"COMPARISON OF HAEMODYNAMIC RESPONSES BETWEEN CLINICAL ASSESSMENT-GUIDED TRACHEAL INTUBATION AND NEUROMUSCULAR BLOCK MONITORING-GUIDED TRACHEAL INTUBATION: ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL STUDY"

By

REG NO.BA0118001

Dissertation

Submitted to the
KLE Academy of Higher Education & Research
(Deemed University) Belagavi, Karnataka
In Partial Fulfillment
of the requirements for the degree of

M. D.
in
ANAESTHESIOLOGY

DEPARTMENT OF ANAESTHESIOLOGY,

JAWAHARLAL NEHRU MEDICAL COLLEGE,

BELAGAVI, KARNATAKA

APRIL - 2021

KLE ACADEMY OF HIGHER EDUCATION AND RESEARCH, BELAGAVI, KARNATAKA

ENDORSEMENT

This is to certify that the dissertation entitled **"COMPARISON OF HAEMODYNAMIC RESPONSES BETWEEN CLINICAL ASSESSMENT-GUIDED TRACHEAL INTUBATION AND NEUROMUSCULAR BLOCK MONITORING-GUIDED TRACHEAL INTUBATION: ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL STUDY"** is a bonafide research work done by **REG NO. BA0118001.**

DR. RAJESH MANE **M.D.DNB**
Professor and Head of the Department,
Department of Anaesthesiology,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi

DR. (Mrs) N.S MAHANSHETTI **MD(paed)**
Principal,
J. N. Medical College,
Nehru Nagar, Belagavi – 10

Date:
Place: Belagavi

PLAGIARISM ACCEPTANCE LETTER

KLE

JAWAHARLAL NEHRU MEDICAL COLLEGE

(Recognized by Medical Council of India, New Delhi)

Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)

Nehru Nagar, Belagavi- 590 010, Karnataka, INDIA

0831 - 2471350 0831 - 2470759 www.jnmc.edu principal@jnmc.edu

Ref No: MDC/PG/ Date: 08-09-2020

ACCEPTANCE LETTER

The softcopy of thesis entitled: **"COMPARISON OF HAEMODYNAMIC RESPONSES BETWEEN CLINICAL ASSESSMENT-GUIDED TRACHEAL INTUBATION AND NEUROMUSCULAR BLOCK MONITORING-GUIDED TRACHEAL INTUBATION: ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL STUDY"** has been submitted for Anti-Plagiarism check through Turnitin software. The scan has been carried out and the scanned output reveals a match percentage of **09%** which is within the acceptable limits of **10%** as per the guidelines given by UGC.

KAHER BELAGAVI J. N. MEDICAL COLLEGE

Dr. (Mrs.) N.S. Mahantashetti.
Chairperson-Antiplagiarism Committee &
Principal,
J. N. Medical College, Belagavi.

To,
Reg. No. BA0118001.
Postgraduate Student,
2018-19 Batch,
Department of Anesthesiology,
J. N. Medical College, Belagavi.

ABBREVIATIONS

AChRs-	Acetyl Choline Receptors	
AMG/ACG	-	Acceleromyography
AP	-	Adductor Pollicis
ASA	-	American Society of Anaesthesiologists
ACE	-	Acetyl cholinesterase
Ach	-	Acetyl choline
BMI	-	Body mass index
CAD	-	Coronary artery disease
Ca^{2+}	-	Calcium
CVS	-	Cardiovascular system
CNS	-	Central nervous system
DMR	-	Depolarizing muscle relaxant
DBP	-	Diastolic blood pressure
EEG	-	Electroencephalography
ED	-	Effective Dose
EMG	-	Electromyography
HR	-	Heart Rate
HTN	-	Hypertension
Hz	-	Hertz
K^{+}	-	Potassium
kDa	-	Kilo daltons
Mg	-	Milligram
Mamps/mA	-	Milli Amperes
mSec/ms	-	Milli second

MAP	-	Mean arterial pressure
MPG	-	Mallampati grading
MMG	-	Mechanomyography
mg/kg	-	Milligram per kilogram
mcg/kg	-	Microgram per kilogram
MEPP	-	Miniature end-plate potentials
Na^+	-	Sodium
nm	-	Nano meter
NDMR	-	Non-Depolarizing Muscle Relaxant
NMB	-	Neuro Muscular Block
NMJ	-	Neuromuscular junction
OO	-	Orbicularis Oculi
PC	-	Personal computer
SBP	-	Systolic blood pressure
SNARE	-	Soluble N-ethylmaleimide-sensitive attachmentprotein receptors
SNAP – 25	-	Synaptosome-associated protein of 25kDa
Sch	-	Succinyl choline
TOF	-	Train of Four
TOFR	-	Train of Four Ratio
Wt	-	Weight

ABSTRACT

Background: The purpose of this study was to compare the haemodynamic responses of tracheal intubation guided via Train of Four (TOF) monitoring and the Clinical assessment.

Method: In this prospective randomized clinical study, 70 adults, ASA -1 and ASA – 2, MPG - 1 and MPG - 2 undergoing elective surgery under general anaesthesia with tracheal intubation were allocated to two groups (n = 35) according to TOF guided (Group T) or Clinical assessment guided (Group C) tracheal intubation. Anaesthesia was induced with propofol 2mg/kg and after standardization of supramaximal stimulus Inj. Vecuronium 0.1 mg/kg was administered. In group T, trachea was intubated after TOF ratio became zero in Adductor Pollicis muscle, whereas in group C, trachea was intubated after clinical assessment of jaw muscle relaxation, airway tone and ease of ventilation was done. Changes in heart rate, mean arterial pressure, mean systolic blood pressure, mean diastolic blood pressure were recorded along with intubating conditions which were scored on a Kreig*et al* score. Results wereanalysed by Paired-t test and chi square test.

Results: Heart rate, mean arterial pressure, mean systolic blood pressure and mean diastolic blood pressure were observed to be significantly higher in Group C compared to Group T ($P<0.05$). Excellent and good intubating conditions were found in both the groups. However, 91.43% excellent intubating conditions were found in Group T compared to 57.14% in Group C.

Conclusion: Neuromuscular block monitoring of Adductor Pollicis muscle based endotracheal intubation can be a suitable, non-pharmacological method in assessing

appropriate time of intubation, providing excellent intubating conditions hence significant attenuation of haemodynamic response to laryngoscopy and tracheal intubation.

Keywords: Haemodynamic, intubating conditions, Neuromuscular blockade monitoring, Tracheal intubation, Train of four, Adductor Pollicis.

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

LIST OF PHOTOGRAPHS

INTRODUCTION

General Anaesthesia being the most common anaesthetic technique used in the anaesthesia practice, securing and maintaining a patent airway is a vital aspect of providing adequate oxygenation and ventilation. [1] Hence, it is very important for an anaesthesiologist to secure airway and endo tracheal tube intubation is the best and safe method to prevent aspiration.[2] Intubation is done by direct laryngoscopy and this is known to cause increased sympathetic response, which is exaggerated during inadequate or difficult intubating conditions.

Intubating conditions can be assessed clinically or using Neuro muscular monitoring, which is the best non-invasive technique. In clinical practice Neuro muscular block is monitored by assessing the response of Adductor Pollicis after ulnar nerve stimulation or Orbicularis oculi after facial nerve stimulation using neuro muscular monitor – Train of Four (TOF). Complete relaxation of the jaw, laryngeal, vocal cord, pharyngeal muscles and diaphragm is needed for excellent intubating conditions in order to reduce the risk of Vocal cord and laryngeal trauma which later can cause laryngeal oedema. Response to intubation is seen by both muscular block and the depth of anaesthesia, and is possible to intubate a patient with incomplete paralysis if a sufficient depth of anaesthesia is present.

Intubating conditions can be improved by using combined dose of narcotics and neuromuscular blocking agents. If only narcotics are used then the required dose for acceptable intubating conditions will produce significant hypotension. It has been demonstrated that poor intubating conditions are associated with an increased

incidence of hoarseness of voice and vocal cord damage. Hence, giving neuromuscular blocking agents improved the quality of intubating conditions.

Strong stressor stimuli during direct laryngoscopy and endotracheal intubation often lead to unintended sympathetic nervous system stimulation producing haemodynamic changes which are usually transient and do not result in significant adverse effects.[3] In patients with CAD, hypertension(HTN) or intracranial pathology, exaggerated haemodynamic parameters may lead to cardiac arrest or secondary brain damage for which many drugs are successfully used to blunt the stressor response.[4] However, administration of more drugs can cause change in haemodynamic effects or increase the depth of anaesthesia. Hence, a non-pharmacological measure is preferred to reduce the response.

Type and depth of general anaesthesia, age, concomitant or systemic diseases like Diabetes Mellitus, HTN and any drugs used along with the duration of laryngoscopy and intubation also the ease of procedure effect the changes in hemodynamic responses.[4,5,6] Therefore, adequate neuromuscular block with neuromuscular blocking drugs is very vital in attenuation of the sympathetic response.

A previous study showed that if a neuromuscular block monitoring is used to assess the time of intubation, more time was required between the administration of the muscle relaxant and intubation and it also improved the intubating conditions and reduced the haemodynamic responses.[7]

Hence a study was under taken to assess the complete neuromuscular blockade through neuromuscular block monitoring device (Train of Four – Guard

acceleromyographic response) guiding in attenuation of haemodynamic responses and proper timing of intubation.

This study "Comparison Of Haemodynamic Responses Between Clinical Assessment-Guided Tracheal Intubation And Neuromuscular Block Monitoring-Guided Tracheal Intubation" was done in "KLES Dr. Prabhakar kore hospital and medical research center". This would determine which method of assessment is a better predictor for intubating condition, to attenuate the haemodynamic responses.

OBJECTIVES

1. To compare the haemodynamic responses in response to tracheal intubation directed by either clinical judgement or neuromuscular monitoring with the aid of train-of-four assessment.

2. Comparison of intubating conditions in both the groups.

REVIEW OF LITERATURE

In 18th century tubes were passed down the trachea during resuscitation from drowning and were done blindly but were not used for delivery of anaesthetic agents. In early part of 20th century endotracheal anaesthesia was introduced to the clinical practice and metal tubes and chloroform were used for endotracheal intubation before Sir Ivan Magill and Stanley Rowbotham actually introduced endotracheal intubation during World War 1.[8]

Premedication, regional anaesthesia and general anaesthesia were introduced as a concept of balanced anaesthesia by John S Lundy in 1926. "Analgesia, relaxation and narcosis are the basic three components of anaesthesia given by Rees and Gray of Liverpool." [9] Most of the intubations were done using inhalational agents which had severe side effects like bronchospasm and laryngospasm because of inadequate depth due to lack of relaxants. Further making the patient sufficiently deep to obtain intubating conditions led to haemodynamic disturbances because of higher concentration of inhalational agents that were used. A major development happened in 1942 by introduction of d-tubocurarine by Harrold Griffith which helped in jaw relaxation to facilitate endotracheal intubation. This soon led to invention of famous Macintosh laryngoscope in 1943 by R.R. Macintosh.

Nerve stimulator to monitor neuromuscular block was first described by Christie and Churchill-Davidson in 1958[10] but it was in 1970 when Ali *et al* described the (TOF) Train of Four pattern of stimulation which then was widely accepted in clinical practice.

Day NS and Dretchen KL studied characterization of Train of four responses in fast and slow muscle using, d–tubocurarine, pancuronium and vecuronium in 1983. They concluded that morphology of Neuro muscular junction is responsible for the observed difference in sensitivity of a given muscle to muscle relaxant.[14]

Smith CE, studied different effects of pancuronium on masseter and Adductor Pollicis muscles in humans in 1989. They said Adductor Pollicis is made up of slow oxidative type of fibres which are more sensitive to nondepolarizing muscle relaxant. They concluded that after administration of pancuronium, NMB was earlier and better at the masseter compared to Adductor Pollicis. This suggests that return of Adductor Pollicis function may not imply complete masseter muscle recovery.[15]

Donati F in 1990 demonstrated the NMB among diaphragm, Orbicularis Oculi and Adductor Pollicis. They anaesthetised adult patients with alfentanil, propofol and Vecuronium 0.04 or 0.07mg/kg and applied Train of four stimulation to phrenic, facial and ulnar nerves. They observed that the onset time of Adductor Pollicis response to ulnar nerve stimulation was prolonged than that of the diaphragm by phrenic nerve and Orbicularis Oculi response to facial nerve stimulation was similar to that of the diaphragm. Hence, they concluded that Orbicular oculi would be a better predictor of neuromuscular block of diaphragm than the Adductor Pollicis.[16]

Meistelman C in 1992 demonstrated that with Rocuronium (ORD 9426), at a dose of 0.25 and 0.5mg/kg in humans, neuromuscular blockade at adductor muscles of larynx has faster onset and recovery but the blockade is less profound than that at the Adductor Pollicis. These findings are similar to the observations of a similar study with vecuronium, except the onset was faster at both the muscles.[17]

A study by Dan Ungureanu and Jeanne Frossard in 1993 demonstrated that Orbicularis Oculi muscles are better predictors of the onset of atracurium block at the Vocal Cords than the Adductor Pollicis. Their study was to compare the better visual predictors using Train of four stimulation at Adductor Pollicis or Orbicularis Oculi muscles in atracurium administered neuromuscular block at the laryngeal adductor muscles. They applied Train of four stimulation to the facial, recurrent laryngeal and ulnar nerves and measured the pressure changes in the tracheal tube cuff placed between the Vocal Cords. The responses were evaluated visually by two observers using Train of four stimulator detecting onset and completion of the block. In patients administered with atracurium 0.5 mg/kg, laryngeal and Orbicularis Oculi responses were abolished faster than the Adductor Pollicis muscle with significant correlation ($r = 0.94$; $p<0.001$) between onset time among laryngeal adductors and Orbicularis Oculi compared to laryngeal and thumb muscles. Hence, they concluded that on administration of atracurium, laryngeal adductors and Orbicularis Oculi blocks have similar intensities and time coursed.[18]

Donati F studied the pharmacokinetic and pharmacodynamics factors of the muscle relaxants in 1994. They concluded that the differences in circulation time and muscle blood flow causes faster onset of neuromuscular block at Orbicularis Oculi than at Adductor Pollicis. Muscles which are closer to central circulation like the Orbicularis Oculi or the diaphragm have relatively greater perfusion and tend to be paralyzed more rapidly than the more peripheral muscle like Adductor Pollicis.[19]

Koscielnaiak Nielsen ZJ, VibyMogensen J in 1996, evaluated the duration of tracheal intubation by monitoring the loss of response to Train of Four stimulation of Orbicularis Oculi, Adductor Pollicis or using a stopwatch in 120 patients on

administration of Vecuronium 0.1mg/kg. They intubated trachea on abolition of the visual response to Train of Four stimulation of the Orbicularis Oculi muscle to facial nerve stimulation or the Adductor Pollicis to ulnar nerve stimulation or after waiting 3 min or 4 mins. They observed that the loss of response of Orbicularis Oculi was significantly earlier than the Adductor Pollicis ($p = 0.021$). However, in Orbicularis Oculi group, the intubating conditions were poor in four patients (14%) whereas, none in Adductor Pollicis group and only one in stopwatch group. Hence, loss of visual response of Orbicularis Oculi did not guarantee good or satisfying intubating conditions and in fit adult patients it is as good to wait 3 mins after administration of vecuronium 0.1 mg/kg before tracheal intubation, instead of using a nerve stimulator. [20]

G. Haller in 1998 studied about the tracheal intubating conditions on determining the intubation time by onset of neuromuscular block in Adductor Pollicis (AP) or Orbicularis Oculi muscles (OO). The intubating conditions in AP were excellent in 95%, while in OO they were excellent in 65% and poor in 15%. They concluded that determining the appropriate tracheal intubation time and conditions by monitoring neuromuscular activity using Train of Four in patients administered with rocuronium is more significant in Adductor Pollicis than Orbicularis Oculi.[21]

Frederique Le Corre in 1999 conducted visual estimation of onset time at Orbicularis Oculi, after administration of muscle relaxants i.e., Atracurium, Mivacurium, Rocuronium, Succinylcholine and Vecuronium. They concluded that difference in onset time of muscle relaxants observed at Adductor Pollicis were similar at Orbicularis Oculi. The visual response at the Orbicularis Oculi correctly predicted in more than 90% cases for adequate intubating conditions.[22]

H.J Lee in 2009 did comparison of Adductor Pollicis, Orbicularis Oculi and corrugator supercilia as indicators of adequate muscle relaxation for tracheal intubation. Onset time in Orbicularis Oculi was shorter than in Adductor Pollicis ($p < 0.001$), but was associated with poor intubating conditions. They concluded that on Rocuronium administration, Adductor Pollicis block monitoring frequently provided excellent intubating conditions but had long delay before intubation while Orbicularis Oculi monitoring allowed faster intubation with acceptable incidence of inadequate intubating conditions. They had used TOF – Watch acceleromyograph, neuro muscular monitor for knowing ideal time to intubate the patient.[23]

Laryngoscopy and endotracheal intubation for the induction of general anaesthesia are generally done based on the clinical assessment after a standard duration according to the onset of neuromuscular blocking agent used. Smith I, has concluded that the time required for adequate onset of neuromuscular block by Vecuronium is more than the time assessed clinically in their study comparing time required for intubating conditions in between Vecuronium and Rocuronium by clinical criteria.[11]

Very few clinical studies have been conducted on attenuation of stressor responses by nonpharmacological techniques on laryngoscopy and tracheal intubation. Nandi R in their study has compared the haemodynamic changes during laryngoscopy and tracheal intubation guided by time based clinical assessment and neuromuscular block monitoring. Changes in haemodynamic parameters were significantly low in neuromuscular block monitoring compared to clinical assessment hence concluding significance of complete paralysis of laryngeal muscles detected by neuromuscular block monitoring in attenuation of stressor responses.[12]

BASIC SCIENCES

The term trachea is derived from Greek word meaning “Rough Vessel”. Development of endotracheal intubation technique was stimulated by the need for safe anaesthesia during operations on head and neck. “C. Kite of Gravesend” described oral and nasal intubation for resuscitation of apparently drowned patients in 1788.

“William McEwen of Glasgow” first performed endotracheal intubation in 1880, as is known today. “Franz Kuhn of Kassel (1866 – 1929) in 1901”, extended the technique by using flexible metal tube introduced on a curved guide through the mouth. A year later he described nasotracheal intubation.

“Alfred Kirstein (1863 – 1922) of Berlin” and “Gustav Killian (1860 – 1921) of Freiburg”, the original bronchoscopist, pioneered direct laryngoscopy in 1895 and 1912 respectively.

A pilot balloon was described in “1893 by Victor Eisenmenger (1864 – 1932)”. Before the days of muscle relaxant blind nasal intubations was popular because it was quicker than oral intubation under direct vision and deep inhalation anaesthesia. The use of muscle relaxant to facilitate intubation was pioneered by Bourne.

The first laryngoscope prototype was introduced by “Chevalier Jackson (1865 – 1958)”. It was later modified by “Magill, Paluel. J. Flagg (1886 – 1970)” of New York, “Miller and Robert Macintosh of Oxford in 1897”.

Neuro Muscular Junction[24]

"Otto Loewi in 1921" identified Acetyl choline as chemical neurotransmitter. "Gopfert and Schaefer in 1938" described the current concepts about neuro muscular transmission. They said stimulation of a motor nerve of a curarized muscle produced a transient electro negativity in the region of synaptic button.

Dale *et al* said acetyl choline was released at nerve terminal during activity and Cowen *et al* said that addition of Acetyl choline to a bath of nerve muscle preparation causes a slow monophasic potential similar to that seen with nerve stimulation, served as the heralded start of our understanding of neuromuscular transmission in 1936.

Doyere in 1840 described the first vertebrate Neuro muscular junction. "Liddel and Sherrington" described the term Motor unit in 1925. Current concepts of Neuro Muscular junction are attributed to Couteaux for his extensive work over 40 yrs.

