" COMPARATIVE STUDY OF THE ONSET TIME OF CISATRACURIUM FOR TRACHEAL INTUBATION WITH AND WITHOUT PRIMING DOSE OF CISATRACURIUM IN ADULT PATIENTS UNDERGOING GENERAL ANAESTHESIA: A ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL TRIAL"

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ENDORSEMENT

This is to certify that the dissertation entitled **"COMPARATIVE STUDY OF THE ONSET TIME OF CISATRACURIUM FOR TRACHEAL INTUBATION WITH AND WITHOUT PRIMING DOSE OF CISATRACURIUM IN ADULT PATIENTS UNDERGOING GENERAL ANAESTHESIA: A ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL TRIAL"** is a bonafide research work done by **REG NO. BA0119007** Department of Anaesthesiology, Jawaharlal Nehru Medical College, Nehru Nagar, Belagavi – 590 010.

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ABBREVIATIONS

ASA	-	American society of Anesthesiologists
ATP	-	Adenosine triphosphate
Ach	-	Acetylcholine
Da	-	Dalton
ED	-	Effective dose
HS	-	Highly significant
HR	-	Heart rate
I.V	-	Intravenous
K^+	-	Potassium
ml	-	Millilitre
mv	-	Millivolt
ms	-	Millisecond
mA	-	Milli ampere
mm^2	-	Square milli metre
mg/kg	-	Milligram per kilogram
MAP	-	Mean arterial pressure
MEPP	-	Miniature end plate potential
MgSo4	-	Magnesium sulphate
Na^+	-	Sodium
NMBA	-	Neuro muscular blocking agents

NAchR - Nicotinic acetylcholine receptor

nm - Nano meter

NMT - Neuromuscular monitoring

NMJ - Neuromuscular junction

NDMR - Non depolarizing muscle relaxant

NS - Not significant

PH - Potential of hydrogen

RCT - Randomised controlled trial

SNAP-25 - Synaptosome associated protein of 25 Kda

SV - Synaptic vesicle

Sec - Second

SNARE - Soluble N-ethylmale-imide-sensitive factor-attachment protein receptors

TOF - Train of four

ABSTRACT

TITLE: "COMPARATIVE STUDY OF THE ONSET TIME OF CISATRACURIUM FOR TRACHEAL INTUBATION WITH AND WITHOUT PRIMING DOSE OF CISATRACURIUM IN ADULT PATIENTS UNDERGOING GENERAL ANAESTHESIA: A ONE YEAR HOSPITAL BASED RANDOMIZED CLINICAL TRIAL".

INTRODUCTION: Endotracheal intubation is important for securing the airway for administering general anaesthesia for surgical procedures and muscle relaxants aid in securing the airway. Cisatracurium is a unique intermediate acting neuromuscular blocking agent that is more potent than atracurium but has a delayed onset time. Therefore, various methods have been used to shorten the time of onset of these drugs by using higher dose, priming etc.

OBJECTIVES: To compare the onset of action of Cisatracurium for tracheal intubation and to compare the Intubating conditions with priming by using 0.01mg/kg Cisatracurium as priming dose and using 0.14mg/kg Cisatracurium as intubating dose and without priming by using 0.15mg/kg Cisatracurium as intubating dose in patients posted for elective surgeries under general anaesthesia.

METHODOLOGY: After randomization a total of 60 patients were divided into two groups. Patients in group A received priming dose of 0.01mg/kg Cisatracurium three minutes before the intubating dose of 0.14mg/kg Cisatracurium and group B received

normal saline three minutes before and 0.15mg/kg Cisatracurium as intubating dose. TOF monitoring was done and the time of onset of neuromuscular blockade and intubating conditions were noted.

RESULTS: The Intubating conditions were excellent in 28(93.3%) patients and good in 2(6.7%) in group A and 25(83.3%) patients had excellent intubating conditions and 5(16.7%) patients had good intubating conditions in group B. The mean onset time was 2.818 ± 0.108 minutes in group A and 3.175 ± 0.118 minutes in group B with p value <0.005.

CONCLUSION: To conclude, the priming dose of Cisatracurium of 0.01 mg/kg accelerates the onset time of neuromuscular blockade with 0.14mg/kg of intubating dose of cisatracurium and also provides good intubating conditions compared to 0.15mg/kg Cisatracurium as intubating dose without priming.

KEYWORDS: Priming, Cisatracurium, Intubation.

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INTRODUCTION

Endotracheal intubation obtained with the aid of muscle relaxants is essential for securing the airway for administering general anaesthesia for surgical procedures. Rapid onset and short duration of action are the ideal properties of a neuromuscular blocking drug to achieve successful laryngoscopy and tracheal intubation which can be important during difficult airway or in patients with full stomach.[1]

Succinyl choline, is a depolarizing muscle relaxant with rapid onset of action but has adverse effects like muscle contractions leading to post op muscle pain, hyperkalemia, bradycardia, increased intra ocular pressure, intragastric pressure and intracranial pressure.[2] Therefore, in situations where succinylcholine is contraindicated the need for better drugs without its side effects paved a way to the development of non-depolarizing neuromuscular blocking drugs.

Amino-steroid and Benzyl-iso-quinoline are the two classes of non-depolarizing neuromuscular blocking agents and drugs like Atracurium, Vecuronium etc were introduced which were devoid of the side effects of Succinylcholine. These drugs lack a rapid onset of action which is important for securing an airway in emergency situations.

Atracurium is a nondepolarizing neuromuscular blocking drug and is advantageous over other neuromuscular blocking drugs because of its rapid degradation and non-organ dependent elimination i.e, by Hoffmann elimination and therefore safe to use in geriatric patients and patients with organ failure but it is associated with histamine release and hypotension.[3]

Cisatracurium is a unique intermediate acting neuromuscular blocking agent introduced recently into clinical practice in India. It undergoes Hoffmann elimination with the advantage of no histamine release, higher autonomic stability and more potent than

Atracurium with a stable cardiovascular state during induction.[4] But both of these drugs have a delayed onset time.

