channels cannot open, and a neuromuscular blockade occurs ***(Martyn, 1995).***

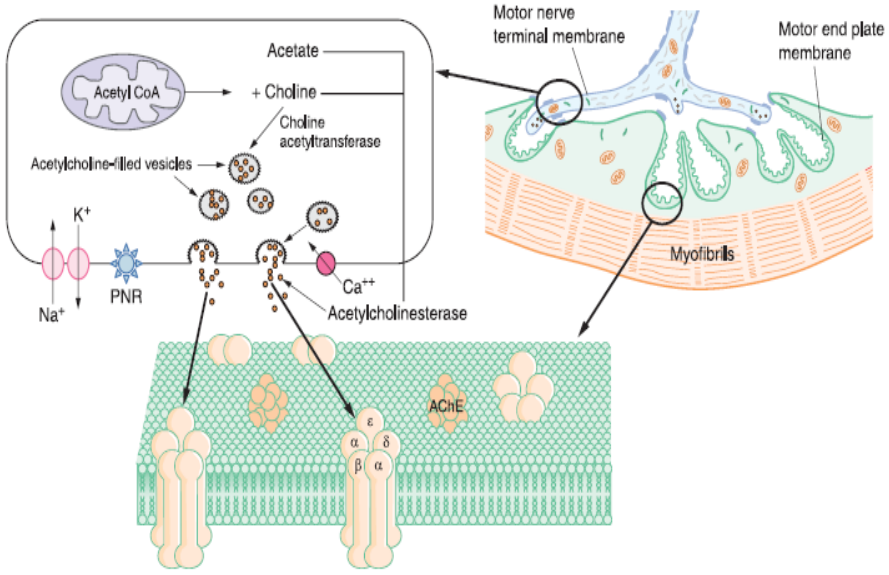

Figure 1: Structure of acetylcholine receptor within NMJ ***(Pino and Ali, 2008).***

Acetylcholine receptors:

Post-junctional receptors:

Most of the released Ach molecules cross the synaptic clefts, bind to post-junctional receptors, and induce depolarization of the muscle cell through the influx of Na^+ through specific channels, decreasing the membrane potential from –90 to +50 mV. During depolarization, as the membrane potential ~ 0 mV, K^+ channels open and Na^+ channels close to limit the voltage flux to +10 mV. The action potential is self-propagating through a decrease in the adjacent membrane potential of ~ 15 mV, which open Na channels and depolarizes the membrane ***(Katz, 1976).***

Calcium is released from the sarcoplasmic reticulum of the muscle upon depolarization to activate actin–myosin

coupling within myofibrils resulting in contraction. Upon completion of depolarization, the ionic gradient is restored via a Na^+/K^+-dependent adenosine triphosphates (ATPase) to repolarize the membrane, and a refractory period follows during which time depolarization is not possible ***(Katz, 1976).***

Pre-junctional receptors:

The response of muscle contraction is also modulated by pre-junctional receptors of the motor neuron. Ach interacts with pre-junctional nicotinic receptors to augment transmitter release. These receptors are believed to control a sodium-specific ion channel in contrast to the nonspecific cation channels of the post-junctional receptors. Sodium is essential for the synthesis and mobilization of Ach, but it is not directly involved in the release process. Therefore, non-depolarizing NMBDs can bind to these ion channels, decrease the mobilization of Ach, and reduce its release from nerves that are stimulated with high-frequency stimuli. The clinical equivalent is seen in the fade to tetanic and train-of-four (TOF) stimulation ***(Martyn and Richtsfeld, 2006).***

Extrajunctional receptors:

Muscle cells can also exhibit extrajunctional receptors that are embryologic remnants of the muscle cell membrane. In the fetus, these receptors are found throughout the muscle cell membrane. With maturation, extrajunctional receptors become markedly reduced while junctional receptors predominate. They are less sensitive to stimulation by Ach but have channels that remain open