Neuro Muscular Monitor[25]

Use of nerve stimulator to monitor neuromuscular block was first described by "Christie and Churchill – Davidson in 1958" but it was the Train of Four pattern of stimulation described by "Ali *et al* in 1970", this equipment came into regular practice.

Muscle Relaxants

The arrow poison used for hunting by the native people of South America has been known for centuries. "Benjamin Brodie (1783 – 1862)" and "Edward Nathaniel

Brancroft (1772 – 1842)" showed that the poison paralyzed the respiratory muscles and that an animal given curare could be kept alive if ventilated. Claude Bernad's study of effects of curare on neuromuscular transmission described the site of action of curare as the NMJ.

Neuromuscular Anatomy and Physiology [26]

Neuromuscular Transmission

Acetylcholine (Ach) plays a major part in neuromuscular transmission. It is synthesized by nerve and stored in vesicles. On nerve excitation, vesicles migrate to neuromuscular membrane, rupture and releases Ach into the Neuromuscular Junction (NMJ). Acetylcholine receptors (AChRs) present in muscle end plate open their Na^+ ion channels in response to depolarization. This end plate potential is sustained alongside the muscle membrane to initiate muscle contraction. Then the Ach disengages from the receptors and is then broken down by the acetyl cholinesterase (ACE) enzyme, which is also present in the junction (Fig 1,4).

Drugs such as the Depolarizing muscle relaxants or nicotine and carbachol (which is an artificial preparation of Ach and can't be broken up by the ACE), have effect on the AChRs mimicking Ach and causing the end plate to depolarize. Hence called agonists of the receptor.Nondepolarizing muscle relaxants (NDMRs) act on AChRs to prevent binding of Ach to the receptors, hence preventing depolarization and are known as antagonists of AChRs.

Reversal agents of neuromuscular paralysis (e.g., Neostigmine) inhibits ACE present in the NMJ and hence prevents it from degradation and causes the Ach to

accumulate which then competes with NDMRs and shifts them from the AChRs (i.e., law of mass action) and reverses the effect of NDMRs.

Morphology

The nerve and the muscle are interconnected via a specialized connection called the NMJ, for transferring of chemical messages. All the motor neurons originate from the ventral horn of spinal cord or medulla till the NMJ as large, myelinated axon (Fig 1). On advancing towards the muscle, they branch to communicate with several muscle cells thereby forming a functional group identified as a motor unit. As the nerve extends towards the muscle fibre, it loses myelin and forms an array of terminal branches on the muscle surface which is covered by Schwann cells. This arrangement is the architecture on the synaptic area of muscle membrane. There is a gap of approximately 20nm between nerve and surface of the muscle membrane, known as junctional or synaptic cleft. Basal lamina is the protein filaments which span the cleft between nerve and end plate holding it in tight alignment. The total surface area of the muscle end plate is very large due to deep invaginations of junctional cleft (primary and secondary clefts between muscle membrane) making muscle surface highly corrugated.

NMJs have long junctionalfoldings and deep gutters. AChRs are densely populated in the shoulders of the folds (around 5 million in each junction) and sparse in the depths. The deep gutters contain Na^+ channels and the trophic function of the nerve is important in development and maintenance of neuromuscular function. The NMJs at the time of birth are intermingled with terminal branches of different axons, however, at birth they progressively segregated to all but one nerve and a single end

plate remains. Once nerve – muscle contact formed, the end plate is durable and a new nerve will innervate the similar area of the muscle on dying of the older nerve.

The nerve-endings on fast twitch muscles are large and complex as compared to the slow twitch muscles which produces different response to muscle relaxants.

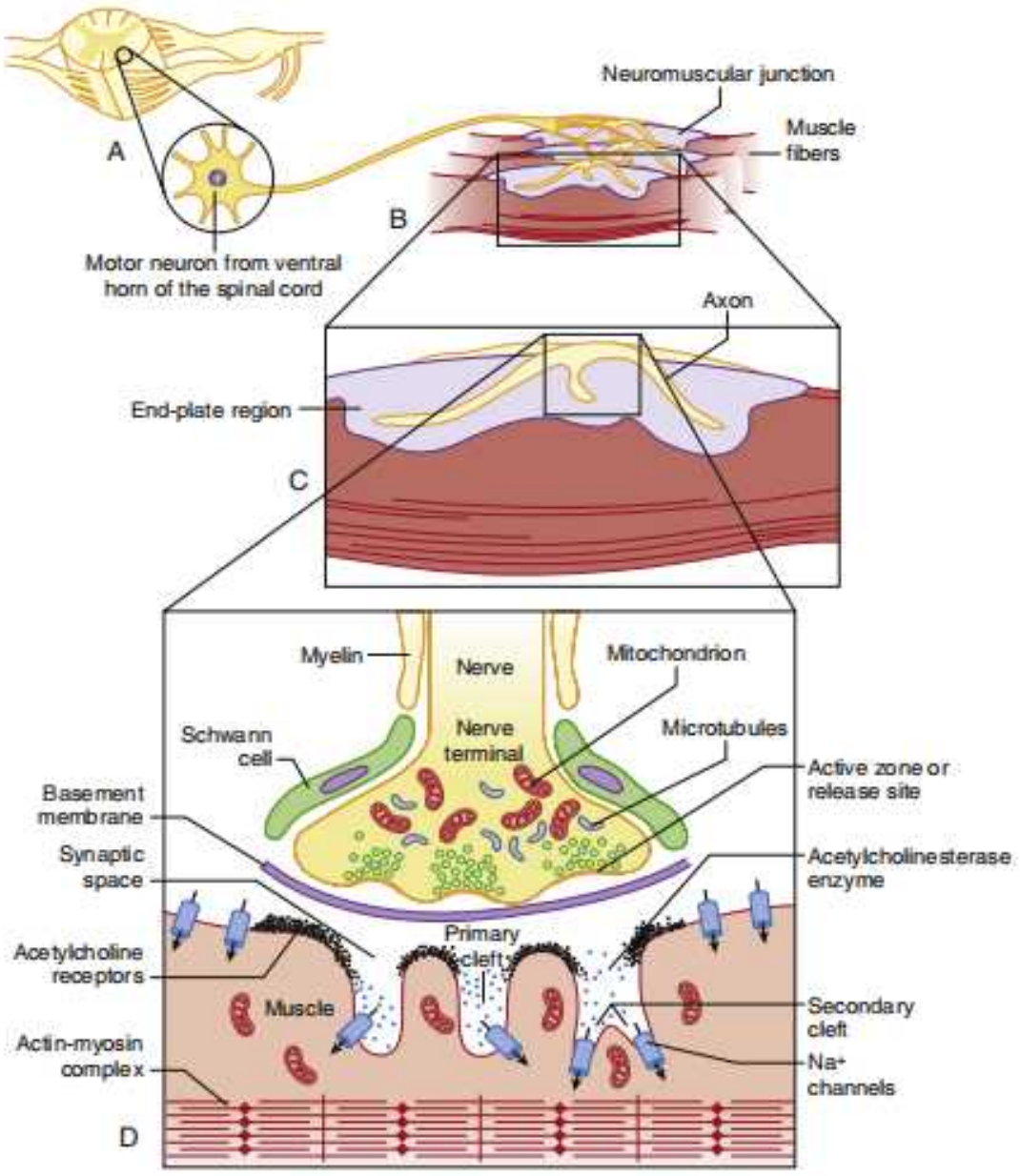


Figure 1: Structure of Neuromuscular Junction

All muscle cells in a single motor unit are stimulated by a single neuron which contracts synchronously, called as *fasciculat*. All adult human muscles comprise of only one NMB per cell except for few present in the extraocular muscles which are tonic type and have multiple innervations with a number of NMJ present along the surface of each muscle cell. In contrast with others, the adult ocular muscle encloses both mature and immature foetal receptor isolated into discrete synapses on different fibres. They contract and relax slowly when compared with other striated muscle fibres and sustain steady contraction or contracture; a strength proportional to the stimulus. They are of significance for an anaesthesiologist as depolarizing muscle relaxants can lead to long lasting contracture of the muscles thereby tugging on the eye ball against the bony orbit and raising the intraocular pressure.

The part of muscle just outside the junctional area is known as prejunctional zone and it contains a mixture of low density AChRs and high density of Na^+ channels. This mixture helps in enhancing the capacity of the zone to respond to depolarization and convert it into a wave which courses along the muscle to commence muscle contraction. The Na^+ channel density in the prejunctional area is more as compared to other distant parts of the muscle membrane and the zone being close enough to the nerve endings gets easily influenced by the transmitter released. Alternates (i.e., isoforms) or any mutations of receptors or Na^+ channels can lead to different responses to muscle relaxants that can be observed in patients with varied pathologic conditions and ages.

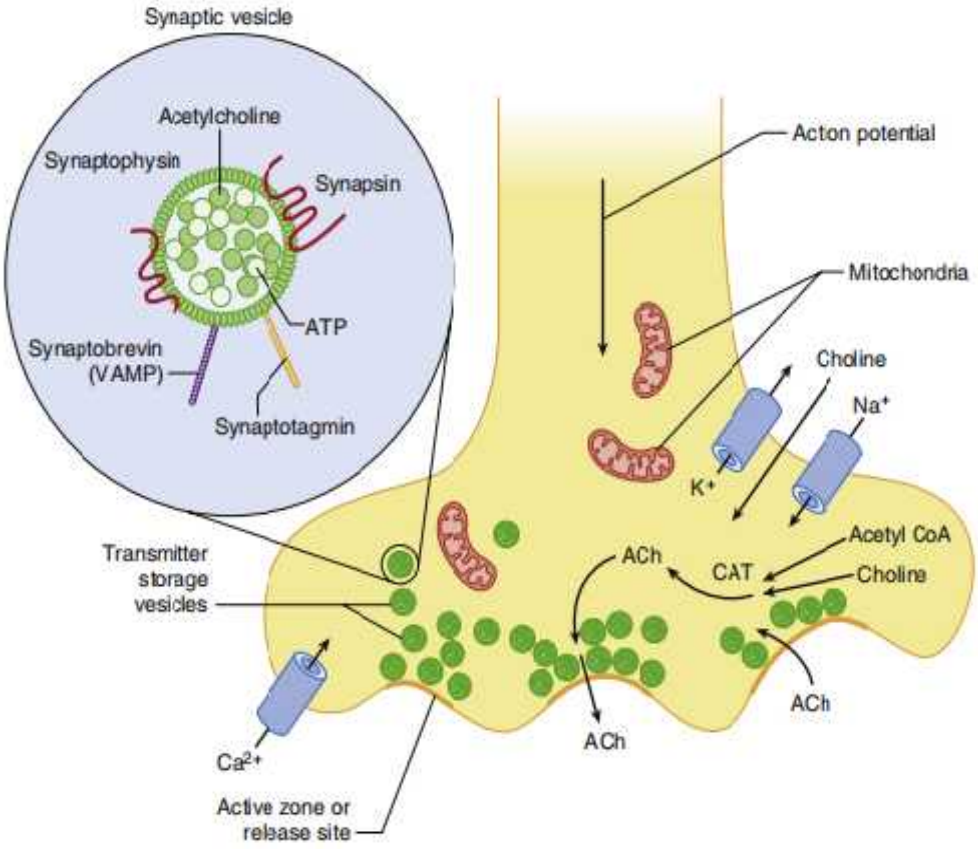


Figure 2: Working of a chemical synapse

Quantal Theory

Non homogenous contents form the nerve endings and the vesicles are collected towards the neuromuscular membrane while mitochondria, microtubules and other supportive structures are located on the other side. The vesicles are sited in group along small, broad, electron dense patches of membrane identified as active zones (Fig 2). Vesicles attach to this area which is a band across the synaptic surface of nerve ending before they rupture into junctional cleft. Voltage-gated calcium channels permit ca^{2+} to enter the nerve and release of vesicles and neurotransmitter at 200µsec signifying the channels are adjacent to release sites.

Miniature end-plate potentials (MEPPs) are small, spontaneous depolarizing potentials at NMJ having one hundredth the magnitude of conjured potential at the end-plate on excitation of the motor nerve. They are unitary responses, synthesized by constant sized packages or quanta, of transmitter liberated from the nerve (in the absence of excitation).

Stimulus-evoked end-plate potential is several hundred vesicles discharge quanta synchronously producing multiple depolarizations. This action potential is spread to the nerve endings permitting ca^{2+} entry inside the nerve through voltage-gated calcium channels, movement of vesicles to the neural membrane, union of vesicles and release acetylcholine into the junctional cleft. As the release sites are situated directly after peri-junctional area, the response is rapid and directly linked to the signal from nerve.

Adhesion molecules or specific cell-surface proteins are situated on either side of junction and grasp both verges of synaptic junction and hold the prejunctional and postjunctional synaptic apparatuses together. Neurexin is a synapse adhesion molecule binding to neuroligins on the postsynaptic membrane to keep it together. Around 200 quanta of 5000 molecules each of acetylcholine is released on each nerve impulse and activates around 5,00,000 molecules of AChRs. Na^{+} and Ca^{2+} ions drift through channels of activated AChRs creating depolarization of the end plate more than the threshold potential for excitation of the muscle. This signal is conveyed by molecules greater than required and response evoked is more than essential whereas, a minor portion of the existing vesicles and receptors or channels are used to direct each signal. Therefore, transmission has a considerable margin of safety, and simultaneously the system has extensive reserve.

Formation of Ach at Motor Nerve Endings

Motor nerve axon carries all the apparatus to convert electrical signal into chemical signal. Membrane components, ion channels, macromolecules needed in production, release of Ach and other trophic factors are produced in cell body and transported to nerve ending by axonal transport.[27] (Fig 2). Choline and Acetate are taken from the surroundings of nerve ending, Acetate in form of Acetyl coenzyme A from mitochondria and choline is from extracellular fluid to the cytoplasm. Enzyme choline acetyltransferase combines choline and acetate to form Ach which is stored in cytoplasm until transported into vesicles for release.

Nerve Action Potential

Na^+ from outside the neuronal membrane flows inside on action potential producing depolarization, opening of Ca^{2+} channels and allowing entry of Ca^{2+} ions into the neuronal membrane releases Ach. Quanta released is directly proportional to the concentration of Ca^{2+} in extracellular fluid, on doubling of Ca^{2+} there is 16-fold increase in quantal release. This persists till the action potential is back to equilibrium on K^+ release from inside by the K^+ channels located on the nerve terminal. K^+ channels limit entry of Ca^{2+} and hence depolarization and drugs like K^+ channel blockers (e.g., “4-aminopyridine, tetraethylammonium”), can prolong Ca^{2+} current by blocking outflow of K^+.

Post tetanic potentiation is seen clinically in the nerve paralysed with NDMR and stimulated at higher tetanic frequencies. This happens because of accumulation of Ca^{2+} in the nerve as the Ca^{2+} entry happens but reduced exit due to frequent tetanic stimulations. So, any stimulation applied to nerve produces higher volume of Ach

release due to accumulated Ca^{2+}, antagonizing the relaxant and producing elongated twitches.

Ca^{2+} channels are specialized proteins and are of two types: P-channels and slower L-channels. P-channels are voltage dependent, located immediately after active zones and are responsible for normal release of Ach. At neuronal terminals many forms of K^{+} channels are present – voltage gated and Ca^{2+}– activated. These check the neuronal depolarization and hence any changes in entry of Ca^{2+} will alter the release of Ach. Ca^{2+} entry and transmission can be hindered by high volume of bivalent inorganic cations (e.g., "Magnesium, Cadmium, Manganese"). Ca^{2+} channel blockers (e.g., "verapamil, diltiazem, nifedipine") affects the P-channels and have intense effects on slower L-channels present in Cardio Vascular System. Due to this, the L-channel blockers do not have any notable effect on release of Ach or potency of neuromuscular transmission at therapeutic doses.

Synaptic Vesicles and Recycling

Ach are released from two pools of vesicles, VP1 – a reserve pool and VP2 – a readily releasable pool. VP2 are smaller and are bound to active zones on neuronal membrane for release while VP1 are the synaptic vesicles sequestered and tethered to cytoskeleton in a filamentous network composed of actin, synapsin, synaptotagmin and spectrin.

SNARE (soluble N-ethylmaleimide-sensitive attachment protein receptors) proteins hold P-channels on the active zones, release Ach on entry of Ca^{2+} and also help in fusion, docking and release of Ach. "Docking is entry of Ca^{2+} into the vesicle and activating proteins in the neuronal membrane forming a pore to release Ach into

the junctional cleft."[28] In these, "some of them release and don't disintegrate completely into the membrane (kiss and run) while few disintegrate completely and do not restore till another stimulus (stranded)."[29]

VP1 vesicles have substantial reserve and are placed deep into the neuronal ending, tightly fastened to cytoskeleton by proteins like actin, synapsin (actin-binding protein), synaptotagmin and spectrin. They are moved to VP2 store for release to put back the used vesicles or when stimulated frequently or for longer time. In too stressed situations Ca^{2+} enter more deeper than usual in the nerve or from the L-channels to turn on the Ca^{2+} dependent enzymes which release the synapsin links and allows the vesicles to move to the release zone. Summation of all the steps which help in refilling all the stores of vesicle with Ach on frequent excitation, i.e., from acquiring choline, synthesis of acetate to moving the vesicles to release zone and rupture is known as Mobilization. Taking up of choline, action of choline acetyl transferase for synthesis of Ach are the rate limiting steps.

Process of Exocytosis

It is the release of Ach from the vesicles on Ca^{2+} entry and on generation of the action potential. The SNAREs comprise Synaptobrevin (synaptic -vesicle protein), Syntaxin (Plasmalemma-associated proteins) and SNAP – 25 (synaptosome-associated protein of 25kDa). Syntaxin, SNAP -25 are adhered to plasma membrane and Synaptobrevin on vesicle forms a triple complex on coming in contact with them. Synaptotagmin acts like a Ca^{2+} sensor helping in moving the vesicles to the release zones, docking them and stabilizes them in this state. The triple protein complex locates the vesicle nearby active zone for release (Fig 3). On production of action potential, Ca^{2+} enters and vesicles rupture to release new Ach in the junction. Few

vesicles release Ach in part or completely and some of them are recycled to form new vesicles.[29]

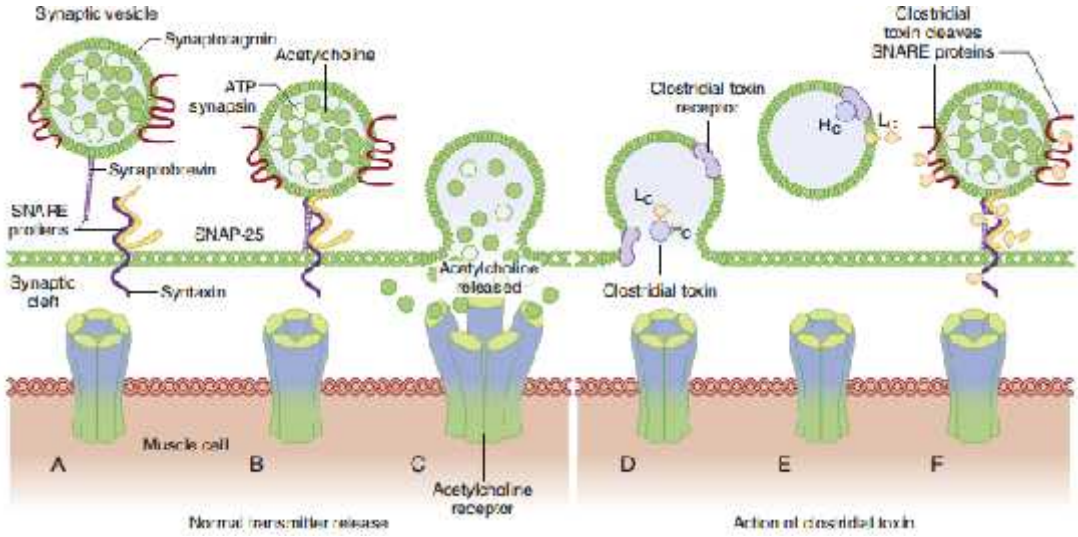


Figure 3: Model of protein-mediated membrane fusion and exocytosis

Acetylcholine Esterase (ACE)

ACE is a type B carboxylesterase enzyme, asymmetric or a 12-form protein secreted by muscle and present under the end plate attached by thin stalk of collagen to basement membrane (Fig 4). Ach released from nerve reacts with the receptors present to commence contraction of the muscle. Few Ach doesn't get bind immediately with the receptor and gets degenerated instantly by ACE present in the junction. Normally, one Ach molecule attaches to only one receptor before it gets hydrolysed. Life of Ach is very short and is destroyed in less than a millisecond after its release.