Therefore, various methods have been used to shorten the onset time of these drugs by using higher dose, priming. Use of higher doses can increase the onset of neuromuscular block but there can be prolonged duration of block and delayed recovery.[5]

Priming is a technique which consists of giving a small sub paralyzing dose three or six minutes prior to giving the dose for intubation of the same or other class of drug which will help in decreasing the time of onset of the intermediate and long - acting muscle relaxants.[6]

Thus, this study was considered to compare the onset time of Cisatracurium with or without priming technique for intubation and also to study the intubating conditions with both the techniques in patients undergoing elective surgeries under general anaesthesia.

AIMS AND OBJECTIVES

The objectives of the study were to compare:

1.The onset of action of Cisatracurium for tracheal intubation and

2.The Intubating conditions

Between 0.01mg/kg as priming dose along with 0.14mg/kg Cisatracurium as intubating dose and 0.15mg/kg Cisatracurium as intubating dose without priming in patients posted for elective surgeries under general anaesthesia.

REVIEW OF LITERATURE

The introduction of neuromuscular blocking drugs has changed the management of anaesthesia and enabled a new era of surgery. Narcosis, muscle relaxation and analgesia became the triad of general anaesthesia. Before the introduction of neuromuscular blocking drugs endotracheal intubation was done with the help of inhalational agents which caused trauma, respiratory and cardiac depression.[7]

Neuromuscular blocking agents are classified as depolarizing and non-depolarizing agents based on their action at the postjunctional acetylcholine receptors. Succinylcholine is the common depolarizing neuromuscular blocking agent used for its rapid action and short duration for tracheal intubation for many years. The many negative effects associated with it like raised intra cranial pressure, intra ocular pressure, masseter spasm, malignant hyperthermia etc have led to the search of newer agents with better conditions for intubation without the negative effects.[7]

Savarese and Kitz et al in 1975 mentioned the characteristics of an ideal neuromuscular blocking agent that it should have short duration of action, it should be a nondepolarizing agent and should be selective for neuromuscular junction and should be easily reversible.[8]

Atracurium was introduced in the 1980s.It undergoes Hoffmann elimination which is dependent on temperature and PH and is not affected by renal or hepatic failure. The onset time is more than Succinylcholine and if given at higher dose can increase the onset time but associated with histamine release which may cause hypotension and increased heart rate. Laudanosine is formed after its metabolism which has epileptic properties and can be harmful in older patients and patients with kidney failure.[18]

Cisatracurium is an isomer of Atracurium which also undergoes Hoffmann elimination and is devoid of histamine induced cardiovascular effects and Laudanosine is merely produced when compared with Atracurium and it is three times more potent than Atracurium. Despite these advantages the time of onset is not as rapid as Succinylcholine and various methods to fasten the onset were introduced. [4]

Krishna Prasad Deepika et al. in 1999 conducted a randomized study in the University of Miami on 60 females aged 18 to 65 years posted for various gynecologic surgeries requiring general anesthesia and belonging to ASA grade Ⅰ, Ⅱ and Ⅲ to study the changes on pharmacodynamics and the conditions of intubation associated with the use of Cisatracurium in various doses and also by giving 0.01mg/kg Cisatracurium as priming dose.[6]

They studied these patients by considering them into four groups. Priming technique was used in three groups and placebo was given to group four patients. For priming, Cisatracurium of 0.01mg/kg was given to patients in groups Ⅰ, Ⅱ and Ⅲ. Priming time was taken as four minutes and after that 0.09mg/kg Cisatracurium was used as intubating dose in group Ⅰ patients and 0.14mg/kg Cisatracurium was used in group Ⅱ patients and 0.19mg/kg Cisatracurium was used in group Ⅲ patients. Cisatracurium of 0.2mg/kg was given to group Ⅳ patients. Train of four monitoring was done and intubation was done when the height of the first twitch was 10-15% of the control group. The difference in onset time of group one and group four patients was more when compared with other groups. They also concluded that in group three patients in whom 0.19mg/kg Cisatracurium was given as intubating dose after priming dose, the onset time did not decrease much as compared to group two patients where Cisatarcurium 0.14mg/kg was used as intubating dose and the pharmacodynamics were similar to those patients who

received 0.2mg/kg Cisatracurium without priming along with an advantage of smaller duration.

Peter H. K. Mak and Michael G. Irwin conducted a double blinded RCT in Queen Mary hospital of Hong Kong in 2002 to demonstrate the effect of priming using Rocuronium and Cisatracurium on the time of onset of Cisatracurium on ninety patients of 18 and 59 years of age of both genders posted for various surgical procedures who required general anaesthesia.[9]

90 patients were divided into three groups of 30 each and anaesthesia was induced with fentanyl followed by propofol in all the three groups. Cisatracurium 0.015mg/kg was given to group Ⅰ patients and Rocuronium 0.09mg/kg was given to group Ⅱ patients and normal saline was given to group Ⅲ which was taken as control group. Priming time was taken as six minutes after which Cisatracurium 0.135mg/kg was given to group Ⅰ and group Ⅱ patients and Cisatracurium 0.15mg/kg was given to group Ⅲ patients. 10 seconds after giving the priming dose, train of four ratios and height of the first twitch in all the three groups were recorded. When the height of the first twitch was recorded to be less than 15% of the baseline height, intubation was done. When Cisatracurium of 0.015mg/kg and Rocuronium 0.09mg/kg were used for priming the onset of neuromuscular blockade was sooner when compared with the group Ⅲ in which normal saline was used for priming and the conditions for intubation were good in all the patients belonging to the three groups.

Yigal Leykin et al in 2008 at Santa Maria Degli Angeli hospital Italy conducted a study on 124 patients who were listed for surgeries electively and who require general anaesthesia and belonging to ASA grade one and two to observe the changes associated with using Ephedrine and also by using Cisatracurium as priming on the conditions of intubation.[10]

31 patients were allocated into four groups and Propofol and Sufentanil was used for induction in all the patients. 70microgram/kg Ephedrine was given to group E, and to group PE along with it 0.005mg/kg Cisatracurium was given for priming, in group P only 0.005mg/kg Cisatracurium was given and in group NPE no Ephedrine or priming was done. Priming time was taken as three minutes and later 0.145mg/kg of Cisatracurium was given as intubation dose in group P and group PE. Cisatracurium 0.15mg/kg as intubation dose was given to patients in group E and group NPE. 60 seconds after giving the intubation dose, if the intubation was done within 20 seconds it was considered as successful intubation. The observation which they made was that in group PE all the patients had successful intubation and in group P only 74%, in group E only 77% and in group NPE it was only 64% which was successful. Excellent conditions of intubation were seen in all patients in group PE and only 52% in group P and E and 64% in group NPE patients. They observed that when Ephedrine was given along with priming dose of Cisatracurium before giving the intubating dose of Cisatracurium the conditions of intubation are ideal after 60 seconds.

Shih Pin Lin et al. in 2009 did a prospective study in Taipei Veterans General Hospital, Yang Ming University Taiwan on ASA grade one and two patients to observe the use of rocuronium on the time of onset of Cisatracurium by using priming technique.[11]

Three groups with 20 patients in each were studied after randomization. Priming technique was used in group Ⅰ and Ⅱ with 0.06 mg/kg Rocuronium and 0.01 mg/kg Cisatracurium respectively and patients in group Ⅲ were given normal saline. Priming interval was taken as three minutes and after that 0.14mg/kg Cisatracurium was given as intubation dose in groups Ⅰ and Ⅱ and in group Ⅲ, 0.15mg/kg Cisatracurium was used as intubating dose. Train of four monitoring was done to find the time of onset

in all the three groups. They observed that the onset time in group Ⅰ and Ⅱ was less than that of group Ⅲ and that priming with Rocuronium made the onset faster when compared with priming by Cisatracurium.

A.M.EI-Kasaby et al.in 2010 conducted a study on 64 patients belonging to both genders aged from 20 to 65 years at Suez canal university hospital, Egypt to understand and compare the time of onset ,duration of neuromuscular block ,intubating conditions and effects of histamine between Atracurium and various doses of Cisatracurium.[12]

Four groups were allocated to study these patients with 16 in each group. 0.5mg/kg Atracurium was given to patients in group Ⅰ and 0.1mg/kg Cisatracurium given to patients in group Ⅱ, 0.2mg/kg Cisatracurium given to patients in group Ⅲ and 0.3mg/kg Cisatracurium was given to patients in group Ⅳ respectively. The time of onset was less with group Ⅰ when compared with group Ⅱ. The time of onset was low and block duration was more in groups Ⅲ and Ⅳ when compared with groups Ⅰ and Ⅱ.They observed that 0.5mg/kg Atracurium had faster onset when compared with 0.1mg/kg Cisatracurium and that higher dose of Cisatracurium had better conditions for intubation with no release of histamine and better haemodynamics when compared with Atracurium 0.5mg/kg or Cisatracurium 0.1mg/kg.

Sang Hun Kim et al. conducted a prospective study in 2012 on 48 patients in Chosun University Hospital, Gwangju, Korea belonging to ASA grade one and two and aged 18-65years of either gender to understand the use of Magnesium Sulfate when given before induction of anaesthesia by Cisatracurium to see the change in the time of onset and recovery time of Cisatracurium.[13]

All the Patients were studied by allotting them equally into two groups. MgSo4 30 mg/kg in 0.9%NS was given to patients in group M and patients in group C were given 0.9% normal saline, 15 minutes prior to the induction. Cisatracurium 0.15mg/kg was used for intubation in both the groups. Train of four monitoring was done to study for the time of onset, lag time, time taken for total recovery, recovery index, recovery time and duration of action. The lag time and time of onset was statistically significant in group M patients when compared with patients in group C. They observed that MgSo4 decreases Cisatracurium's onset time and has no effect on its duration of action.

Byung-Ryang Ahn et al in 2012 at Chosun university school of medicine, Gwangju, Korea conducted a study on 120 patients to observe the changes associated by giving Ketamine along with using Cisatrcurium as priming dose on the conditions of intubation and the time of onset of Cisatracurium.[14]

30 patients were present in each group with a total of four groups. Normal saline was given to patients in group C, Cisatracurium 0.01mg/kg was given to patients in group P ,0.5mg/kg Ketamine was given to patients in group K and Ketamine 0.5mg/kg along with Cisatracurium 0.01mg/kg was given to patients in group PK. Priming time was taken as three minutes and after which 0.15mg/kg Cisatracurium was given to patients in group C and K and 0.14mg/kg Cisatracurium was given to patients in group P and group PK. The time of onset and conditions of intubation were observed in all the groups. Less time of onset and ideal intubating conditions were seen in group PK when compared with other groups. Faster onset time was seen in group P and group K when compared with group C. They observed that when 0.01mg/kg Cisatracurium was used for priming along with Ketamine the conditions of intubation were good and the onset time taken was less.

Hyun Jung Lee et.al in 2013 conducted a study on 52 patients belonging to ASA grade one and two aged 27 to 61 years in Korea to observe the conditions of intubation after using Propofol and Remifentanil for rapid sequence induction with Rocuronium or Cisatracurium.[15]

26 patients were allocated per group and studied in two groups and 2mg/kg propofol and remifentanil 0.5microgram/kg was used in all the patients for induction followed by Rocuronium 0.9mg/kg to patients in group R and Cisatracurium 0.15mg/kg to patients in group C. The onset time in group R was less than group C. They observed that although Cisatracurium had slower onset time when compared with Rocuronium, excellent intubating conditions were achieved by supplementing with Propofol and Remifentanil which can be compared with Rocuronium and which can be useful in patients with liver and kidney problems who need faster onset of neuromuscular block.