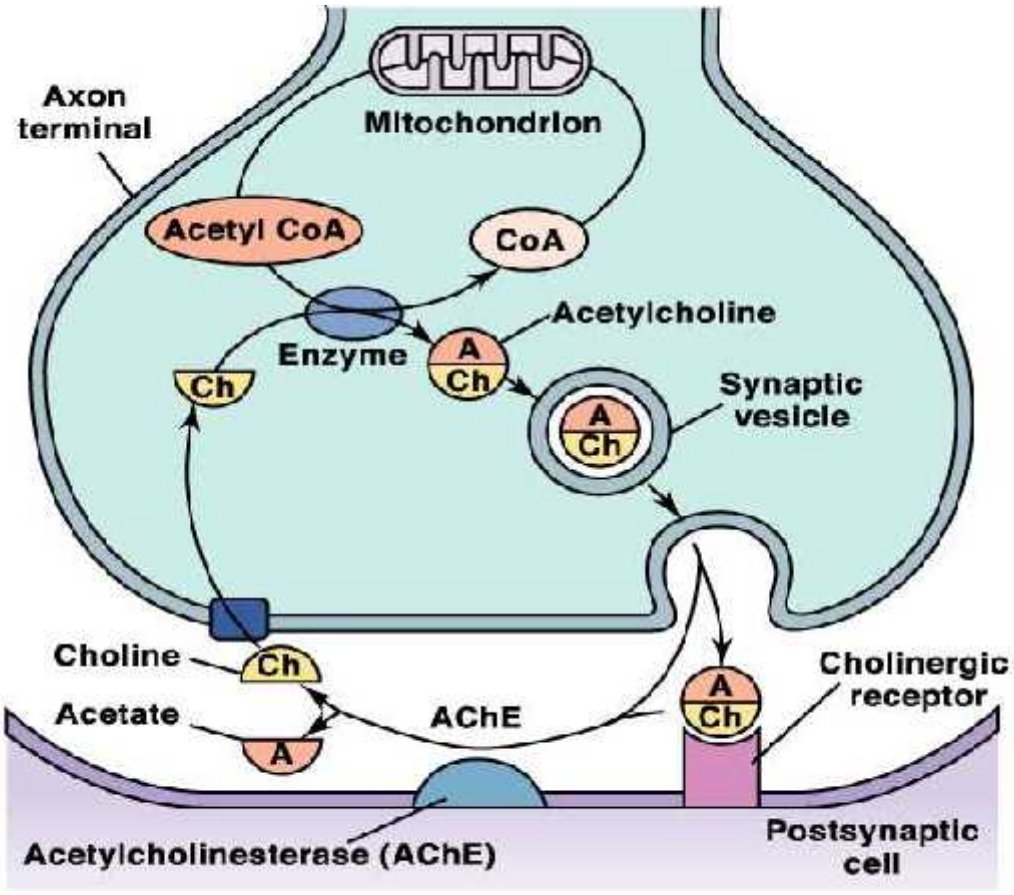


Figure 4: Life cycle of Acetyl Choline

Postjunctional Ach Receptors

They are nicotinic AChRs, existing in three isoforms: Junctional or mature receptor, an extrajunctional or immature (fetal) receptor and neuronal α7 receptors (Fig 5). They are formed in muscle and are adhered to muscle membrane by a special 43kDa protein (Rapsyn) in equal ratio. These are made of 5 subunit proteins placed in a cylindrical form with a central pore for ion movement and a molecular mass of 250,000 Daltons.

Mature receptors are made of 2α, β, δ, ε subunits, immature receptors of 2α, β, δ, γ subunits and neuronal α 7 receptors of 5 – α7 subunits. Every subunit consists of

around 400 – 500 amino acids and the receptors are placed through the membrane into the cytoplasm via extracellular surface. Ach binds to both of the α subunits to which both the agonist and the antagonists compete to bind and occupy. They are located near cysteine residues (unique to the α – chain) at amino acid positions 192 – 193 of the α – subunit.

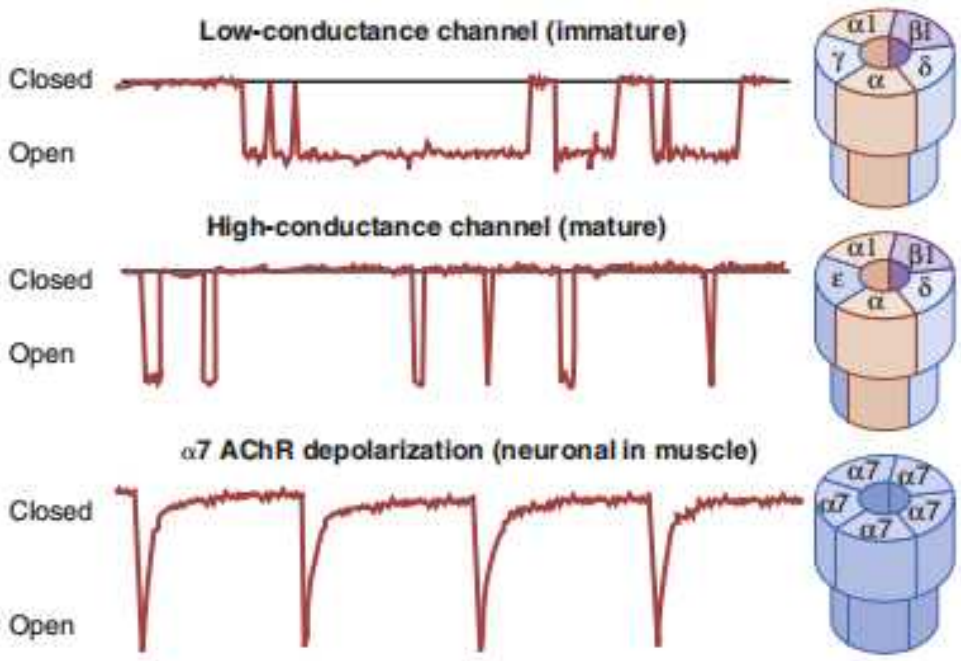


Figure 5: Sketch of acetylcholine receptor (AChR) channels and tracings of cell-patch records of receptor channel openings

Basic Electrophysiology of Neurotransmission

The central pore of the receptor opens and closes by approximation of the cylinders. So, on an agonist occupying both the α – subunits (Fig 5), the central pore opens up due to conformational change of the protein molecule and the ions flow along the concentration gradient from outside to inside of the cell. The Na^+ and Ca^{2+} ions flow outside to inside and K^+ flows inside to outside, excluding anions like

chloride. This flow of ions depolarizes and an end plate potential is generated to stimulate the muscle to contract.

The current stops on closure of the ion channel when the agonist detaches from the receptors. This current through the channel is around 10^4 ions/msec (picoamperes), however, for contraction of the muscle each burst of Ach releases about 500,000 channels simultaneously for adequate depolarization. The summation of all depolarization generated by multiple ion channels produce the end plate potential.

To keep the channel open, both the α subunits have to be occupied simultaneously by the agonists (Fig 6), and remains closed if only one is occupied. NDMRs (tubocurarine) binds to one or both the α subunits preventing binding of Ach from opening the channel and this interactivity is competitive and the outcome depends on the concentration and the binding capacity of the drugs.

The strength of the neuromuscular transmission along with the contraction of muscle can be influenced by many conformational changes in the individual channels. They open for variable duration, actions are slow, pass more or less ions and open briefly and repeatedly. They are also influenced by the drugs, temperature, electrolyte balance, changes in fluidity of the membrane.

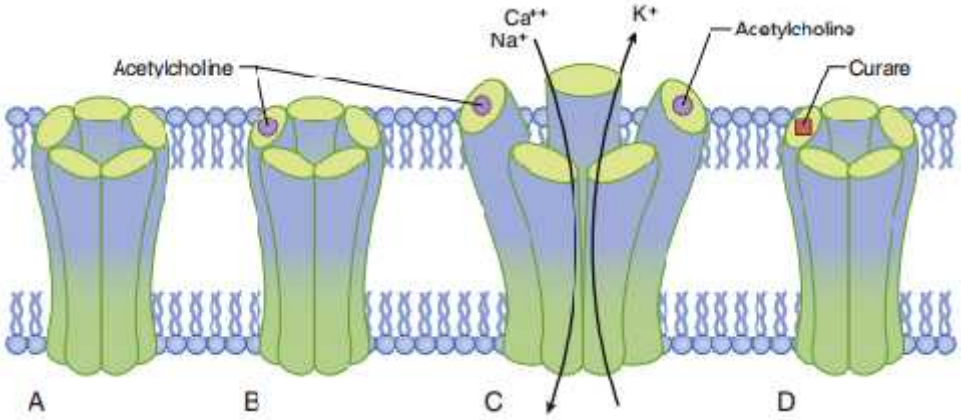


Figure 6: Actions of acetylcholine or curare on end-plate receptors

Pre synaptic acetyl choline receptors

The form and functions of these receptors are not understood completely and only that was shown by pharmacological and molecular biology techniques. The differences between pre synaptic and post synaptic AChRs are that the presynaptic receptors may bind to "β -bungarotoxin" only, post synaptic receptors adhere to α-bungarotoxin and different responses of these receptors to different agonists and antagonists are seen.

These receptors sense the Ach availability in the cleft where by the means of positive and negative feedback systems will cause the release or closedown of Ach. It is assumed that "tetanic fade" and "TOF fade" on NMB is the cause of non-depolarizing NMB arising at presynaptic receptors (α3β2) where they are inhibited near the motor nerve endings. Succinylcholine (Sch) doesn't inhibit presynaptic α3β2 receptors at clinically significant concentration, so this could be the reason for lack of TOF fade during Sch induce NMB.

Actions of Non-Depolarizing Muscle Relaxants

Blockade or impairment of Ach from binding to its receptor (α subunit) in a competitive manner is the action by which all NDMRs act. In fig.6, one can see that out of the two receptors if one is getting attached with an Ach molecule the channel remains closed. Only when two Ach gets attached to two sites on the receptors, the channel opens and flow of ions happen. If one receptor site is occupied with a tubocurarine molecule, then even if the other receptor site is occupied by a Ach molecule the channel remains closed. The channel should remain open for the ions to flow through it, thereby allowing the membrane to get depolarised. Attachment of even one tubocurarine molecule to the receptor will prevent the agonist from attaching to the receptor. So, presence of moderate amount of tubocurarine with reduce the membrane end plate-potential by reducing the current flow through it. If enough concentration of the NDMR (Tubocurarine) is present there will be complete block in the transmission of impulse (neuromuscular). Thereby causing neuro-muscular paralysis.

ACE is an enzyme that metabolizes the Ach from the NMJ. This will aid the tubocurarine in its competition with the Ach increasing the chance of better blockade. If an ACE inhibitor (neostigmine) is administered, then the metabolization of Ach gets hampered and more amount of Ach will be found in the NMJ. This will increase the chance of winning of the Ach in its competition of binding to the Ach receptor against Tubocurarine resulting in higher odds of the neuromuscular blockade getting reversed (2 Ach molecules getting attached to the recognition site on the receptors). If taken in numerical value, the Ach concentration (amount) should be double that of the tubocurarine concentration in order to overpower it. Therefore, reversing the blockade

caused by a larger dose of NDMR will be more difficult when compared to a block produced by a lower concentration of NDMR. So, in order to reverse a block caused by a large dose of NDMR, one should wait till its concentration gets reduced to a lower level in the peri-junctional area before giving the reversal agent.

Actions of Depolarizing Muscle Relaxants (DMRs)

Sch or Decamethonium mimics Ach action and hence are considered to be agonists despite having neuromuscular blocking effect. They act similar to Ach, attach to the receptors, channel port is opened briefly and depolarizes the neuronal membrane but due to biphasic action they initially contract the muscle followed by prolonged relaxation lasting for longer time. As they can't get degenerated by ACE, they are available for longer time in the junctional cleft until eliminated from plasma and continuously depolarize the end plate by repeatedly acting on the receptors.

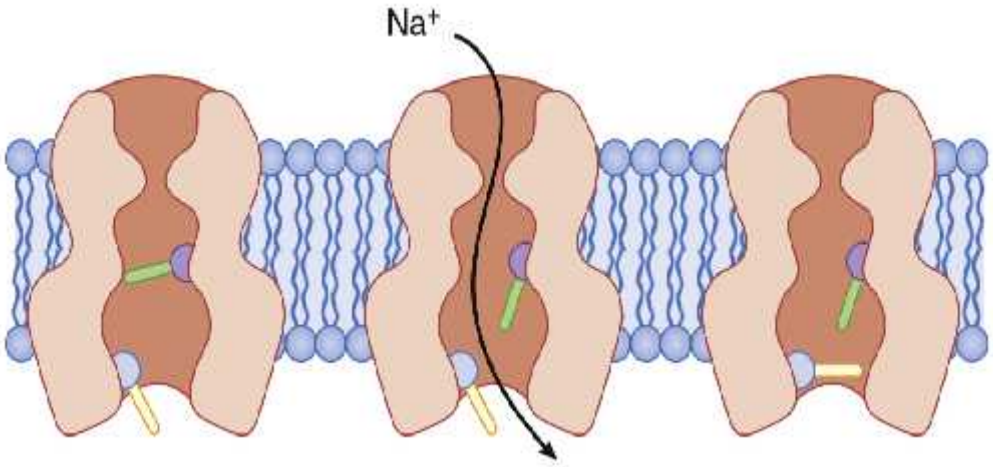


Figure 7: Sketch of a sodium channel

Since the end plate is close to the edge of the muscle membrane, its continuous depolarization occurs and it is a different kind of Na^+ channel which responds to transmembrane voltage change and not to the chemicals. It is a cylindrical

transmembrane protein with two parts acting as gates. These gates act sequentially in allowing or stopping the flow of Na^+ ions and therefore, have three functional conformational stages moving from one stage to another (Fig 7).

The Na^+ channel has to two gates: the lower gate ("time dependent or inactivation gate") and the upper gate ("voltage dependent gate") (Fig 7). In its resting state the upper gate is closed, lower gate is open so the Na^+ ions cannot pass. On depolarization there is sudden change in the voltage, so the upper gate opens and as the lower gate is still open, the Na^+ ions pass through. The upper gate remains open till there is depolarizing influence surrounding the membrane. However, shortly after upper gate opens, the lower gate closes and blocks the flow of ions and cannot open until the upper gate closes. As and when depolarization stops, the upper gate closes and the Na^+ channels come to its resting state. This is brief with Ach but as DMRs are not degenerated rapidly the depolarization action is prolonged.

Initially DMRs produce muscle contraction due to similar action to Ach but due to prolonged depolarization, the Na^+ ions cannot flow through the channel and there is no depolarization of the prejunctional muscle membrane and channels downstream of the prejunctional zone are free of the effect. Due to this, it turns to a buffer zone shielding rest of the muscle membrane from the effects. Hence, these separate the muscle membrane into three zones: depolarized end plate, frozen Na^+ channels in the prejunctional muscle membrane and rest of the muscle membrane and any burst of Ach can't overtake the dormant Na^+ channels in the prejunctional zone producing neurotransmission blockade, a phenomenon known as Accommodation. During this phase, on applying any electrical stimulation over the muscle will contract

the muscle as the Na^+ channels beyond the prejunctional area are in resting but can be excited.

In contrast are the external orbital muscles, which are tonic, innervated by many nerves, whole of its surface can be stimulated and express both mature and fetal receptors. Here, accommodation doesn't occur and undergo sustained contracture due to Sch, thus, generating a force pressing the eye against the orbit and increasing the intraocular pressure.

Phase II Block

It's a complex phenomenon occurring due to continuous exposure to the depolarizing agents. Here, the junction is initially depolarized but gradually recovers towards normal potential even in the presence of the drug but the neuromuscular transmission remains blocked throughout the exposure. There are several factors involved likely, repeated opening of channels can lead to electrolyte imbalance distorting the function of the junctional membrane, Ca^{2+} ions entering the channels can disrupt the receptors and the sub-end plate, Na^+ K^+ ATP pump activity in membrane increases with increase in intracellular Na^+ and by pumping Na^+ out and K^+ in to the cell to maintain ion balance and potential of the membrane towards equilibrium. Receptor channel remains patent and ion flow through them stays high till the depolarizing drug is present.

Mechanism of Antagonism

The NDMRs are predominantly competitive antagonists and best way to antagonise its effect is to increase concentration of Ach, as this will change the agonist-to-antagonist ratio, increase the chances of Ach binding to the post synaptic receptors and also the unoccupied receptors. The other factor is the increased

availability of Ach in the cleft, as the NDMRs bind to the receptor longer than the time of spontaneous degeneration of Ach by ACE. This can be done by – "K^+ channel blockers, ACE inhibitors and γ-cyclodextrin derivatives" and may be used for reversal of muscular paralysis by NDMRs.

Neuro Muscular Monitoring

Neuro Muscular Monitoring is used to check the depth of neuromuscular block (NMB) due to administration of muscle relaxants as to prevent any over or under dosage of the drugs. As the responses to muscle relaxants varies in every individual, diseased conditions and any medications.

It is done by providing an electrical stimulation to a surface motor nerve and assessing the response of the muscle(s) supplied by the nerve. The stimulator should be compact, light and simple to operate and may also be found with multi parameter monitor. Most available are battery operated and should be able to give automated record.

A motor nerve supplying a muscle needs to be stimulated with sufficient current for all muscle fibres to be stimulated for muscle contraction. This is known as maximal current and current more than maximal for maximum stimulation is known as supramaximal intensity. 30 milliamperes (mA) is required for supramaximal of ulnar nerve and higher currents for posterior tibial nerve. In general, it is 2.5 to 3 times higher than the lowest stimulation required. Low currents (5 to 8mA) is required if needle electrodes are used. Submaximal current is better for awake or on reversal of anaesthesia and is good in detecting residual NMB but not for general NMB monitoring.

"Hertz (Hz) = cycles/second is the unit for frequency and 0.1Hz is 1 stimulus every 10 seconds. On NDMR, increase in frequency will reduce onset duration and increase the action." [30,31] The waveform produced is square and monophasic while biphasic waves may cause repeated stimulation underestimating the dept of block. The time needs to be $\leq$ 300 µs otherwise if > 0.5 msec, a second action potential may be triggered.

Train-of-four (TOF, T4, T4/T1)

"TOF is a four equal intensity pulses given at 0.5 seconds (2Hz) (Fig 8) of interval. It should not be repeated less than every 10 seconds as it will result in short onset time for every 10s for NMB than used every 20s."[31,32] Normally, all the four response will be of equal intensity, with NDMR block the intensity of each twitch will be depressed compared to previous one(fade) (Fig 8) and as whole of the muscle gets paralysed the intensity of twitches reduce and gets eliminated individually and on recovery it appears in reverse order of disappearance. In DMR block, in phase I there will be constant decrease in all four twitches and in phase II fade will be observed.

The advantages are that it is more sensitive than single twitch and can distinguish between NDMR or DMR block. The disadvantage is that it is not sensitive during deep relaxation or near complete recovery. In TOF ratio above 0.4-0.5, visual or tactile observation has little value.

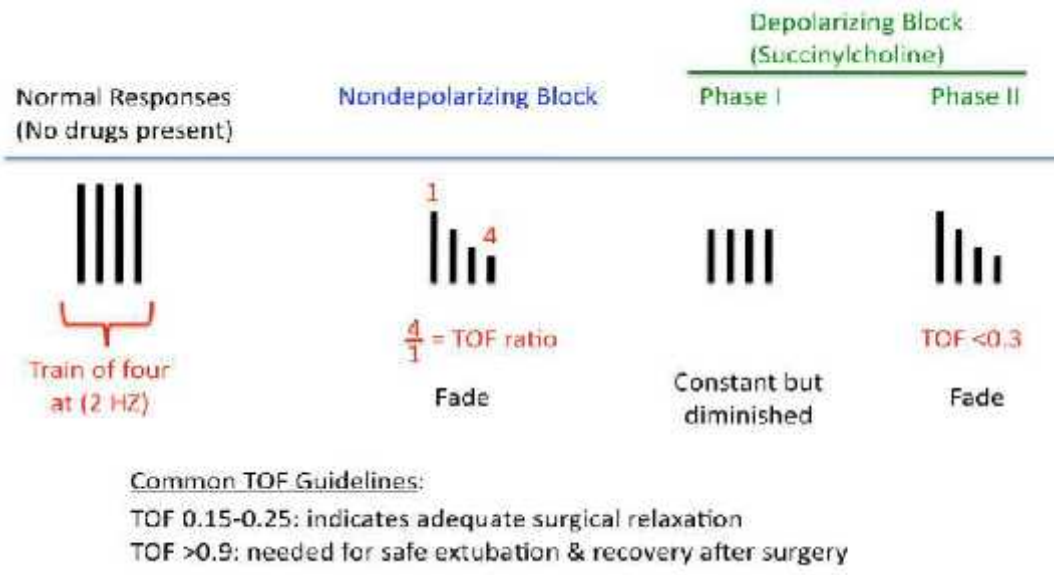


Figure 8: Patterns of stimulation and response to train-of-four stimulation

Two electrodes (one negative and other positive) are needed to be placed along the nerve to pass current through it for stimulation of the nerve and these electrodes can be placed over the skin surface or under the skin (per cutaneous) with needle electrodes. Direct current is generated by stimulators flow from negative to positive electrode and maximum response can be attained by placing negative electrode on most the superficial part of the nerve.[33]

Responses can be assessed by:

1. Visual – In TOF number of responses can be counted and fade can be seen at an angle of 90^{o} to the motion. Determining TOFR accurately or comparing twitch height to the control would be difficult visually. "Submaximal stimulus would be optimal to recognize the fade with TOF." [34]

2. Tactile – It is done by placing fingertip's lightly (better with dominant hand) over the muscle stimulated to feel the strength of contraction. "It's more

sensitive compared to visual assessment for NMB using TOF." [35] TOFR can be assessed if all four responses are present and it would be difficult to estimate the fade unless it is < 40%.

3. Mechanomyography (MMG) – It uses transducers attached to finger or any distal part which can move over stimulation. It changes the contraction to an electrical signal which is boosted and shown on the monitor. Twitch height, TOFR can be measured precisely but it's inconvenient and difficult to use. Transducer direction, isometric condition and stable preload are required. "MMG is infrequently utilized clinically however is viewed as the best quality level for logical estimation of neuromuscular response." [36]

4. Acceleromyography (AMG) - a slender piezoelectric transducer or a little aluminium pole with terminals on the two sides is fixed to the moving part and on movement a voltage is produced. This requires the muscle to have unlimited movement and can be used at the hand with free thumb.

   Most examinations show a genuine connection between TOFRs estimated by ACG and the MMG [37,38,39] or electromyography (EMG) [40,41], despite the fact that the outcomes are not compatible.

   Accelerometery is simple and advantageous to utilize, moderately reasonable and can be interfaced with a PC. It doesn't need a preload. It gives more exact outcomes than visual or tactile evaluation. [42,43]

5. Piezoelectric Film - A dispensable piezoelectric film is used spanning over a mobile joint. The film bends and creates a voltage on muscle movement relative to bending. It has been utilized on the thumb, fifth digit and the great

toe. This technique isn't as exact as MMG or EMG however may foresee recuperation of the TOFR superior to visual or tactile assessment.

6. Electromyography (EMG) – It measures the summated electrical activity generated by the muscle on excitation of the motor nerve. Total 5 electrodes are used in which 2 are placed over the nerve, 2 are for sensing and recording over the muscle, the best would be to place one on the belly and other on the tendon insertion site and 1 grounding is placed in between stimulating and recording electrode to reduce artifacts. Clean skin and electrodes placed 15 mins earlier provide best results. A specialized ET tube with inbuilt wire electrodes or electrodes wrapped around the tube and placed in between the Vocal Cords can be used in measuring EMG of laryngeal muscles.[44]

   The displayed EMG waveform is corrected, intensified and at a slower speed. Peak of the major deflections and summated value of the positive, negative and the zone under deflections are measured. The machine measures the supramaximal stimulus, control response, stimulates at selected timings, measures and records the responses. On block with NDMR, there is decrease in intensity and fade is seen with TOF. The amplitude doesn't return to 100% on recovery but the TOFR will come to 100% approx.

   EMG is better compared to MMG as it provides less immobilization, no bulky apparatus, no extension of arm required and can assess NMB by regional anaesthesia. "Muscles like diaphragm and laryngeal muscles can be monitored which can't be done with MMG." [45] But it is expensive, response varies according to muscle, senses electrical interference, change in electrode

position varies the response and variations are seen due to change in temperature.

Ulnar Nerve is the most common site for monitoring used and Adductor Pollicis (thumb) muscle regularly evaluated. It can be evoked at the elbow, wrist or hand. At elbow, it will produce hand adduction, at wrist thumb adduction and finger flexion and if EMG or MMG is used then the electrodes need to be placed at the wrist to reduce hand motion.

"At wrist, positive electrode is placed on the palmar surface approx. 2 cm above the wrist crease and the negative electrode distally to the positive one." [46] Positive one can also be placed on the dorsal surface of the wrist. At elbow, they are placed on the sulcus of the medial epicondyle of humerus. On hand, negative one in between the base of thumb and 2nd finger and positive one on dorsal surface of hand.

For EMG, electrodes are placed on hypothenar, thenar or dorsal interosseous muscle. Dorsal interosseous muscle - receiving electrode in the web between index finger and thumb and the other one at the base of second finger.Hypothenar muscle – both placed on the hypothenar eminence or the receiving electrode is placed on hypothenar eminence and the other one below the second line on the ring finger or at the base of the dorsum of the fifth finger. Thenar eminence - the proximal phalanx of the middle or index finger or the lateral side of the base of the thumb.

Tactile assessment can be done by placing the thumb in mild abduction and the examiner's fingertip can be placed over distal phalanx on the palmar side

and can be better assessed by placing a rubber band over the thumb. Important to know that Adductor Pollicis can also be supplied by median nerve. "It is important to know that the NMB for laryngeal muscles and the diaphragm occur earlier than peripheral muscles." [18,36,45]

Other nerves that can be used are:

1. Facial nerve
2. Peroneal nerve
3. Muscular branch of the Femoral Nerve
4. Mandibular nerve
5. Spinal accessory nerve
6. Recurrent laryngeal nerve
7. Median nerve
8. Posterior tibial nerve
9. Tibial nerve

TOF can used for

- Intubation – indicated by abolition of all four twitches. Double burst stimulation is a better indicator for optimal intubating conditions.[47]
- Electroconvulsive therapy – Can be applied on complete abolition of response on Posterior tibial nerve stimulation. Single stimulus is preferred at 1 Hz.

- Maintenance - used for titration of muscle relaxants during procedure. TOF is most preferred and supramaximal currents are used. "For abdominal muscle relaxation TOF should be maintained at the least one response in a peripheral nerve." [48] On no response, relaxants are not indicated, on two - relaxation may be adequate with balance anaesthesia, on three – adequate relaxation on using volatile anaesthetic agent. On using facial muscles, one twitch to be added on above recommendations.

- Recovery and Reversal – it allows to know the time of reversal and adjustment of dose of reversal agents. Many studies show residual NMB post operatively may be life threatening. "A study suggests that probability of detecting fade in index finger is greater than thumb or great toe." [49] On recovery, the twitches on TOF gradually appear and the fade will disappear. "Reversing of NDMR block is inversely related to the response at the time of reversal."[50] "Peripheral muscle is considered best to monitor recovery as its recovery would show any residual paralysis to maintain airway patency or respiration is not possible."[44,51] "TOFR of > 0.7 is required to prevent hypoxemia, pulmonary complications, visual disturbances, swallowing difficulty. Many investigators recommend TOFR at Adductor Pollicis to be > 90% by MMG for extubation." [51]

Clinical criteria to confirm the return of muscle strength:

- Open the eyes for 5 seconds and not experience diplopia
- Sustain tongue protrusion
- Sustain head lift for at least 5 seconds
- Sustain hand grip

- Sustain leg lifting in children
- Coughing
- Swallowing.

Clenching on to the laryngoscope blade might be a more sensitive test. In an asleep patient, generation of adequate tidal volume and an inspiratory force of at least 25 cm H_2Onegative pressure can be used as a clinical criterion. These doesn't exclude any residual paralysis.

Hazards

- Electrical burns
- Neuronal damage
- Needle electrodes causing infection, bleeding and pain.
- Affecting the functioning of implanted pacemaker or producing artifacts in ECG tracing.
- Wrong interpretation of degree of NMB due to low batteries.

METHODOLOGY

Materials and Methods

Source of Data: "**KLE'S Dr. PrabhakarKore Hospital and Medical Research Centre**, Nehru Nagar, Belagavi".

On patients undergoing elective surgical procedures requiring general anaesthesia from January 2019 to December 2019.

METHOD OF COLLECTION OF DATA:

a) Study design: A one-year hospital based randomized controlled study.

b) Sample size: A total sample size of 70 adult patients divided into 2 groups.

Group C: Patients intubated following clinical assessment of neuromuscular blockade -35 cases.

Group T: Patients intubated following neuromuscular block monitoring by TOF-GUARD Acceleromyograph (Organon – Teknika, Belgium) – 35 cases.

c) Sample Size Calculation:

The minimum sample size formula based on mean and standard deviation is

$$n = \frac{(Z\alpha+Z\beta)^2(S_1^2 + S_2^2)}{(d)^2}$$

where Zα is linked with the level of significance and Zβ is linked with the power of the test.

For 5% level of the significance Zα = 1.96 and Zβ = 0.84 for 80% power of the test.

d is the difference between the means of the Heart rate of the two groups.

S1 is the standard deviation of the heart rate in the first group (14) and S2 is the standard deviation of the heart rate in the second group (14).

With these values the minimum sample size obtained is 31.

For ease of calculations and sake of consistent results, sample size has been taken as 35. There are two groups of 35 each.

d) Place:

"KLE'S Dr. PrabhakarKore Hospital and Medical Research Center, Jawaharlal Nehru Medical College, Belagavi".

e) Selection Criteria:

Inclusion Criteria:

- Patients undergoing elective surgical procedures under general anaesthesia aged 18-60 years.
- ASA physical status I and II.
- Mallampati grade I and II.

Exclusion Criteria:

- Anticipated difficult airway.
- Pts having CVS, hepatic, renal or neurological disease.
- Receiving any drug known or suspected of interfering with neuromuscular function.
- Pathology of the neck or upper respiratory tract.
- Pregnant women.
- BMI >30.

f) Methodology:

Following institutional ethical board approval, written informed consent was obtained from patients aged 18 - 60 years, ASA I and II, MPG I and II, scheduled for elective surgical procedures requiring general anaesthesia. Standard anaesthesia monitors including non-invasive blood pressure, pulse oximeter, electrocardiogram, $EtCO_2$ (end-tidal carbon dioxide) and Neuro Muscular monitor – Train of Four (TOF – Guard) acceleromyograph monitor were attached. Baseline blood pressure, heart rate and peripheral O_2 saturation were recorded.

The patients of both groups were premedicated with Ondanseteron 4 mg, Ranitidine 50mg 15 mins before surgery. Glycopyrrolate 0.005mg/kg, Midazolam 0.05mg/kg, Fentanyl 1mcg/kg were administered intravenously. Following pre-oxygenation for 3 minutes, anaesthesia was induced with propofol 2mg/kg till the disappearance of the eyelash reflex. After the disappearance of the eyelash reflex, a

supramaximal TOF stimulus was applied to the ulnar nerve at the wrist through surface electrodes (stimulation current set at 60mA) using acceleromyograph after automatic calibration. Baseline TOF ratio percentage was noted. After standardization of supramaximal stimulus intravenous Vecuronium 0.1 mg/kg was administered over 5s. After the administration of the vecuronium, lungs were ventilated with 100% oxygen till the tracheal intubation.

In group C, the trachea was intubated following clinical assessment of neuromuscular blockade. In group T, the trachea was intubated following neuromuscular block monitoring by TOF Guard acceleromyograph (Organon-Teknika, Belgium).

In group C, the timing of the intubation was judged based on clinical assessment starting at 1 min after administration of muscle relaxant and at every 30s thereafter. The timing of laryngoscopy was based on ease of ventilation, jaw and upper airway tone. Jaw tone was assessed by attempting to open patient's mouth, whereas upper airway tone was determined by amount of jaw support necessary to maintain patent airway.

In Group T, intubation was attempted after complete loss of all 4 responses to TOF stimulation (TOF count zero), carried out every 30s starting at 1 min after administration of vecuronium. The electrical stimulation was done with 60 mA, 2 Hz current lasting 0.2 ms.

The trachea was intubated with endotracheal tubes of appropriate sizes. The cuff of endotracheal tube was inflated over 5s.The patients who had oesophageal intubation were excluded from the study. Thereafter, mechanical lung ventilation was

carried out using isoflurane in oxygen: nitrous oxide (50:50). The ventilator parameters were adjusted to maintain end-tidal carbon dioxide ranging from 25 to 30 mm hg. Intubation conditions were graded using scoring scale described by Kreig*et al.* [52]This scale distributes intubating conditions into four classes: excellent, good, poor and inadequate.

Points	**1**	**2**	**3**	**4**
Vocal Cords	Open	Moving	Closing	Closed
Coughing	None	With Diaphragm	Clear	Severe
Laryngoscopy	Easy	Fair	Difficult	Impossible
Total Score	3-4	5-7	8-10	11-12
IntubatingConditions	Excellent	Good	Poor	Inadequate
Class	1	2	3	4

Intubating Condition =

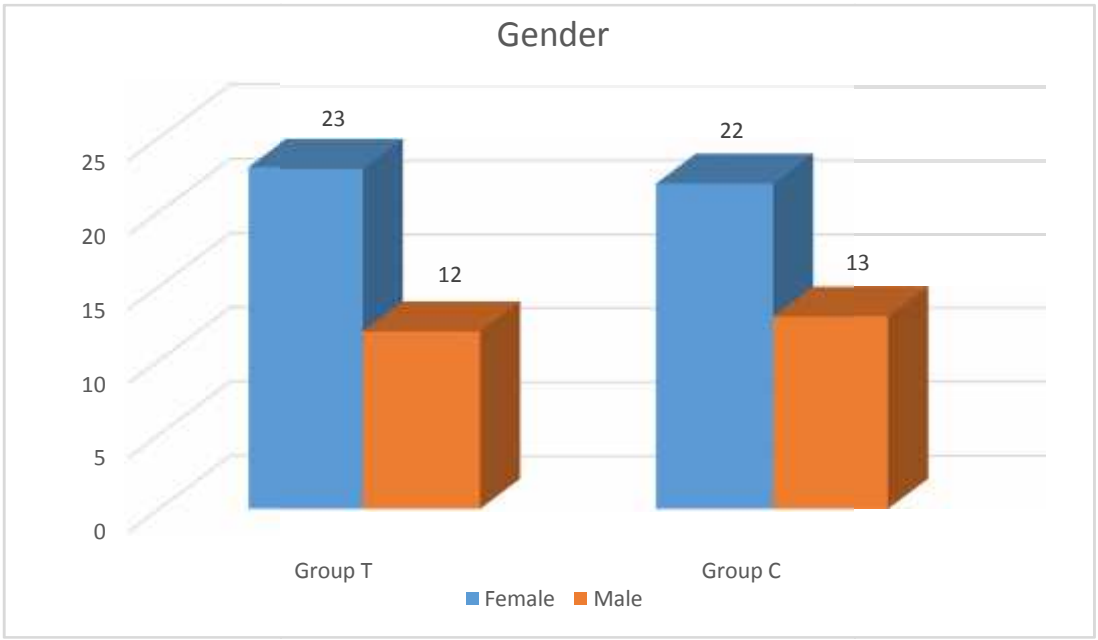
RESULTS

INTER GROUP COMPARISON

Table 1:Gender Distribution

	Group T		Group C		P Value
	NUMBER	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**	
F	23	65.71	22	62.86	0.8030
M	12	34.29	13	37.14	
TOTAL	35	100.00	35	100.00	

Graph 1:Gender Distribution

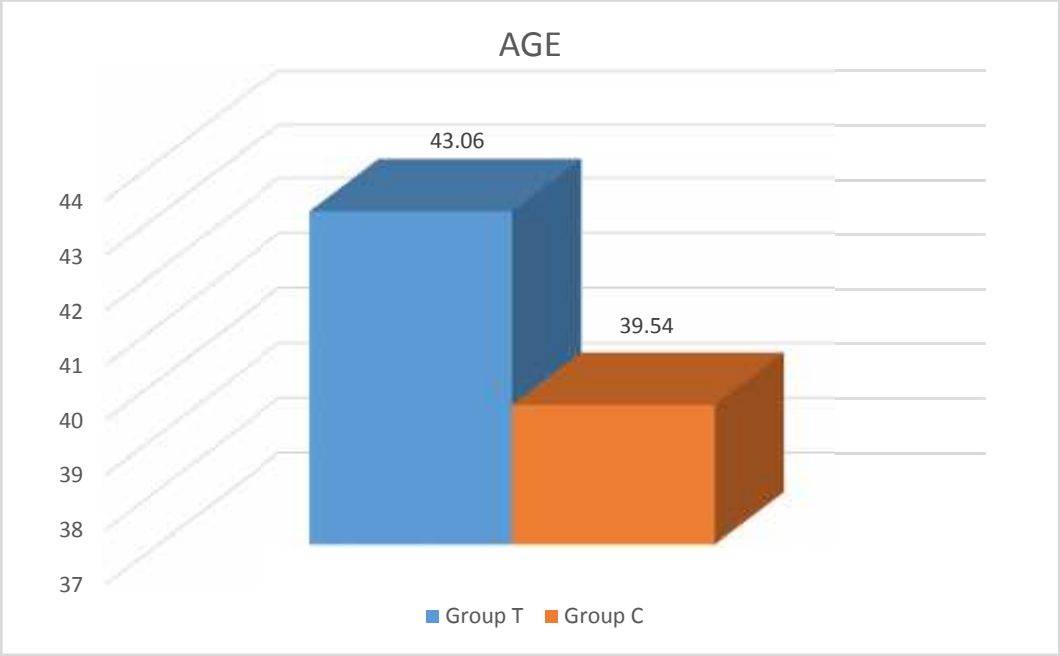


In this study, there were 23 female, 12 male patients in Group T and 22 female, 13 male patients in Group C, sex distribution did not account to statistical significance.