Ki Tae Jung et al in 2014 conducted a study in Chosun University of Korea to study the duration of action and recovery time of Cisatracurium by using priming principle with 0.06mg/kg Rocuronium and 0.01mg/kg of Cisatracurium as priming agents on 36 patients of both genders who were listed for surgeries electively and requiring general anaesthesia belonging to ASA grades Ⅰ and Ⅱ.[16]

The study was done by taking 12 patients in each group with three groups. Normal saline was given to patients in group Ⅰ.Rocuronium 0.06mg/kg was given to patients in group Ⅱ and Cisatracurium 0.01mg/kg was given to group Ⅲ patients respectively as priming agents. Priming time was taken as three minutes and for intubation group Ⅰ patients were given Cisatracurium of 0.15mg/kg and Cisatracurium of 0.14mg/kg was given to patients belonging to both groups Ⅱ and Ⅲ. Train of four monitoring was done to study the time of onset, duration of action, time of recovery, total time for recovery,

and index for recovery in all the three groups respectively. The results of the study showed that the time of onset in group Ⅱ in which Rocuronium of 0.06mg/kg was used was less than the other two groups and it was statistically significant with p value of less than 0.05. They concluded that when Rocuronium and Cisatracurium were used as priming agents the time of onset for neuromuscular blockade was decreased and that by using these agents as priming the duration of action or the recovery of the drugs was not affected.

Harpreet Kaur et al in 2016 conducted a study on a total of 60 patients of age 18 to 65 years and who were listed for laparoscopic cholecystectomies to observe the time of onset, duration of neuromuscular block and recovery by using Atracurium and Cisatracurium.[3]

30 patients were studied in each group with two groups in total. Atracurium 0.5mg/kg was given to patients in group A and 0.1mg/kg Cisatracurium was given to patients in group C. Onset time was measured by using train of four monitoring which was less in group A. However, the duration of action and recovery time were similar in both the drugs.

BASIC SCIENCES

HISTORY [7,19]: Centuries of innovation, trial and error have created our current endotracheal airway technology.

The Greek philosopher Hippocrates (460 – 380 BCE) described a method of tracheal intubation to support ventilation.

In 16thcentury Andreas Vesalius (1514–1564), a Renaissance physician became the earliest recorded pioneering practitioner of tracheal intubation.

In 1754, a surgeon named Benjamin Pugh created a pipe with coiled wire wrapped in leather to save an asphyxiated neonate by blindly inserting it into trachea and giving breaths through it intermittently. Although the attempt was successful it was not practically possible for others to follow, as it was a blind technique. Later on metal cannulas were used by various people to save people from drowning.

Benjamin Babington in 1828 made a Glottiscope to visualise the trachea which gave a framework for laryngoscopy.

In the 19th century, tracheotomies were used for managing patient's airways.

Rowbotham and Magill made endotracheal tubes with rubber.

Chevalier Jackson in 1865 made a handle-held laryngoscope for placing endotracheal tubes.

William Macewin in 1880 became the first physician to administer an anaesthetic through an orotracheal tube.

In 1885, Joseph O'Dwyer presented a laryngeal intubation method.

In 1941, Robert Miller created a laryngoscope with a curved tip and Sir Robert Macintosh made his curved blade, both of which are still used today.

In 1960s rubber was replaced with plastic and cuffed endotracheal tubes were made.

Tracheal intubation remains the `gold standard' for control of the airway.

Sir Henry Dale discovered the role of acetylcholine and the chemical basis of neuromuscular transmission.

Harold king isolated d-tubocurarine from a sample of curare.

In 1942, Griffith and Johnson used curare on a patient undergoing appendicectomy and took the credit of introducing curare to anaesthesia and since then neuromuscular blocking drugs have become an established part of anaesthesia practice.

John Halton and Cecil Gray used curare on many patients and laid the basis for Liverpool Technique – triad of narcosis, analgesia and muscle relaxation.

Daniel Bovet in 1947 synthesized Gallamine the first synthetic neuromuscular blocking drug used clinically. He also described the neuromuscular blocking properties of Succinylcholine and was awarded Nobel prize for medicine in 1957.

In 1964, Hewett and Savage synthesised Pancuronium. Later Savage demethylated Pancuronium to form Vecuronium.

All the drugs had limitations and the quest for ideal drug continued.

In 1981, Stenlake synthesised Atracurium. In 1989, D A Hill and G L Turner, first synthesized Cisatracurium.

NEUROMUSCULAR JUNCTION [20]

PHYSIOLOGY

When action potential reaches the distal motor nerve ending it causes opening of voltage gated calcium channels instantly and the intracellular calcium concentration increases. This causes a series of events causing the neurotransmitter containing vesicles to reach the surface of the nerve to release acetylcholine into the cleft. The acetylcholine released activates the nicotinic acetylcholine receptors and they open their channels causing influx of sodium ions into the muscle causing depolarization. The end plate potential which is

formed propagates along the muscle membrane by the opening of sodium channels present throughout the muscle membrane which leads to muscle contraction. Acetylcholine detaches from the receptor immediately and is destroyed by acetylcholinesterase located in the synaptic cleft.

ANATOMY

Electrical signals from the brain through the spinal cord travel through the axon of the motor neuron. The axon then branches through the muscle and connects to the individual muscle fibres at the neuromuscular junction. The NMJ is responsible for the transmission of signals from the motor nerve to the muscle, allowing appropriate muscle contraction and muscle tone.

The NMJ consists of three parts:

1.The presynaptic part (distal motor nerve ending)

2.The synaptic cleft

3.The post synaptic part (motor endplate) part of muscle cell membrane.

The presynaptic nerve terminal contains synaptic vesicles filled with Ach and mitochondria, the synaptic cleft contains basal lamina to which acetylcholinesterase enzyme responsible for hydrolysis of free Ach is attached, the post synaptic muscle membrane that opposes the nerve terminal is highly infolded and these folds are called secondary folds. Nicotinic acetylcholine receptors (NAChRs) are concentrated at the crests of these folds and voltage-gated sodium channels are present in the troughs of the folds.