Table 2: Age Distribution

	Group T				Group C					
	MEAN	**S.D.**	**MINIMUM**	**MAXIMUM**	**MEAN**	**S.D.**	**MINIMUM**	**MAXIMUM**	**P VALUE**	**INFERENCE**
AGE	43.06	13.75	18	60	39.54	13.27	18	60	0.2806	NS

Graph 2: Age Distribution

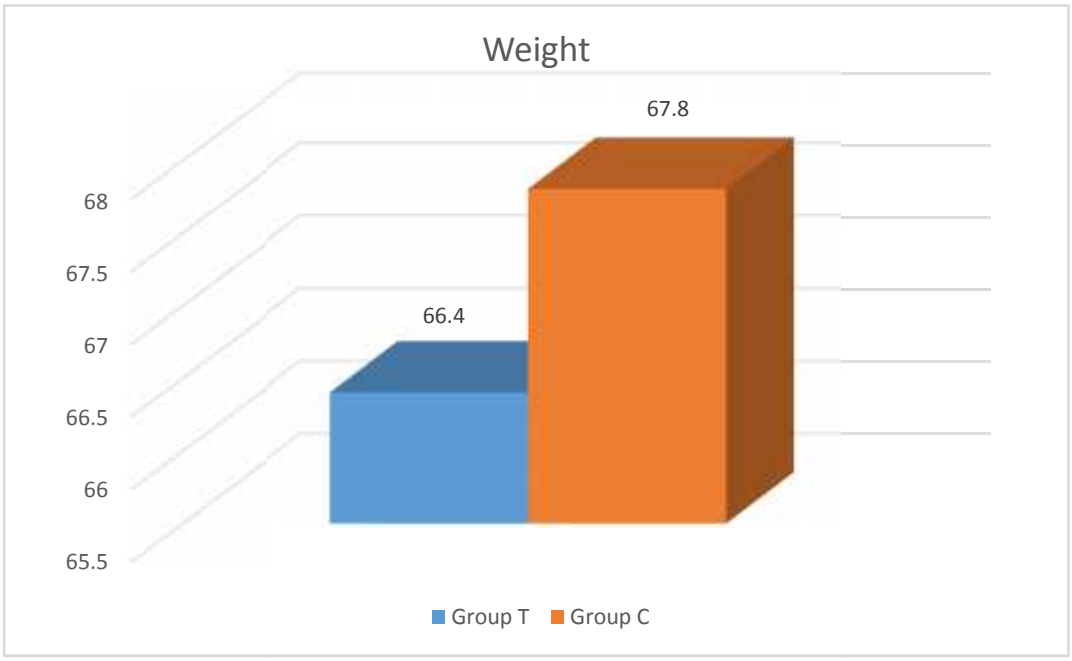


The mean age was 43.06 ± 13.75 years in Group T and 39.54 ± 13.27 years in Group C. There was no statistically significant difference between both the groups.

Table 3:Weight Distribution

TOF - GUARD ASSESSMENT GUIDED				CLINICAL ASSESSMENT GUIDED					
MEAN	**S.D.**	**MINIMUM**	**MAXIMUM**	**MEAN**	**S.D.**	**MINIMUM**	**MAXIMUM**	**P VALUE**	**INFERENCE**
66.4	7.8	50	77	67.8	7.28	50	83	0.393	NS

Graph 3: Weight Distribution

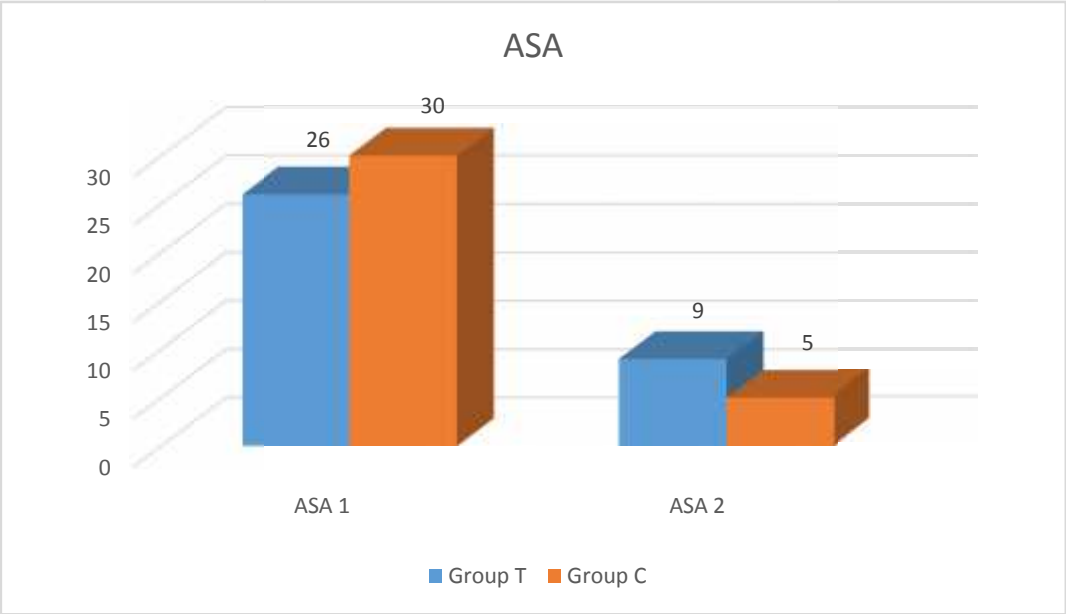


The mean weight in Group T was 66.4±7.8kg and in Group C67.8±7.28kg, which was not statistically significant. Both groups were comparable with respect to weight.

Table 4:ASA Distribution

	Group T		Group C	
	NUMBER	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
1	26	74.29	30	85.71
2	9	25.71	5	14.29
TOTAL	35	100.00	35	100.00
	THE P VALUE USING CHI-SQUARE TEST IS 0.2320 (NS)			

Graph 4: ASA Distribution

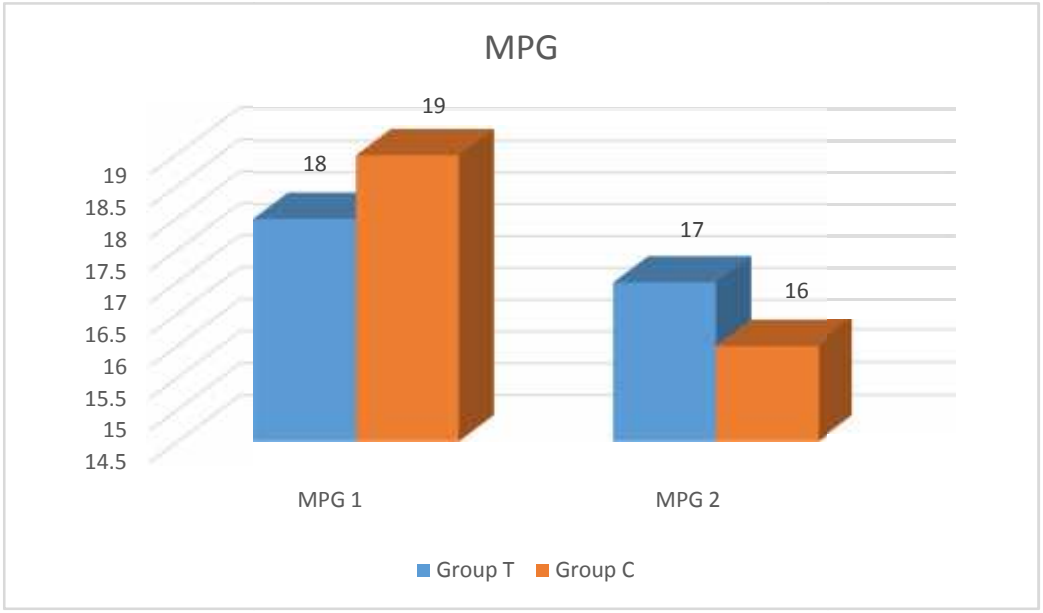


In this study, among the patients who were scheduled for surgery, 74.29% in Group T belonged to ASA grade 1 compared to 85.71% in Group C and 25.71% in Group T belonged to ASA 2 compared to 14.29% in Group C. There is no statistical significance between two groups.

Table 5: MPG Distribution

	TOF - GUARD ASSESSMENT GUIDED		CLINICAL ASSESSMENT GUIDED	
	NUMBER	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
1	18	51.43	19	54.29
2	17	48.57	16	45.71
TOTAL	35	100.00	35	100.00
	THE P VALUE USING CHI-SQUARE TEST IS 0.8108 (NS)			

Graph 5: MPG Distribution



In the present study, 51.43% of patients in Group T had MPG 1 in comparison to 54.29% of patients in Group C and 48.57% in Group T had MPG 2 in comparison to 45.71% in Group C. Both groups were comparable with respect to MPG Grading.

Table 6:Intergroup comparison of Heart Rate

HR										
	Group T				Group C					
TIME	MEAN	S.d.	Minimum	Maximum	Mean	S.d.	Minimum	Maximum	P value	Inference
T0	77.06	6.54	64	92	76.26	7.08	64	90	0.6250	NS
T1	80.40	7.09	68	96	79.40	8.38	60	98	0.5918	NS
T2	80.69	7.73	70	101	80.46	8.74	62	98	0.9081	NS
T3	85.17	7.50	72	98	88.54	6.07	80	105	0.0458	S
T4	82.69	7.21	70	96	85.80	5.71	76	100	0.0493	S
T5	80.20	6.18	68	93	83.09	5.69	72	98	0.0460	S
T6	79.83	5.53	69	90	82.31	4.14	74	91	0.0417	S

Graph 6: Intergroup comparison of Heart Rate

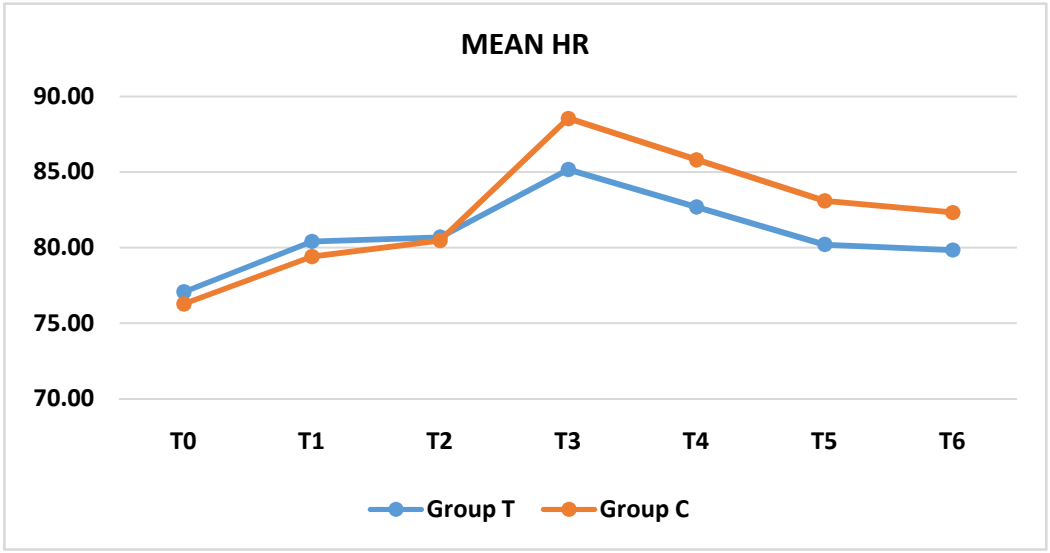


Table 7: Intergroup comparison of MAP

MAP										
	Group T				Group C					
TIME	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	95.33	6.17	84.67	106.67	93.75	10.67	70.00	113.33	0.4508	NS
T1	84.42	9.24	60.67	104.00	85.70	9.50	67.33	103.33	0.5708	NS
T2	83.47	7.80	65.33	102.67	85.24	9.45	68.00	103.33	0.3954	NS
T3	88.45	8.40	71.00	107.33	101.91	6.12	93.33	116.33	< 0.0001	HS
T4	88.12	6.90	70.67	104.67	99.92	5.14	89.33	114.67	< 0.0001	HS
T5	88.36	6.98	64.00	104.67	96.79	5.88	82.67	110.00	< 0.0001	HS
T6	88.74	5.48	76.00	104.00	95.10	5.98	79.33	109.33	< 0.0001	HS

Graph 7: Intergroup comparison of MAP

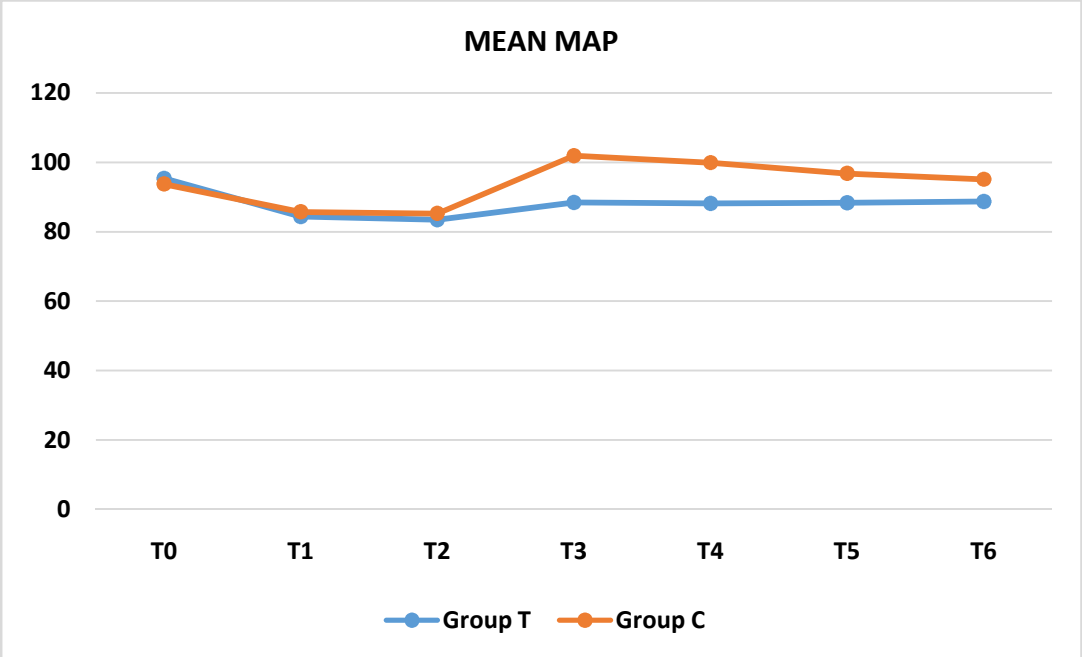


Table 8: Intergroup comparison of SBP

SBP										
	Group T				Group C					
TIME	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	126.00	11.98	106	155	123.43	15.83	90	150	0.4462	NS
T1	111.20	14.04	90	143	110.74	15.70	80	135	0.8982	NS
T2	109.60	12.53	90	145	110.80	16.52	80	134	0.7330	NS
T3	117.06	12.79	97	150	136.49	7.87	114	156	< 0.0001	HS
T4	116.89	11.07	94	150	134.97	7.17	120	150	< 0.0001	HS
T5	117.14	10.53	96	154	130.20	9.24	96	150	< 0.0001	HS
T6	118.40	9.00	105	152	128.03	8.30	98	148	< 0.0001	HS

Graph 8: Intergroup comparison of SBP

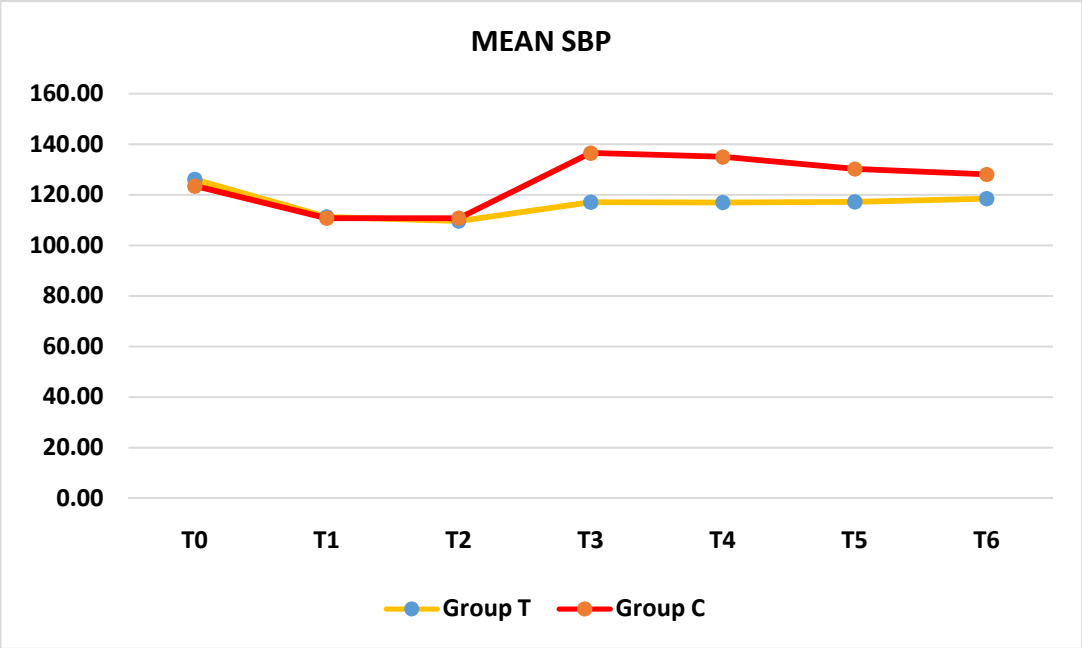
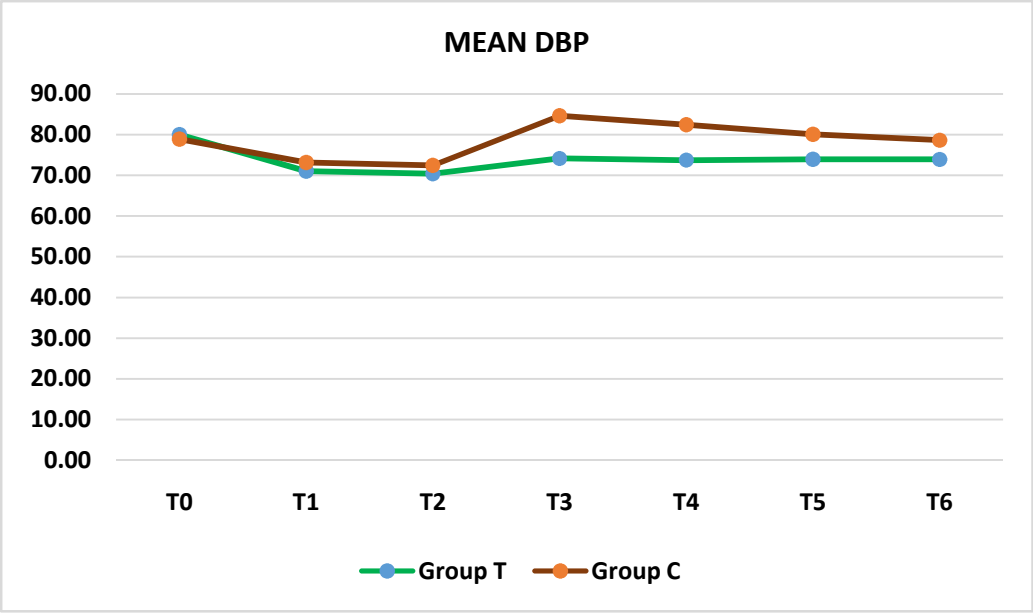


Table 9: Intergroup comparison of DBP

DBP										
	Group T				Group C					
TIME	MEAN	S.D.	MINIMUM	MAXIMUM	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	80.00	5.68	68	90	78.91	9.57	60	100	0.5657	NS
T1	71.03	8.19	45	92	73.17	7.96	60	92	0.2711	NS
T2	70.40	6.92	52	90	72.46	6.78	62	88	0.2135	NS
T3	74.14	7.62	57	94	84.63	7.25	72	103	0.0000	HS
T4	73.74	6.07	59	90	82.40	5.84	72	100	0.0000	HS
T5	73.97	6.68	48	88	80.09	6.12	72	96	0.0002	HS
T6	73.91	5.39	61	86	78.63	6.36	70	95	0.0013	VS

Graph 9: Intergroup comparison of DBP



The mean HR, mean arterial pressure, mean SBP, mean DBP were higher in Group C with statistical significance ($P < 0.05$) at the T3, T4, T5, T6 points of time compared to Group T at the same time points. This suggests mean HR, mean arterial pressure, mean SBP, mean DBP increased in Group C after laryngoscopy and tracheal intubation in comparison to Group T. At T0, T1, T2 time points (i.e., in pre intubation period), the mean HR, mean arterial pressure, mean SBP, mean DBP were comparable among both the groups ($P > 0.05$).

TOF - GUARD ASSESSMENT GUIDED

Table 10a: Intragroup analysis of Heart Rate (Group T)

TIME	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	77.06	6.54	64	92	---	---
T1	80.40	7.09	68	96	< 0.0001	HS
T2	80.69	7.73	70	101	< 0.0001	HS
T3	85.17	7.50	72	98	< 0.0001	HS
T4	82.69	7.21	70	96	< 0.0001	HS
T5	80.20	6.18	68	93	0.0004	HS
T6	79.83	5.53	69	90	0.0002	HS

Table 10b: Intragroup analysis of MAP (Group T)

TIME	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	95.33	6.17	84.67	106.67	---	---
T1	84.42	9.24	60.67	104.00	0.2356	NS
T2	83.47	7.80	65.33	102.67	0.0373	S
T3	88.45	8.40	71.00	107.33	0.0006	VS
T4	88.12	6.90	70.67	104.67	0.0015	VS
T5	88.36	6.98	64.00	104.67	0.0014	VS
T6	88.74	5.48	76.00	104.00	0.0009	HS

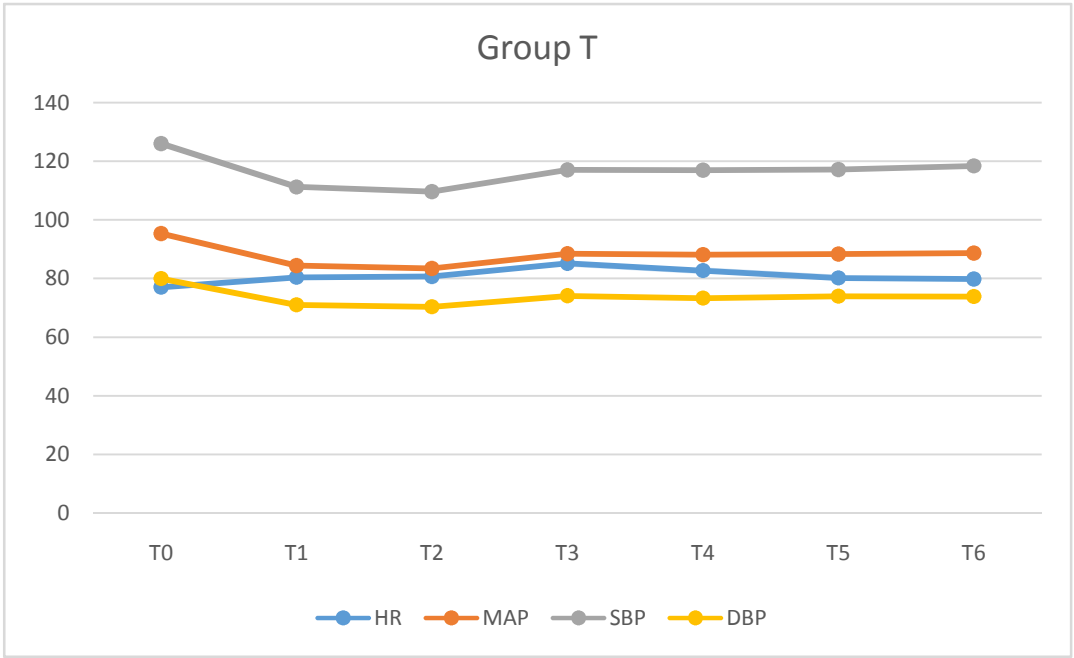
Table 10c: Intragroup analysis of SBP (Group T)

TIME	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	126.00	11.98	106	155	---	---
T1	111.20	14.04	90	143	< 0.0001	HS
T2	109.60	12.53	90	145	< 0.0001	HS
T3	117.06	12.79	97	150	< 0.0001	HS
T4	116.89	11.07	94	150	< 0.0001	HS
T5	117.14	10.53	96	154	< 0.0001	HS
T6	118.40	9.00	105	152	< 0.0001	HS

Table 10d: Intragroup analysis of DBP (Group T)

TIME	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	80.00	5.68	68	90	---	---
T1	71.03	8.19	45	92	< 0.0001	HS
T2	70.40	6.92	52	90	< 0.0001	HS
T3	74.14	7.62	57	94	< 0.0001	HS
T4	73.74	6.07	59	90	< 0.0001	HS
T5	73.97	6.68	48	88	< 0.0001	HS
T6	73.91	5.39	61	86	< 0.0001	HS

Graph 10: Intragroup comparison of variables at different time points



CLINICAL ASSESSMENT GUIDED

Table 11a: Intragroup analysis of Heart Rate (Group C)

TIME	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	76.26	7.08	64	90	---	---
T1	79.40	8.38	60	98	0.0008	HS
T2	80.46	8.74	62	98	< 0.0001	HS
T3	88.54	6.07	80	105	< 0.0001	HS
T4	85.80	5.71	76	100	< 0.0001	HS
T5	83.09	5.69	72	98	< 0.0001	HS
T6	82.31	4.14	74	91	< 0.0001	HS

Table 11b: Intragroup analysis of MAP (Group C)

TIME	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	93.75	10.67	70.00	113.33	---	---
T1	85.70	9.50	67.33	103.33	0.2456	NS
T2	85.24	9.45	68.00	103.33	0.2660	NS
T3	101.91	6.12	93.33	116.33	< 0.0001	HS
T4	99.92	5.14	89.33	114.67	< 0.0001	HS
T5	96.79	5.88	82.67	110.00	< 0.0001	HS
T6	95.10	5.98	79.33	109.33	< 0.0001	HS

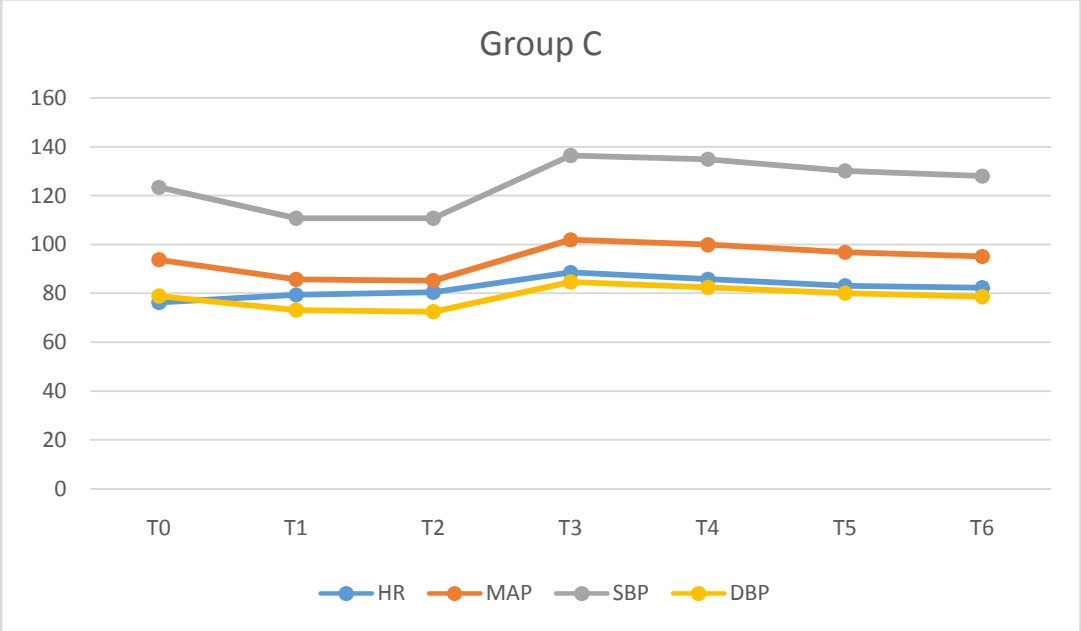
Table 11c: Intragroup analysis of SBP (Group C)

TIME	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	123.43	15.83	90	150	---	---
T1	110.74	15.70	80	135	< 0.0001	HS
T2	110.80	16.52	80	134	< 0.0001	HS
T3	136.49	7.87	114	156	< 0.0001	HS
T4	134.97	7.17	120	150	< 0.0001	HS
T5	130.20	9.24	96	150	0.0062	VS
T6	128.03	8.30	98	148	0.0278	S

Table 11d: Intragroup analysis of DBP (Group C)

TIME	MEAN	S.D.	MINIMUM	MAXIMUM	P VALUE	INFERENCE
T0	78.91	9.57	60	100	---	---
T1	73.17	7.96	60	92	< 0.0001	HS
T2	72.46	6.78	62	88	< 0.0001	HS
T3	84.63	7.25	72	103	< 0.0001	HS
T4	82.40	5.84	72	100	0.0081	VS
T5	80.09	6.12	72	96	0.1767	NS
T6	78.63	6.36	70	95	0.4112	NS

Graph 11: Intragroup comparison of variables at different time points

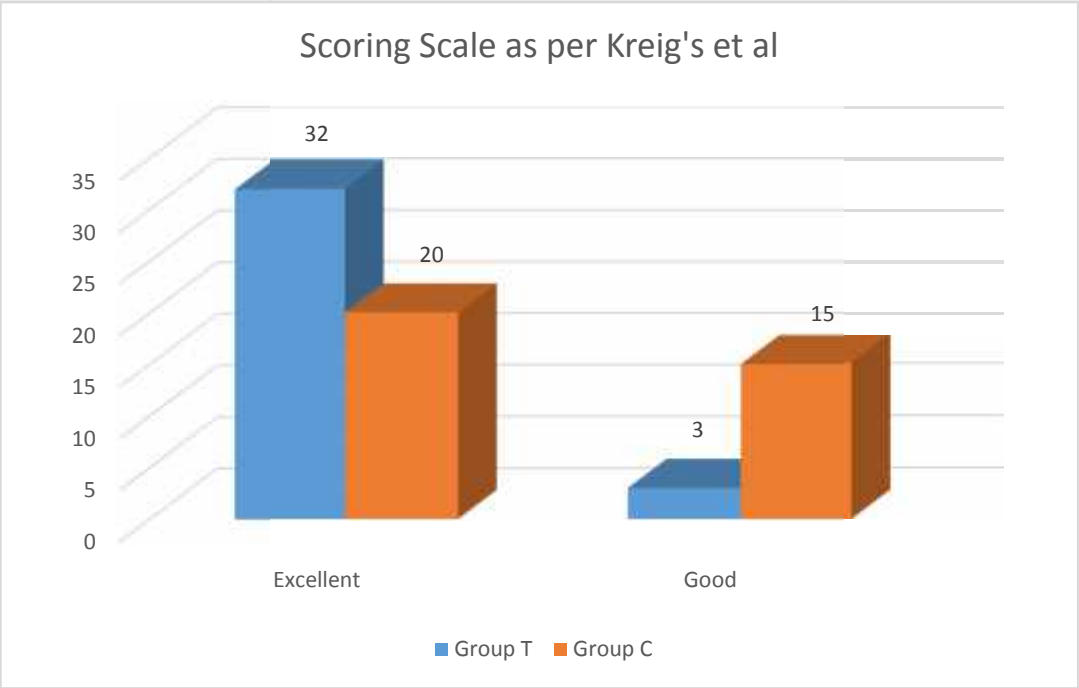


Intragroup analysis shows significant rise in mean HR, mean arterial pressure, mean SBP, mean DBP after Laryngoscopy and tracheal intubation in both the groups but the raise in mean HR, MAP, mean SBP, mean DBP were significantly lower in Group T compared to the Group C.

Table 12: Intergroup analysis of scoring of intubating conditions as per Kreig's et al.

	Group T		Group C	
	NUMBER	**PERCENTAGE**	**NUMBER**	**PERCENTAGE**
Excellent	32	91.43	20	57.14
Good	3	8.57	15	42.86
TOTAL	35	100.00	35	100.00
	THE P VALUE USING CHI-SQUARE TEST IS 0.0010 (VS)			

Graph 12: Intergroup comparison of scoring of intubating conditions as per Kreig's et al



Intubating condition in Group T (Excellent - 91.43%, Good – 8.57%) were significantly better than in Group C (Excellent – 57.14%, Good – 42.86%) with P value 0.001. All the patients had Excellent or Good intubating conditions, however, Group T had higher percentage of excellent intubating condition compared to the other group. None of the patients in both the groups had poor or inadequate intubating conditions.

DISCUSSION

As commonly observed during Laryngoscopy and endotracheal intubation, there is significant Tachycardia and Hypertension due to strong stressor stimuli producing sympathetic stimulation and intracranial changes. Usually these changes are transient and due not produce any significant adverse effects. But in patients of Concomitant Coronary artery disease, known Hypertensive, with intracranial pathology these changes might lead to myocardial ischemia or secondary brain damage. Many pharmacological drugs have been used to attenuate the stressor stimuli but these drugs can cause unnecessary increase in depth of anaesthesia or adverse haemodynamic changes. Hence, a non-pharmacological measure is important in attenuating these responses. We observed in this study that neuromuscular monitoring-based timing for tracheal intubation produces lesser haemodynamic changes compared to clinical based timing along with better intubating conditions.

There are many studies which have shown that haemodynamic responses depend on the duration of laryngoscopy and ease of intubation. Hence, complete neuromuscular blockade with a muscle relaxant is very important to prevent any undue stimulation of sympathetic system and assessment will help in proper timing for intubation. This assessment was done with response to TOF stimulation and complete paralysis has occurred when the TOF count becomes zero. We had assessed neuromuscular blockade via TOF – Guard in group T and intubation was done when the TOF ratio was Zero on TOF electrical stimulation.

Laryngoscopy and endotracheal intubation elicit strong stressor response like sympathetic stimulation by increase in heart rate and arterial pressure, EEG changes

due to central nervous system stimulation.[53] In this study, we have observed that patients in Group C i.e., intubation by clinical based timing have shown higher mean values of mean heart rate, mean arterial pressure, mean systolic blood pressure, mean diastolic blood pressure compared to patients in Group T i.e., intubation by Neuromuscular monitoring based timing ($P < 0.05$). This shows that patients with incomplete paralysis, laryngoscopy and tracheal intubation can produce stronger sympathetic stimulation.

In study by Smith I et al, trachea was intubated after administration of Vecuronium or Rocuronium on basis of clinical assessment of jaw relaxation, airway tone and ease of ventilation comparing with twitch height from baseline. [11] They found that on attempting laryngoscopy after administration of vecuronium, the median twitch height was 8% whereas in Rocuronium the height was 0%. This means on vecuronium administration when laryngoscopy was attempted complete relaxation was not achieved compared to Rocuronium where complete relaxation was achieved on laryngoscopy based on clinical judgment.

Adductor Pollicis muscle was chosen in this study to monitor the neuromuscular block. Study by Debaene B et al showed that in Orbicularis Oculi, the TOF becomes Zero more faster compared to Adductor Pollicis muscle on administration of muscle relaxant and lead to early intubation and unsatisfactory intubating conditions. [54] In studies like Witkowska M et al and Le Corre F et al, where Adductor Pollicis was used, there were more favorable intubating conditions and therefore reduced haemodynamic surge. [7,21] Hence, Adductor Pollicis was chosen for monitoring and being a peripheral muscle was easier to monitor.

We have observed all patients having excellent or good intubating conditions in both the group. However, 32 out of 35 patients were of excellent intubating condition in Neuromuscular monitoring group compared to 20 out of 35 in clinical assessment group. Hence, majority showed excellent intubating condition on moment of intubation was chosen by loss of reaction to TOF stimulation, assessed visually and also by acceleromyography. Many studies have shown 95% to 100% excellent intubating conditions on assessing similarly to reaction on TOF stimulation of the ulnar nerve. [7,21] Thus, this can be considered as a suitable method in assessing optimal conditions for intubation.

Neuromuscular monitoring during endotracheal intubation is not a common practice and is mainly used to monitor the muscle relaxation intraoperatively and to measure any residual paralysis before extubation. Hence, this is a suitable non pharmacological method which can be used during endotracheal intubation.

CONCLUSION

In this study, we have observed that Neuromuscular block monitoring based endotracheal intubation has lower haemodynamic changes compared to clinical assessment based endotracheal intubation. Also, 91.43% of the patients had excellent intubating conditions in Neuromuscular block monitoring group compared to 57.14% of patients having excellent intubating condition in clinical assessment-based group.

Hence, we conclude that Neuromuscular block monitoring of Adductor Pollicis muscle during general anaesthesia can be a suitable, non-pharmacological method to be used during endotracheal intubation helping us in identifying appropriate time of tracheal intubation along with providing excellent intubating conditions, which attenuates the stressor haemodynamic responses produced due to laryngoscopy and endotracheal intubation.

SUMMARY

Strong stressor responses like raised heart rate, raised arterial pressure, EEG changes due to CNS stimulation are seen due to laryngoscopy and endotracheal intubation during induction of general anaesthesia. These are due to incomplete paralysis of the laryngeal muscles leading to inadequate intubating conditions and requiring use of higher pressure for intubation. However, these responses are transient and usually has no significant adverse effects but in cases with Coronary artery disease, intracranial pathology, arterial hypertension, they can lead to myocardial ischemia or secondary brain damage. Many drugs have been successfully used but they might cause unnecessary increased depth of anaesthesia or adverse haemodynamic effects, therefore, a non-pharmacological measure to reduce the response is preferred.

Hence, this study was undertaken to compare the haemodynamic responses of neuromuscular block monitoring guided tracheal intubation to clinical assessment guided tracheal intubation.

Seventy adult patients undergoing elective surgery under general anaesthesia with tracheal intubation were randomized into two groups of 35 each i.e., TOF – Guard guided (Group T) and Clinical assessment guided (Group C). Anaesthesia was induced with propofol 2mg/kg and after standardization of supramaximal stimulus Inj. Vecuronium 0.1mg/kg was administered.

In Group T, trachea was intubated after TOF ratio becomes zero in Adductor Pollicis muscle, whereas in Group C, trachea was intubated after clinical assessment of jaw muscle relaxation, airway tone and ease of ventilation. Changes in heart rate,

mean arterial pressure, mean systolic blood pressure, mean diastolic blood pressure were recorded along with intubating conditions which were scored as per Kreig's et al. Results were analyzed by "Paired-t test and chi square test".

Mean heart rate, mean arterial pressure, mean systolic pressure and mean diastolic pressure were significantly higher in Group C compared to Group T along with 91.43% excellent intubating condition observed in Group T compared to 57.14% excellent intubating condition in Group C.

In conclusion, haemodynamic responses to laryngoscopy and tracheal intubation can be significantly attenuated by detecting appropriate time of intubation by Neuromuscular block monitor of Adductor Pollicis muscle and hence, can be a suitable, non-pharmacological measure in blunting the stressor response to tracheal intubation.

BIBLIOGRAPHY

1. P.F Kotur. Decision Making in Airway Management. Indian Journal of Anaesthesia 2005;49(4):248-50.

2. JayashreeSood. Laryngeal mask airway and its variants. Indian Journal of Anaesthesia 2005;49(4):275-80.

3. Kazama T, Ikeda K. Reduction by fentanyl of the Cp50 values of propofol and haemodynamic responses to various noxious stimuli. Anesthesiology1997; 87:213-27.

4. Kovac AL. Controlling the haemodynamic response to laryngoscopy and endotracheal intubation. J Clin Anesth1996; 8:63-79.

5. Angelard B, Debry C, Planquart X, Dubos D, Dominic L, Gondret R, et al. Difficult intubations. A prospective study. Ann Otolaryngol Chir Cervicofac. 1991; 108(4) :241-3.

6. Morgan JM, Barker I, Peacock JE, Eissa A. A comparison of intubating conditions in children following induction of anaesthesia with propofol and suxamethonium or propofol and remifentanil Anaesthesia 2007; 62:135-9.