Each motor neuron innervates one to multiple muscle fibres forming motor units, but each muscle fibre receives inputs only from one motor neuron

which ensures the synchronized contractions of the multitude of muscle fibres necessary for coordinated movement. The distal part of the motor neuron is demyelinated and surrounded by Schwann cells anchoring the nerve ending into the muscle membrane. Schwann cells ensure the survival of the motor neuron by releasing nerve growth factor and neuregulin by trophic factors released by the nerve ending. The key role of Schwann cells is to maintain the motor nerve terminal and to protect the NMJ.

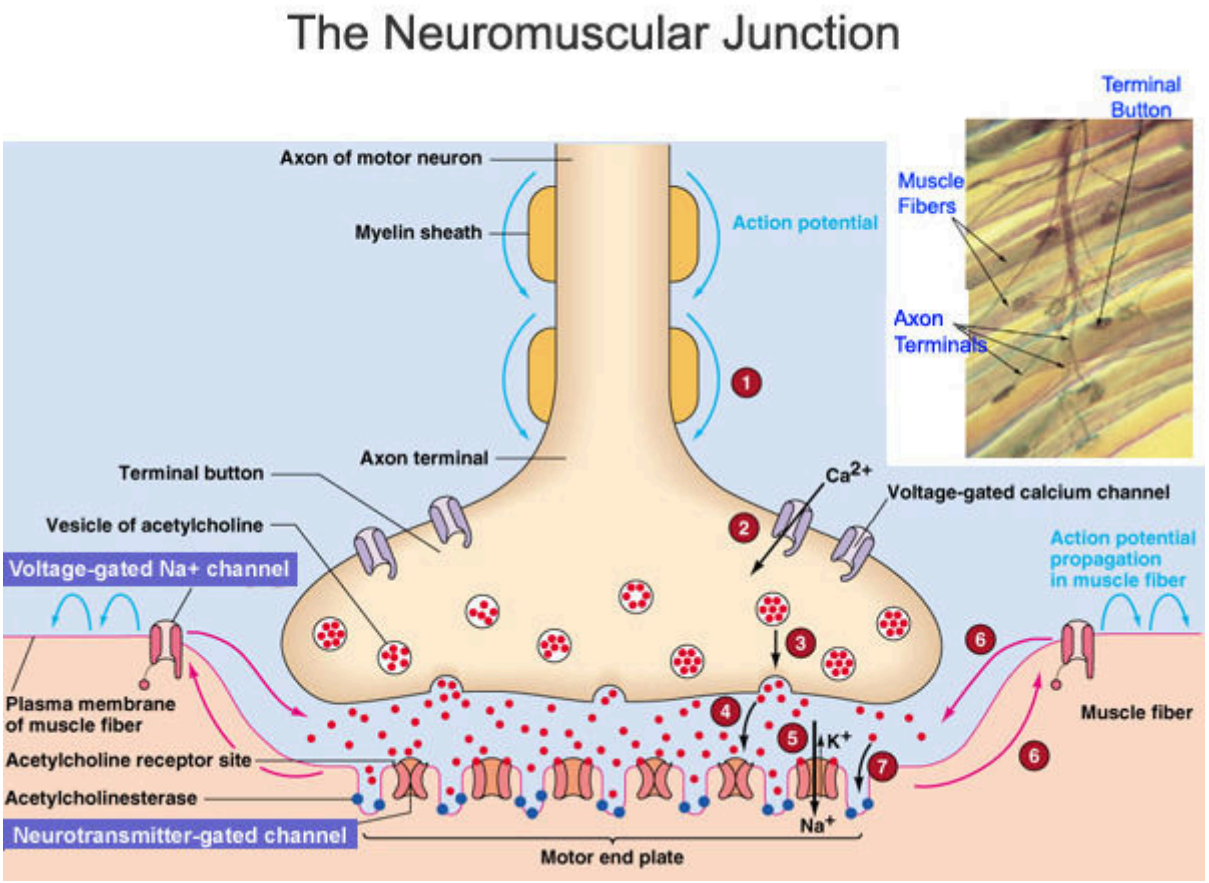


FIGURE 1: STRUCTURE OF NEURO MUSCULAR JUNCTION

NEURO MUSCULAR TRANSMISSION [21]

Although the inside of nerve and muscle cells are good electrical conductors, their membranes act as insulators, making electrical transmission from cell to cell impossible. Therefore, neuromuscular transmission is carried out by the release of a chemical, acetylcholine, at the nerve terminal or synapse. Within the nerve terminal, Ach

is packed in vesicles located near the terminal cell membrane for release. The nerve terminal branches lie in depressions of the postsynaptic membrane called primary synaptic clefts. The space between the nerve terminal and the postsynaptic membrane is about 50 nm. The postsynaptic muscle surface area is increased by invaginations of the plasma membrane into secondary synaptic clefts or folds. The synaptic cleft separates nerve and muscle fibre plasma membranes and encompasses the synaptic basal lamina and is filled with extracellular fluid.

ACETYLCHOLINESTERASE

Acetylcholinesterase enzyme is bound to the basal lamina at the cleft. Acetylcholinesterase is highly concentrated at the NMJ but present in a lower concentration throughout the length of muscle fibres. Acetylcholinesterase is regulated, in part, by muscle activity and by the spontaneous or nerve-evoked depolarization of the plasma membrane. Acetylcholinesterase has nerve growth–promoting activities and it also modulates nicotinic acetylcholine receptors. The concentration of Ach receptors at the endplate is about 15,000 to 20,000 receptors/mm2. The high concentration of Ach receptors and other synapse-specific proteins is partially due to localized gene transcription by the subsynaptic nuclei. The acetylcholine molecules which do not react immediately with a receptor or those released after binding to the nicotinic acetylcholine receptors are destroyed almost instantly by the acetylcholinesterase, which is a type-B carboxyl esterase enzyme located in the synaptic cleft with a small concentration in the extra junctional area.

ACETYLCHOLINE FORMATION [22]

Acetylcholine is a potent messenger, but its actions are very short lived because it is destroyed in less than 1ms after its release.

Acetylcholine is first synthesized in the cytoplasm of the nerve terminal from acetyl coenzyme A and choline in a reaction catalysed by the enzyme choline acetyltransferase. It is then accumulated in the vesicles. Each vesicle contains 5,000 to 10,000 molecules of acetylcholine. The acetylcholine contained in a single vesicle is called as a "quantum" of transmitter.

The synaptic vesicles have two sets of proteins those involved in the uptake of neurotransmitters called as transport proteins and other proteins that mediate synaptic vesicle membrane traffic such as docking, fusion, and budding. The nerve terminal membrane also contains a family of SNAP proteins, syntaxin and synaptosomal-associated protein 25 (SNAP-25). These proteins (syntaxin and SNAP-25) along with synaptic-vesicle protein synaptobrevin are referred to as SNARE (soluble N - ethylmale-imide -sensitive factor attachment protein receptor) proteins and are essential for docking and fusion of SVs to active zones and resulting exocytosis of Ach in the synaptic cleft.

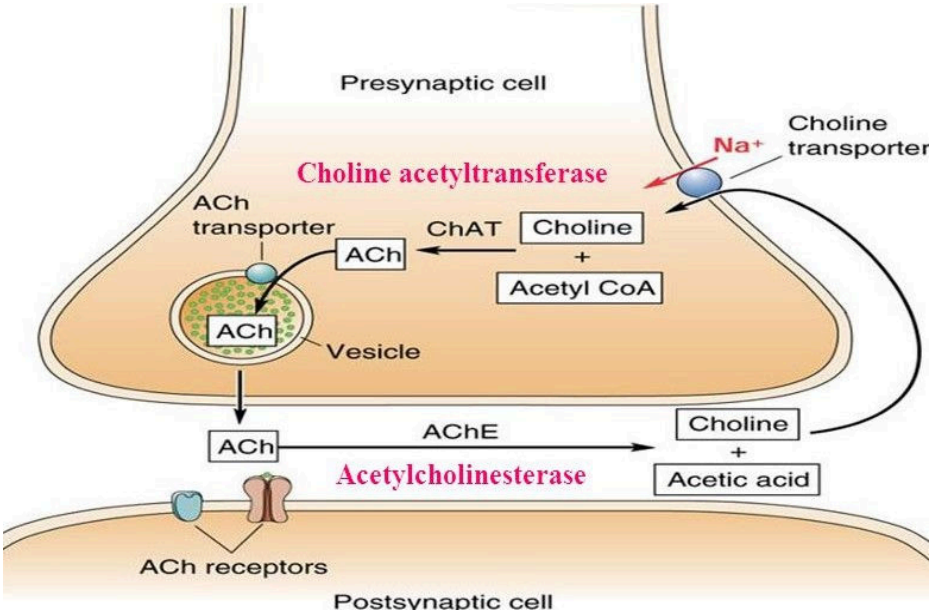


FIGURE 2: ACETYLCHOLINE FORMATION AND METABOLISM

ACETYLCHOLINE RELEASE

The first step in generation of the muscle endplate potential is fusion of synaptic vesicles with nerve terminal membrane leading to the release of Ach. Calcium influx through voltage-gated calcium channels into the nerve terminal initiates synaptic vesicle fusion. When an action potential reaches the nerve terminal, calcium channels are activated and allow calcium entry. Calcium concentration reaches 0.1 to 1 mM in regions where vesicle fusion occurs and triggers fusion. Each synaptic vesicle fusion releases about 10,000 Ach molecules into the synaptic cleft. ATP is also released by synaptic vesicle fusion which will modulate the transmitter sensitivity. The depolarization response of the postsynaptic membrane to the release of the contents of a single vesicle of Ach is called the miniature endplate potential (MEPP), and the net postsynaptic depolarization produced by the release of all the vesicles triggered by a nerve action potential is the endplate potential.

Miniature endplate potential has only one hundredth amplitude of the evoked end plate potential produced when the motor nerve is stimulated, which leads to muscle contraction. An action potential propagating into the nerve terminal stimulates the fusion of 50 to 300 synaptic vesicles. Ach is removed from the synaptic cleft by hydrolysis due to acetylcholinesterase and by diffusion. The products of this hydrolysis are choline and acetate. Choline is recycled into the terminal by a high-affinity uptake system, making it available for the resynthesis of acetylcholine. The exocytosis is restricted to specialized regions known as active zones (or release sites), exactly opposite the receptors on the postsynaptic cell. After exocytosis, the membrane components of the synaptic vesicles are recovered by endocytosis and recycled for future use.

The Peri-junctional zone is the area of muscle immediately beyond the junctional area which is critical to the function of the neuromuscular junction as it contains a mixture of

the receptors which includes a smaller density of nicotinic acetylcholine receptors and higher density of sodium channels. This combination enhances the capacity of this zone to respond to depolarization (end plate potential) produced by nicotinic acetyl choline receptors to transduce it into the wave of depolarization that travels along the muscle to initiate muscle contraction.

QUANTAL THEORY

The number of quanta released by a stimulated nerve is greatly influenced by the concentration of ionised calcium in the extracellular fluid. If calcium is not present, then depolarization of the nerve even by electrical stimulation will not produce release of transmitter. Doubling the extracellular calcium results in a 16-fold increase in the quantal content of an end plate potential. The calcium current persist until the membrane potential is returned to normal by outward flux of potassium from inside the nerve cell. If calcium is increased in the nerve ending it is seen clinically as the post tetanic potentiation, which occurs after a patient is paralyzed with the nondepolarizing neuromuscular blockade and stimulated at high tetanic frequencies.