7. Witkowska M, Karwacki Z, Wierzchowska J, Bukowski P. Neuromuscular block monitoring for optimization of conditions for endotracheal intubation. Anestezjol Intens Ter 2009; 41:140-4.

8. Miller RD, Erikson IL, Millers Anaesthesia, Seventh edition, volume 1, Churchill Livingstone:Elsevier, 2010: 31.

9. Rees, G.J., Gray, T.C. Methyl-n-propyl Ether. British Journal of Anaesthesia 1950, 22: 83

10. Barash PG, Stoelting RK, eds, Clinical Anaesthesia, 7th edition, Philadelphia: Lippincott Williams& Wilkins, 2013: 18

11. Smith I, Saad Rs. Comparison of intubating conditions after rocuronium or vecuronium when the timing of intubation is judged by clinical criteria. Br J Anaesth 1998; 80:235-7.

12. Nandi R, Basu SR, Sarkar S, Garg R. A comparison of haemodynamic responses between clinical assessment-guided tracheal intubation and neuromuscular block monitoring-guided tracheal intubation: A prospective, randomised study. Indian J Anaesth 2017;61:910-5.

13. Day NS, Blake CJ, Standaert FG, Dretchen KL. Characterization of Train of four responses in fast and slow muscle: effect of d-tubocurarine, pancuronium and vecuronium. Anesthesiology 1983; 58: 414-17.

14. Smith CE, Donati F, Bevan DR. Differential effects of Pancuronium on massester and Adductor Pollicis muscles in human. Anesthesiology 1989; 71: 57-61

15. Donati F, Meistelman C, Plaud B. Vecuronium neuro muscular blockade at the diaphragm, the Orbicularis Oculi and Adductor Pollicis muscles. Anesthesiology 1990; 73: 870-5

16. Miestelman C, Plaud B, Donati F. Rocuronium (ORG 9426) neuro muscular blockade at the adductor muscles of the larynx and Adductor Pollicis in humans. Can J Anaesth 1992; 39: 665-9

17. Ungureanu D, Meistelman C, Frossard J et al. Orbicularis Oculi and the Adductor Pollicis muscles as monitors of atracurium block of laryngeal muscles. Anesth Anal 1993; 77: 775

18. Donati F – Pharmacokinetic and pharmacodynamic factors in clinical use of muscle relaxants. Seminar in Anesthesia 1994; 13: 310 – 20

19. Koscielnaik – Nielsen ZJ, Horn A, Sztuk F, Eriksen K, Skovgaard LT, Viby – Mogensen J. Timing of tracheal intubation: monitoring the Orbicularis Oculi, Adductor Pollicis or use a stopwatch? Eur J Anaesthesiol 1996; 13: 130-5.

20. G.Haller, J-P Gardaz, B. Bissonnette. Evaluation des conditions d' intubation sous rocuronium. Can J Anaesth 1998; 45: 312-16.

21. Le Corre F, Plaud B, Benhamou E, Debaene B. Visual estimation of onset time at the Orbicularis Oculi after five muscle relaxants: application to clinical monitoring of tracheal intubation. Anesth Anal 1999; 89: 1305-10.

22. H.J Lee, K.S. Kim, J.S. Jeong. Comparison of Adductor Pollicis, Orbicularis Oculi and corrugator supercilia as indicators of adequacy of muscle relaxation for tracheal intubation. Br J Anaesth 2009; 869-74.

23. Erik Stalberg; Clinical Neurophysiology of disorders of muscle and NMJ, including fatigue, Elsevier; 2003, vol 2; 27-30

24. *http://update.anaesthesiologists.org/wp-content/uploads/2009/10/Neuromuscular-Block-Monitoring1.pdf*

25. J.A.J Martyn, M. Jonsson fagerlund and L.I Eriksson: Basic Principles of Neuromuscular Transmission, Anaesthesia 2009; 64 (Suppl 1): 1-9

26. Naguib M, Flood P, McArdle JJ, Brenner JR: Advances in neurobiology of the NMJ: Implications for the anesthesiologist. Anesthesiology 2002; 96:202

27. Valtora F, Jahn R, Fesce R et al: Synaptophysin (p38) at the frog NMJ: Its incorporation into the axolemma and recycling after intense quantal secretion. J Cell Biol 1988; 107:2717

28. Sudhof TC: Synaptic vesicles: An organelle comes of age. Cell 2006; 127:671

29. Viby-Mogensen J, Engbaek J, Eriksson LI et al. Good clinical research practice (GCRP) in pharmacodynamic studies of neuromuscular blocking agents. Acta Anaesthesiol Scand 1996;40:59-74.

30. Meretoja OA, Taivainen T, Brandom BW et al. Frequency of train-of-four stimulation influences neuromuscular response. Br J Anaesth 1994;72:686-687.

31. Bayly PJM. Frequency of repeated neuromuscular stimulation. Anaesthesia 1990;45:171

32. Berger JJ, Gravenstein JS, Munson ES. Electrode polarity and peripheral nerve stimulation. Anesthesiology 1982;56:402-404.

33. Brull SJ, Silverman DG. Visual assessment of train-of-four and double burst induced fade at submaximal stimulating currents. Anesth Analg 1991;73:627-632

34. Saddler JM, Bevan JC, Donati F et al. Comparison of double-burst and train-of-four stimulation to assess neuromuscular blockade in children. Anesthesiology 1990;73:401-403.

35. Torda TA. Monitoring neuromuscular transmission. Anaesth Intens Care 2002;30:123-133.

36. Loan PB, Paxton LD, Mirakhur RK et al. The TOF-Guard neuromuscular transmission monitor. A comparison with the Myograph 2000. Anaesthesia 1995;50:699-702

37. McCluskey A, Meakin G, Hopkinson JM et al. A comparison of acceleromyography and mechanomyography for determination of the dose-response curve of rocuronium in children. Anaesthesia 1997;52:345-349

38. Eikermann M, Groeben H, Husing J et al. Predictive value of mechanomyography and accelerometry for pulmonary function in partially paralyzed volunteers. Acta Anaesthesiol Scand 2004;48:365-370

39. Dahaba AA, Rehak PH, List WF. Assessment of accelerography with the TOF guard: a comparison with electromyography. Eur J Anaesthesiol 1997;14:623-629.

40. Kopman AF, Klewicka MM, Neuman GG. The relationship between acceleromyographic train-of-four fade and single twitch depression. Anesthesiology 2002;96:583-587.

41. Greer R, Harper NJN, Pearson AJ. Neuromuscular monitoring by intensive care nureses: comparison of acceleromyography and tactile assessment. Br J Anaesth 1998;80:384-385

42. Ansermino JM, Sanderson PM, Bevan DR. Acceleromyography improves detection of residual neuromuscular blockade in children. Can J Anaesth 1996;43:589-594

43. Hemmerling TM, Donati F. Neuromuscular blockade at the larynx, the diaphragm and the corrugator supercilii muscle: a review. Can J Anesth 2003;50:779-794

44. Hemmerling TM, Schimidt J, Hanusa C, Wolf T, Schmidt H: Simultaneous determination of Neuromuscular block at larynx, Adductor Pollicis, Orbicularis Oculi and corrugator supercilia muscles. Br J Anaesth 2000;85:856-60

45. Brull SJ, Silverman DG. Pulse width, stimulus intensity, electrode placement and polarity during assessment of neuromuscular block. Anesthesiology 1995;83:702-709

46. Ueda N, Muteki T, Masuda H et al. Determining the optimal time for endotracheal intubation during onset of neuromuscular blockade. Eur J Anaesthesiol 1993;10:3-8

47. Haraldstead VY, Nielsen JW, Joensen F et al. Infusion of vecuronium assessed by tactile evaluation of evoked thumb twitch. Br J Anaesth 1988;61:479-481

48. Saitoh Y, Nakazawa K, Makita K et al. Evaluation of residual neuromuscular block sung train-of-four and double burst stimulation at the index finger. Anesth Analg 1997;84:1354-1358

49. Kim KS, Cheong MA, Lee HJ et al. Tactile assessment for the reversibility of rocuronium-induced neuromuscular blockade during propofol or sevoflurane anesthesia. Anesth Analg 2004;99:1080-1085

50. D'Honneur H, Guignard B, Slavov V et al. Comparison of the neuromuscular blocking effects of atracurium and vecuronium on the Adductor Pollicis and the geniohyoid muscle in humans. Anesthesiology 1995;82:649-654.

51. Norman J. Assessing paralysis. Br J Anaesth 1999;82:321-322

52. Krieg N, Mazur L, Booij LHDJ, Crul JF. Intubation conditions and reversibility of a new non-depolarizing neuromuscular blocking agent Org NC45. Acta Anaesthesiologica Scandinavica 1980; 24: 423-425.

53. Rundshagen I, Schröder T, Prichep LS, John ER, Kox WJ. Changes in cortical electrical activity during induction of anaesthesia with thiopental/fentanyl and tracheal intubation: A quantitative electroencephalographic analysis. Br J Anaesth 2004;92:33-8.

54. Debaene B, Beaussier M, Meistelman C, Donati F, Lienhart A. Monitoring the onset of neuromuscular block at the orbicularis oculi can predict good intubating conditions during atracurium-induced neuromuscular block. Anesth Analg 1995;80:360-3.

ANNEXURE I

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

Mr/Mrs/Miss. _____ we are requesting you toenroll yourself in **"COMPARISON OF HAEMODYNAMIC RESPONSES BETWEEN CLINICAL ASSESSMENT-GUIDED TRACHEAL INTUBATION AND NEUROMUSCULAR BLOCK MONITORING-GUIDED TRACHEAL INTUBATION: ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL STUDY''** conducted by _____, Post Graduate in M.D. Anaesthesiology under the guidance of _____, PROFESSOR, Department of Anaesthesiology, J.N. Medical College, Belagavi under K.A.H.E.R, Belagavi.

Respected Sir/Madam, we request you to enroll yourself to participate in our study as you are eligible for participating in the study. During the study you will be asked some questions regarding your present complaint and you are supposed to answer to the best of your knowledge.

Your participation in research is voluntary. Your decision to or not to participate in the study will not affect your relationship with J.N. Medical College. If you decide to participate you are free to withdraw at any time.

The purpose of the research is to compare the heart rate, blood pressure, intubating conditions in response to tracheal intubation by clinical assessment-guided tracheal intubation and neuromuscular block monitoring- guided tracheal intubation.

Procedure Involved

If you agree to enroll yourself in my study, you will be pre-medicated with Ondansetron 4mg, Ranitidine 50mg intravenously 15 min before surgery. Midazolam0.02mg/kg, Fentanyl 1mcg/kg are administered intravenously. Following pre-oxygenation for 3 minutes, anaesthesia will be induced with propofol 2mg/kg till the disappearance of the eyelash reflex. After the disappearance of the eyelash reflex, a supramaximal TOF stimulus will be applied to the ulnar nerve at the wrist through surface electrodes (stimulation current set at 60mA) using acceleromyograph after automatic calibration. Baseline TOF ratio percentage will be noted. After standardization of supramaximal stimulus intravenous Vecuronium 0.1 mg/kg will be administered over 5s. After the administration of the vecuronium, lungs will be ventilated with 100% oxygen till the tracheal intubation.

Benefits and Risks

During tracheal intubation there is stressor response present which in patients with concomitant coronary artery disease, arterial hypertension or intracranial pathology may lead to myocardial ischemia or secondary brain damage. Many drugs have been used to reduce this stressor response however it might cause adverse hemodynamic effects or might unnecessarily increase the depth of anaesthesia. Hence, a non-pharmacological measure to reduce the stressor response is helpful and preferred.

Voluntary participation / Withdrawal

Taking part in the study is voluntary, you may choose not to enroll yourself in this study. Your decision will not change present or future health care services offered to you at Dr. PrabhakarKore Hospital.

Alternatives

Even if you decline the participation in the study, you will get the routine line of management.

Confidentiality

All information collected about you during the study will be kept confidential. The code numbers will identify you in this study records and the information from this study may be published but your identity will be confidential in any publication. The only people to know that you are a research subject are members of the research team. No information about you or information provided by you during the research will be disclosed to other without your written permission except:

- In emergency to protect your rights and welfare.
- If required by law.

Authorization to Publish Results

When the results of the research are published or discussed, in a conference, no information will be displayed that would disclose your identity. Any information that is obtained in connection with this study and that can be identified with you will remain confidential.

Financial incentives for participation

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research.

Compensation

In the event of injury, related to the study, treatment will be made available at Dr. PrabhakarKore Hospital and MRC, Belagavi. No reimbursement, compensation or free medical care will be given by law.

Queries/ Contact details

If you have any queries about your right as a study subject, you may call Dr. RoopaBellad, Professor of Paediatrics as Chairman of Institutional Ethics Committee on Human Subjects Research at J.N. Medical College, Belagavi.

Consent for participation in research trial

I, _____ voluntarily agree to participate as a subject for the study. By signing this consent form, I am not giving up any of my legal rights and may withdraw myself from the study anytime. I am signing the consent form after having read or been read form in my own vernacular language, including the risks and the benefits and having all my questions answered.

Subject Name: _____

Signature or the Left Thumb Print: _____ Date: _____

Witness Name: _____

Signature: _____ Date: _____

Investigators Name: _____

Signature: _____ Date: _____ Place: _____

ANNEXURE II

PROFORMA

"COMPARISON OF HAEMODYNAMIC RESPONSES BETWEEN CLINICAL ASSESSMENT-GUIDED TRACHEAL INTUBATION AND NEUROMUSCULAR BLOCK MONITORING-GUIDED TRACHEAL INTUBATION: ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL STUDY''

Patient Name: IP No.:

Age: Gender:

Date of Operation: Occupation:

Address: Anaesthesiologist:

Preanaesthetic Evaluation:

1. Chief Complaints:
2. Past History: HTN / DM / Asthma / Epilepsy / Rx allergy/Other relevant history:
3. Treatment / Drug intake history:
4. History of previous surgeries and anaesthetic exposure:
5. Family history:

General physical examination

Pallor / Icterus / Clubbing / Cyanosis / Lymphadenopathy / Edema

Pulse Rate: BP:

Respiratory Rate: Temperature:

Systemic Examination

RS: CNS:

CVS: Abdomen:

Airway examination:

Jaw movements: Teeth:

Airway assessment: Spine:

Investigations

Hb: Total Leucocyte Count:

Platelet count: Serum Urea:

Serum Creatinine: RBS:

ECG: Chest X-Ray:

Urine R/M: Others:

ASA GRADE: I II III IV V E

Diagnosis:

Proposed Surgery:

Preoperative baseline values:

Pulse: BP:

Group of study belongs to:

Clinical assessment-guided:

TOF- Guard assessment-guided:

Study Parameters:

The haemodynamic changes of both clinical assessment-guided tracheal intubation and TOF-guard guided tracheal intubation is the outcome of study and is recorded at T0 – before shifting the patient to OT table, T1 – immediate after vecuronium administration, T2 – 1 min after vecuronium administration, T3 – after inflation of the cuff following intubation, T4 - 1 min after intubation, T5 – 3 min after intubation, T6 – 5 min after intubation.

Intubation conditions are graded using scoring scale described Krieg et al, ranging from 3(Excellent) to 12(Inadequate).

Definition of variables:

- Heart rate will be measured at

T0 – Before shifting the patient to OT table

T1 – Immediate after vecuronium administration

T2 – 1 min after vecuronium administration

T3 – After inflation of the cuff following intubation

T4 – 1 min after intubation

T5 – 3 min after intubation

T6 – 5 min after intubation

- Mean arterial pressure will be measured at

T0 – Before shifting the patient to OT table

T1 – Immediate after vecuronium administration

T2 – 1 min after vecuronium administration

T3 – After inflation of the cuff following intubation

T4 – 1 min after intubation

T5 – 3 min after intubation

T6 – 5 min after intubation

- Failed intubation is defined as inability to intubate within 3 attempts or more than 10 mins to intubate.

Inclusion Criteria:

- The subjects are adult undergoing surgical procedures under general anaesthesia candidates aged 18-60 years.
- ASA physical status I and II.
- Mallampati grade I and II.
- Both male and female patients will be included.

Exclusion Criteria:

- Patient refusal
- Anticipated difficult airway
- Pts having CVS, hepatic, renal or neurological disease
- Receiving any drug known or suspected of interfering with neuromuscular function
- Pathology of the neck or upper respiratory tract.
- Pregnant women.
- BMI >30.

	Heart rate	Systolic blood pressure	Diastolic blood pressure
T0 – baseline			
T1 – immediate after vec			
T2 – 1 min after Vec			
T3 – After inflation of the cuff following intubation			
T4 - 1 min after intubation			
T5 – 3 min after intubation			
T6 – 5 min after intubation			

Scoring scale as described by Kreig et al

Points	**1**	**2**	**3**	**4**
Vocal cords	Open	Moving	Closing	Closed
Coughing	None	With Diaphragm	Clear	Severe
Laryngoscopy	Easy	Fair	Difficult	Impossible
Total Score	3-4	5-7	8-10	11-12
Intubating Conditions	Excellent	Good	Poor	Inadequate
Class	1	2	3	4

Intubating Condition:

ANNEXURE III – ETHICAL CLEARANCE CERTIFICATE

K.L.E. ACADEMY OF HIGHER EDUCATION AND RESEARCH
(Deemed – to- be- University)
Accredited 'A' Grade by NAAC (2nd Cycle) Placed in Category 'A' by MHRD (GoI)
JAWAHARLAL NEHRU MEDICAL COLLEGE,
NEHRU NAGAR, BELAGAVI-590010 (KARNATAKA-INDIA)
Website: http//www.jnmc.edu
E-Mail : dome@jnmc.edu
Phone: (+ 91-(0)831 Office : 2472550
Principal: 2471701
Fax No. +91 (0)831 – 2470759

Ref: MDC/DOME/32 **Date: 24/11/2018**

REG NO. BA0118001

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"COMPARISON OF HAEMODYNAMIC RESPONSES BETWEEN CLINICAL ASSESSMENT –GUIDED TRACHEAL INTUBATION AND NEUROMUSCULAR BLOCK MONITORING –GUIDED TRACHEAL INTUBATION: ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL STUDY"**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

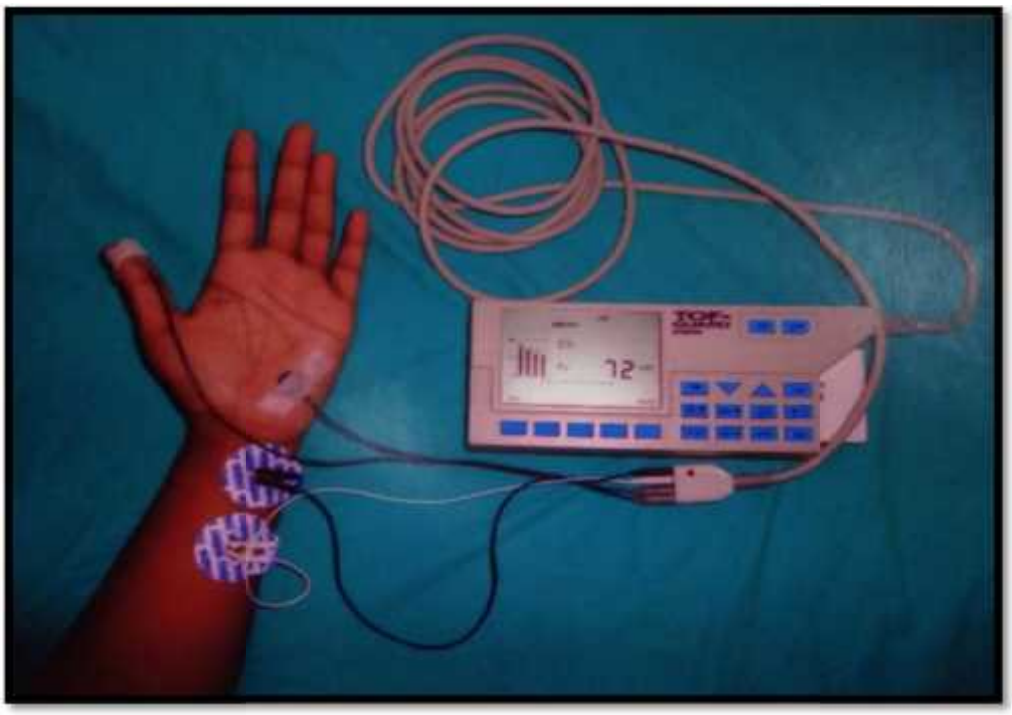
(Dr. Arathi Darshan)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