SYNAPTIC VESICLES [23]

There are 2 pools of vesicles that release acetylcholine. A readily releasable pool, which are a bit smaller and limited to an area very close to the nerve membrane, where they are bound to the active zones. These are the ones that usually release the neurotransmitter. The other pool is the reserve pool and majority of the synaptic vesicles are concealed in it. Exocytosis is the process by which the vesicle releases its content and the SNARE protein plays a pivotal role in the release of acetylcholine. Syntaxin and SNAP 25 are complexes attached to the plasma membrane. After initial contact the synaptobrevin on the vesicle forms a ternary complex with syntaxin and SNAP 25.

Synaptotagmin is the protein on the vesicular membrane that acts as a calcium sensor and localises the synaptic vesicles to synaptic zones rich in calcium channels, stabilising the vesicles in the docked state. The assembly of ternary complex forces the vesicle close to the underlying nerve terminal membrane i.e, active zone, and the vesicle is then ready for release. An action potential in the nerve terminal allows entry of calcium. Hence, the close proximity of release sites, calcium channels and synaptic vesicles and the use of calcium sensor will lead to the burst of new transmitter release which is synchronous with the stimulus. Clostridial toxins including botulinum and tetanus toxins selectively digest one or all of SNARE proteins and block exocytosis of the vesicles causing muscle weakness or paralysis.

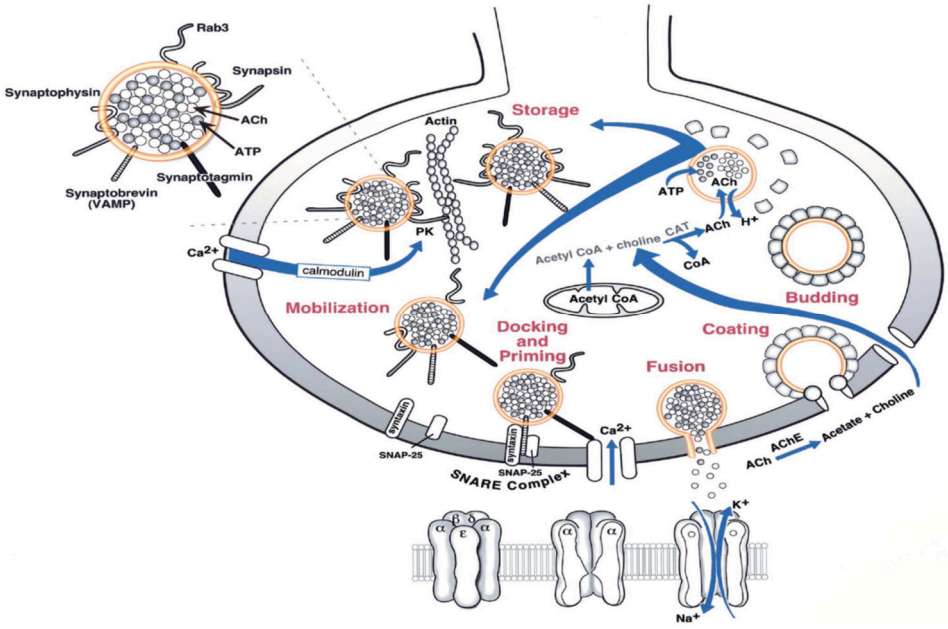


FIGURE 3: SYNAPTIC VESICLE EXOCYTOSIS – ENDOCYTOSIS CYCLE

The lifetime of Ach is approximately 1.0ms and its rapid metabolism prevents repetitive receptor activation. Ach turnover is energy-dependent and may be altered by certain drugs, chemicals, toxins or temperature changes. Under physiological conditions, the amount of Ach released by a nerve action potential is more than sufficient to evoke muscle contractions and there is a reserve in the transmitter capacity.

During rapid nerve stimulation (2 to 100 Hz), a positive feedback mechanism maintains the release of Ach, which itself activates the neuronal nicotinic auto receptors at the nerve terminal. NMBAs inhibit these receptors and lessen the liberation of Ach per stimulus, resulting in progressively reduced muscle contractions (muscular fade). Active, ATP-driven ionic transport systems pump potassium (K+) into the cell and sodium (Na) out. Because the lipid bilayer is more permeable to K+ than to Na, K+ leaks out of the cell more than Na gets in, thus creating a slight excess of positive charges on the outside and a slight deficit on the inside. Thus, at rest the inside of an excitable cell has a negative electrical potential (typically -90mV) with respect to the outside. This is the resting potential.

ACETYL CHOLINE RECEPTORS [23]

Cholinergic receptors are broadly classified as muscarinic and nicotinic, determined by their specific affinity for muscarine and nicotine receptors respectively. In the peripheral nervous system, nicotinic receptors are found post synaptically at the neuromuscular junction and autonomic ganglia. Muscarinic receptors are found at postganglionic parasympathetic nerve endings.

The post-junctional membrane receptors of the motor endplate are nicotinic acetylcholine receptors. There are on average 50 million acetylcholine receptors on a normal endplate, situated on the crests of the junctional folds. The nAChRs belong to the superfamily of Cys-loop ligand gated ion channels. The nAChRs are synthesised in the muscle cells and are anchored to the endplate membrane by a special 43-kDa protein known as rapsyn. This cytoplasmic protein is associated with the nAChR in a 1 : 1 ratio.

Each nicotinic receptor is a protein comprised of five polypeptide subunits that form a ring structure around a central, funnel-shaped pore (the ion channel). The mature adult receptor has two identical α (alpha) subunits, one β (beta),

one δ (delta) and one ε (epsilon) subunit. In the foetus a γ (gamma) subunit replaces the ε(epsilon). The alpha-subunit is the smallest of the five, and is made up of 437 amino acids adding up to a weight of 40000 Da. The other subunits range in molecular weight between 50 and 70000 Da. These different proteins are each coded by a different gene and synthesised within the muscle cells. The whole receptor spans the muscle cell membrane projecting predominantly extracellularly.

The acetylcholine binding site is on both alpha subunits, on the extracellular side, between the amino end and the first membrane domain. At rest, the receptor is closed, i.e. the membrane domains lining the hole in the centre touch each other at one point to prevent passage of ions.