(Dr. Roopa M Bellad)
Chairman,
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

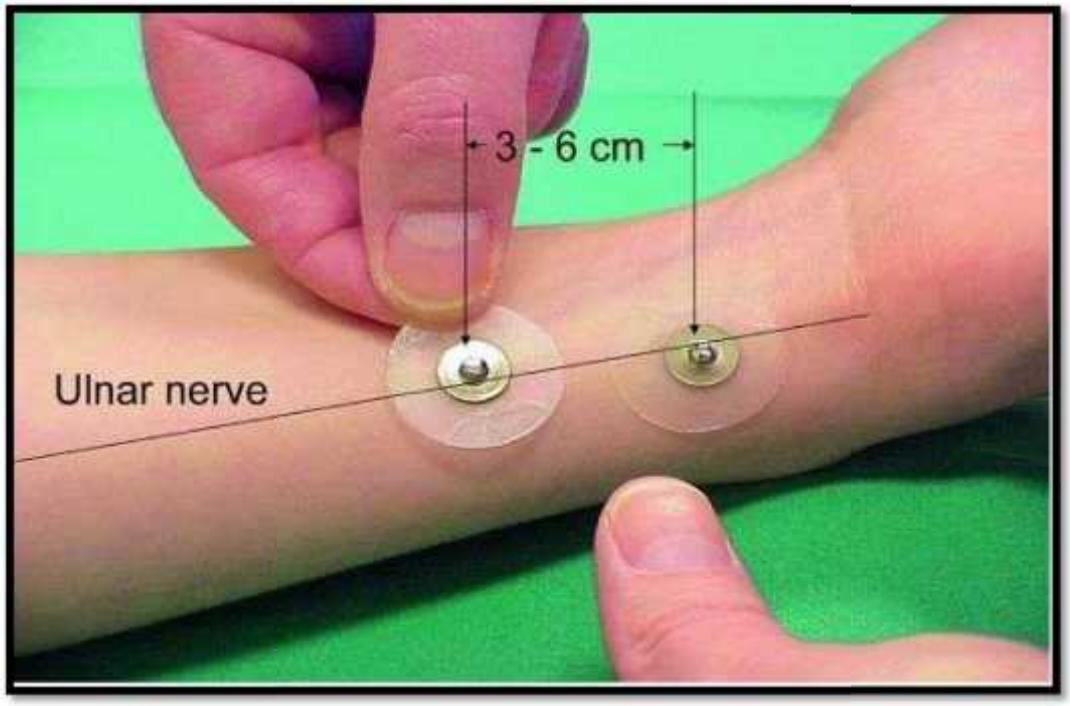
32

ANNEXURE IV: PHOTOGRAPHS

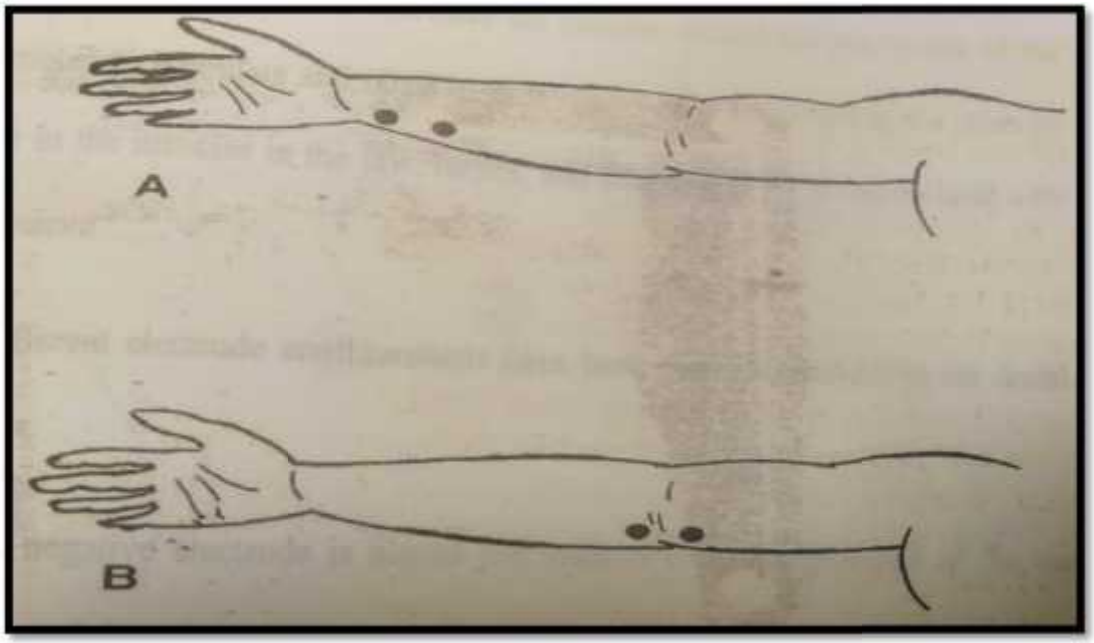
Photograph 1: Train of Four (TOF – Guard) Acceleromyograph (Organon – Teknika, Belgium)



Photograph 2: Placement of Electrodes for Ulnar nerve stimulation along with TOF - Guard



Photograph 3: Electrodes placed in the correct position over the Ulnar nerve of the left forearm



Photograph 4: Position of placement of electrodes for ulnar nerve stimulation

A: Electrodes placed along the ulnar aspect of the distal forearm

B: Electrodes placed over the sulcus of the medial epicondyle of humerus.

ANNEXURES V - MASTER CHART

GROUP T

Sl. No	Randomization no	IP no	Age (yrs)	sex	Weight (Kg)	ASA	MPG	T0 - baseline				T 1 - immediate after VEC				T2 - 1 min after VEC				T3 - after inflation of the cuff following intubation				T4 - 1 min after intubation				T5 - 3 min after intubation				T6 - 5 min after intubation				Scoring scale as described by Kreig et al
								HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	
1	1	946811	58	F	65	1	1	78	130	80	97	80	95	74	81	80	95	76	82	84	100	78	85	80	102	80	87	78	101	80	87	82	105	82	90	1
2	2	945022	56	M	75	2	1	75	155	80	105	75	140	75	97	76	145	76	99	82	150	80	103	80	150	82	105	78	154	80	105	75	152	80	104	1
3	4	920237	55	F	60	1	2	92	130	80	97	96	90	60	70	96	90	60	70	98	100	70	80	96	103	72	82	93	105	70	82	90	110	70	83	1
4	7	949842	21	M	70	1	1	88	126	78	94	96	116	70	85	98	114	68	83	98	122	70	87	94	118	68	85	90	118	72	87	84	122	70	87	1
5	9	948024	27	M	68	1	1	78	112	78	89	88	102	70	81	88	100	68	79	96	128	78	95	92	122	72	89	88	118	70	86	82	118	72	87	1
6	10	946811	58	F	58	1	1	76	130	78	95	76	118	70	86	78	120	70	87	85	128	76	93	83	125	76	92	80	122	74	90	80	120	74	89	1
7	14	948652	60	M	70	2	2	74	136	88	104	85	124	73	90	86	120	72	88	94	132	84	100	90	130	80	97	84	126	74	91	82	123	70	88	2
8	15	920616	58	F	70	1	2	76	108	78	88	76	92	70	77	74	94	70	78	79	100	72	81	82	102	72	82	80	108	70	83	82	110	80	90	1
9	17	920965	48	M	62	1	1	74	128	79	95	78	113	70	84	80	109	72	84	88	119	77	91	90	125	85	98	90	127	88	101	86	125	86	99	1
10	19	921469	58	F	55	1	1	83	144	71	95	88	130	80	97	88	125	78	94	85	109	57	74	88	110	60	77	80	107	67	80	82	112	68	83	1
11	21	921448	60	F	57	1	2	86	143	81	102	90	143	81	102	101	104	79	87	98	131	70	90	94	121	70	87	92	110	68	82	90	110	70	83	1
12	22	946912	42	F	67	1	1	85	108	87	94	88	92	45	61	86	92	52	65	94	97	58	71	91	94	59	71	81	96	48	64	89	106	61	76	1
13	24	960681	26	F	58	1	2	82	110	80	90	80	108	78	88	78	110	80	90	86	115	85	95	84	112	78	89	84	110	80	90	86	115	78	90	1

14	25	960653	28	F	75	1	1	78	110	80	90	87	100	72	81	86	102	70	81	88	128	78	95	82	120	76	91	80	120	78	92	80	118	76	90	1
15	26	960944	45	M	55	1	2	76	116	78	91	84	102	70	81	86	100	68	79	98	124	84	97	94	120	78	92	88	116	72	87	82	110	68	82	1
16	28	960789	58	F	50	2	1	76	140	86	104	82	128	92	104	84	128	90	103	88	134	94	107	84	130	90	103	80	126	88	101	78	126	84	98	1
17	30	961185	18	M	58	1	2	80	130	78	95	82	128	74	92	84	128	70	89	90	132	76	95	88	130	74	93	84	130	76	94	78	132	74	93	1
18	31	961057	50	F	75	1	1	68	128	84	99	72	118	80	93	70	116	78	91	78	126	84	98	74	122	80	94	70	118	78	91	72	122	80	94	1
19	32	961047	55	M	60	2	2	68	138	90	106	72	123	84	97	70	122	80	94	84	128	84	99	82	126	80	95	82	122	80	94	78	118	78	91	2
20	37	925152	53	F	50	2	1	70	130	90	103	72	118	74	89	74	116	72	87	72	122	74	90	70	118	70	86	72	118	72	87	70	123	70	88	1
21	38	928163	21	M	74	1	1	88	122	78	93	86	102	68	79	84	100	68	79	88	105	72	83	84	104	70	81	82	106	72	83	84	110	72	85	1
22	39	920249	52	F	70	1	2	70	130	80	97	72	124	72	89	70	122	74	90	72	126	76	93	70	128	74	92	72	126	74	91	75	124	76	92	1
23	41	919883	28	F	75	1	1	78	126	70	89	80	116	65	82	82	118	64	82	84	123	68	86	82	120	72	88	80	118	70	86	82	115	71	86	1
24	42	920171	55	M	80	2	1	74	140	90	107	71	129	78	95	75	124	74	91	78	127	78	94	75	125	74	91	74	126	78	94	74	124	82	96	1
25	43	923477	36	F	71	1	2	76	120	70	87	80	108	68	81	78	106	67	80	82	112	68	83	80	116	70	85	82	118	74	89	86	121	71	88	1
26	45	933376	38	F	68	1	1	78	116	80	92	82	102	68	79	80	98	68	78	85	102	70	81	84	106	75	85	81	110	72	85	84	112	70	84	1
27	48	933822	33	F	76	2	1	78	138	80	99	76	118	72	87	80	116	70	85	86	118	72	87	82	124	74	91	78	128	70	89	79	124	68	87	1
28	49	933675	52	M	64	1	1	70	132	80	97	76	110	68	82	74	106	64	78	78	109	68	82	76	113	71	85	74	115	75	88	75	116	72	87	2
29	52	932835	25	F	68	1	2	70	116	72	87	74	104	62	76	76	104	64	77	80	105	68	80	78	109	68	82	76	112	71	85	74	118	74	89	1
30	55	935054	48	F	62	2	2	64	118	68	85	68	98	60	73	70	100	62	75	75	105	69	81	71	106	71	83	68	109	70	83	69	114	72	86	1
31	58	936339	28	F	62	1	2	68	106	78	87	72	92	65	74	76	94	66	75	79	99	67	78	78	102	69	80	74	105	72	83	75	106	70	82	1
32	61	936667	35	F	77	1	2	76	112	78	89	88	101	64	76	85	104	64	77	86	110	68	82	80	115	72	86	78	114	78	90	74	111	74	86	1
33	68	937774	56	F	67	2	2	78	132	88	103	76	108	72	84	71	110	70	83	72	115	76	89	70	118	74	89	72	126	76	93	73	129	73	92	1
34	69	935330	36	F	77	1	2	88	118	78	91	84	96	64	75	79	98	66	77	85	104	68	80	85	109	71	84	84	116	74	88	85	119	71	87	1
35	70	938538	30	M	66	1	2	78	132	86	101	82	104	78	87	81	106	74	85	88	112	78	89	81	116	74	88	78	119	78	92	79	124	80	95	1

GROUP C

sl. No	Randomization no	IP no	Age (yrs)	sex	Weight (Kg)	ASA	MPG	T0 - baseline				T 1 - immediate after VEC				T2 - 1 min after VEC				T3 - after inflation of the cuff following intubation				T4 - 1 min after intubation				T5 - 3 min after intubation				T6 - 5 min after intubation				Scoring scale as described by Kreig et al
								HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	HR	SBP	DBP	MAP	
1	3	945889	60	F	70	1	1	66	136	76	96	66	125	68	87	68	126	70	89	80	142	84	103	81	144	82	103	80	138	78	98	80	136	78	97	1
2	5	944283	32	F	71	1	1	70	126	70	89	72	110	62	78	70	110	64	79	82	138	82	101	84	136	80	99	84	132	78	96	84	132	82	99	1
3	6	954923	58	F	80	1	2	70	112	78	89	78	110	80	90	76	115	78	90	82	140	80	100	85	135	82	100	78	130	80	97	78	122	78	93	1
4	8	947058	40	M	74	1	2	80	120	74	89	78	108	68	81	78	110	70	83	88	138	78	98	88	136	80	99	86	130	78	95	80	128	74	92	1
5	11	954882	29	F	65	1	2	90	112	88	96	94	110	85	93	98	92	68	76	105	128	78	95	100	128	80	96	95	126	78	94	91	124	76	92	1
6	12	973046	52	F	64	1	1	68	140	80	100	66	120	78	92	68	126	80	95	80	152	92	112	78	148	78	101	78	142	72	95	78	136	70	92	2
7	13	970459	45	F	80	1	2	74	138	88	105	74	115	80	92	74	110	80	90	82	128	90	103	82	126	88	101	80	128	78	95	86	125	74	91	1
8	16	972925	37	M	73	1	1	78	110	70	83	80	90	65	73	82	92	65	74	88	136	84	101	85	128	80	96	80	126	76	93	82	126	78	94	1
9	18	972845	58	F	67	2	1	68	130	70	90	78	110	62	78	78	115	68	84	82	140	79	99	78	138	80	99	75	136	74	95	82	130	72	91	1
10	20	972256	34	F	63	1	2	76	110	80	90	74	95	70	78	76	99	72	81	82	140	86	104	80	140	84	103	78	132	86	101	78	130	80	97	1
11	23	971719	27	F	71	1	2	86	115	78	90	80	110	68	82	82	110	70	83	88	132	90	104	85	138	86	103	84	136	84	101	84	130	80	97	2
12	27	971975	33	F	58	1	1	88	126	88	101	98	116	80	92	95	122	78	93	102	132	95	107	100	126	90	102	98	125	88	100	88	120	85	97	2
13	29	971413	49	F	72	2	1	68	140	80	100	60	128	75	93	62	132	80	97	86	156	92	113	86	150	90	110	82	146	88	107	80	142	80	101	2
14	33	971537	32	F	68	1	1	78	140	90	107	88	132	72	92	85	130	78	95	88	145	102	116	84	144	100	115	80	138	96	110	82	135	92	106	1
15	34	971107	33	M	73	2	2	80	140	100	113	78	126	92	103	80	130	88	102	86	142	103	116	84	142	96	111	80	138	96	110	78	136	95	109	2
16	35	971025	26	M	58	1	2	88	140	90	107	80	135	72	93	84	132	74	93	92	138	78	98	90	136	74	95	87	134	88	103	88	134	90	105	1
17	36	968153	60	M	50	2	1	68	150	88	109	70	130	85	100	68	134	88	103	86	148	96	113	82	146	90	109	80	150	88	109	74	148	90	109	1
18	40	967212	57	F	83	1	1	80	138	90	106	86	126	82	97	84	120	78	92	88	126	85	99	86	125	80	95	88	122	78	93	86	126	80	95	1

19	44	968174	47	M	77	1	2	65	130	80	97	68	118	72	87	66	120	68	85	90	136	82	100	76	132	80	97	72	128	75	93	84	128	70	89	2
20	46	966482	55	M	65	1	2	80	136	80	99	88	117	74	88	85	123	75	91	92	132	80	97	90	130	78	95	85	126	78	94	87	124	80	95	1
21	47	966767	44	F	66	1	1	84	100	60	73	92	88	62	71	96	86	65	72	100	138	78	98	95	136	76	96	92	96	76	83	90	98	70	79	2
22	50	967194	36	M	69	1	2	78	130	70	90	82	115	68	84	80	124	70	88	86	136	85	102	80	134	80	98	75	130	80	97	80	128	78	95	2
23	51	966966	60	M	60	1	1	74	136	84	101	88	128	80	96	90	126	78	94	96	138	88	105	92	136	80	99	90	132	80	97	83	128	80	96	1
24	53	966968	30	F	66	1	2	80	118	78	91	88	105	72	83	90	102	70	81	85	136	84	101	80	136	80	99	78	122	78	93	80	130	80	97	2
25	54	966478	60	M	71	1	1	64	140	90	107	69	128	88	101	72	123	82	96	86	138	88	105	84	134	86	102	82	130	84	99	78	132	82	99	2
26	56	966427	30	F	67	1	1	76	110	70	83	79	88	68	75	88	80	62	68	96	140	82	101	92	136	80	99	90	130	76	94	86	128	72	91	1
27	57	966438	27	M	63	1	1	80	130	80	97	85	116	72	87	82	110	70	83	88	128	76	93	84	124	72	89	84	120	72	88	80	118	70	86	2
28	59	965459	42	F	62	1	2	74	112	84	93	78	92	75	81	80	96	70	79	88	134	84	101	85	130	86	101	84	128	84	99	82	124	80	95	2
29	60	966161	18	F	67	1	1	74	90	60	70	79	82	60	67	82	80	62	68	88	140	78	99	84	140	80	100	82	130	76	94	82	128	78	95	1
30	62	965613	26	F	64	1	1	70	110	70	83	78	92	68	76	75	96	70	79	85	132	74	93	80	128	74	92	78	124	72	89	76	128	70	89	2
31	63	965674	25	F	66	1	2	70	90	60	70	80	80	62	68	88	82	62	69	92	140	72	95	87	144	80	101	84	142	72	95	82	130	70	90	1
32	64	965779	25	M	69	1	1	80	115	78	90	85	102	70	81	82	106	70	82	88	122	85	97	88	120	84	96	84	118	80	93	82	115	80	92	2
33	65	964899	23	F	72	1	2	78	110	80	90	80	105	72	83	78	103	70	81	85	114	86	95	86	128	84	99	80	128	80	96	82	120	78	92	1
34	66	964850	50	M	64	1	1	88	140	90	107	86	132	82	99	92	128	75	93	98	136	88	104	94	134	84	101	90	130	78	95	90	132	80	97	2
35	67	965131	24	F	76	2	2	78	100	70	80	74	92	72	79	82	88	68	75	89	136	78	97	88	136	80	99	85	134	78	97	78	130	80	97	1

ANNEXURE-VI

KEY TO MASTER CHART

ASA	–	American Society of Anaesthesiologists
DBP	–	Diastolic Blood Pressure
F	–	Female
HR	–	Heart Rate
MPG	–	Mallampati Grade
min	–	Minutes
M	–	Male
MAP	–	Mean Arterial Pressure
SBP	–	Systolic Blood Pressure