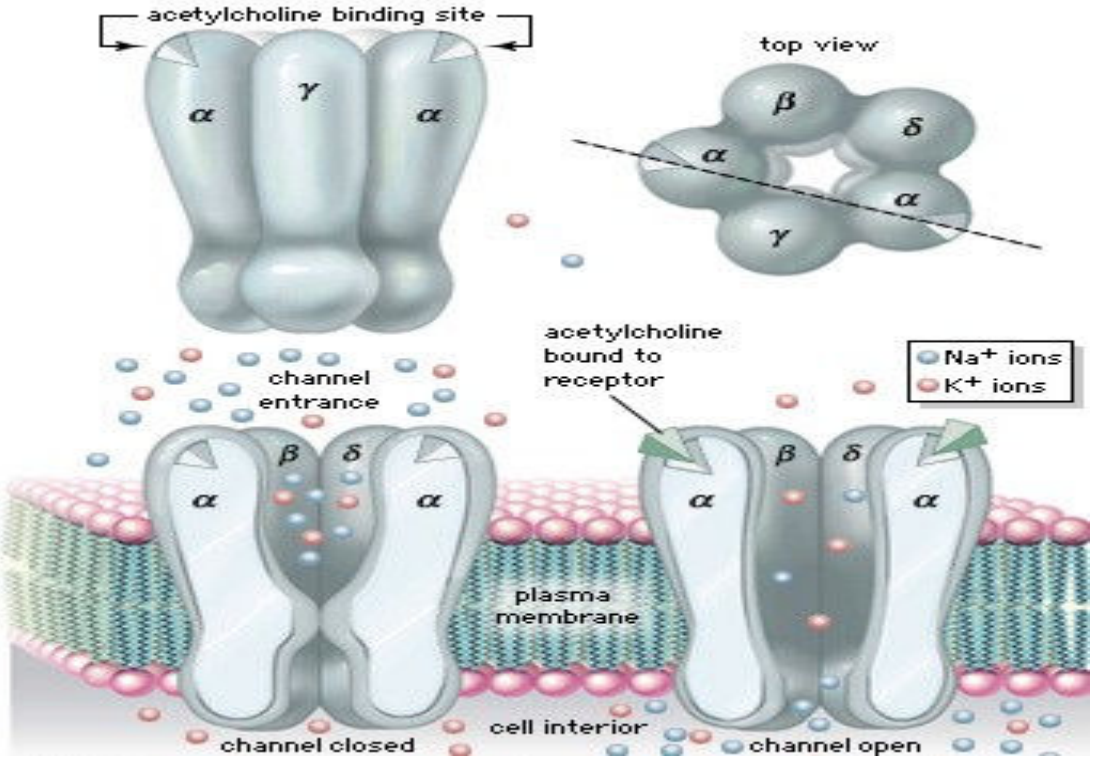


FIGURE 4: PENTAMERIC SUBUNIT STRUCTURE OF THE ACETYLCHOLINE RECEPTOR

When two acetylcholine molecules bind to each alpha-subunit simultaneously, a conformational change in the proteins occurs and a passageway is created between the inside and the outside of the cell opening the ion channel for just 1 msec. The channel

allows movement of all cations, however it is the movement of sodium that predominates in terms of both quantity and effect. This causes depolarisation, the cell becomes less negative compared with the extracellular surroundings. There is a high density of sodium channels in the folds of synaptic clefts and in the peri junctional area. These channels open when the membrane is depolarized beyond a critical point, allowing more sodium to enter the cell, and producing further depolarization. This depolarization generates an action potential, which propagates by activation of sodium channels along the whole length of the muscle fibre. By this method the receptor acts as a powerful amplifier and a switch (acetylcholine receptors are not refractory).

In addition to the post-junctional receptors on the motor endplate, acetylcholine receptors can also be found outside the neuromuscular junction and are called extra-junctional receptors, or on the pre-terminal bulb and are called pre-junctional receptors. The extra-junctional receptors can be present anywhere on the muscle membrane usually in extremely small numbers, though they are found in their greatest concentration around the endplate in the peri-junctional zone.

Early in development, receptors are evenly distributed along the whole length of the muscle fibre. Innervation produces clustering of the receptors in one area of the membrane (the endplate), just beneath the contact with nerve, a change in receptor type at the endplate from the fetal to the adult form, and an increase in complexity of the endplate with the appearance of many folds. In extra junctional areas, there is persistence of fetal type receptors, but their density is reduced.

In humans, the conversion from fetal to adult receptors is almost complete by birth, but the final architecture is not present until the end of the first year of life. Denervation causes loss of adult-type receptors at the junction and an increase in number of extra junctional receptors elsewhere on the muscle membrane. This affects the

physiology and pharmacology of the receptor with increased sensitivity to depolarising muscle relaxants and reduced sensitivity to non-depolarising muscle relaxants.

Pre-junctional receptors on the terminal bulb have a positive feedback role. In very active neuromuscular junction's acetylcholine binds to these receptors and causes an increase in transmitter production via a second messenger system. These receptors may also play a role in the "fade" seen in non-depolarising muscle relaxant blockade by inhibiting replenishment of acetylcholine.

Immature(fetal) receptors have a smaller single-channel conductance and longer mean channel open time up to tenfold than mature receptors. Depolarising drugs such as Suxamethonium and Acetylcholine depolarise these receptors more easily and these channels stay open for a longer time once they are depolarised.

Although the names junctional and extra-junctional imply that each is located in the junctional and extra junctional areas, this is not always true as junctional receptors are mostly confined to the endplate i.e., peri junctional region of the muscle membrane and the immature or extra-junctional receptor, may be expressed anywhere in the muscle membrane. During development and in certain pathologic states, the junctional and extra junctional receptors can coexist in the peri-junctional area of the muscle membrane.

MARGIN OF SAFETY

Neuromuscular transmission also has a margin of safety like many other physiological processes in the body. Under normal conditions the number of post synaptic cholinergic receptors are usually more than that required to produce an action potential. Therefore, atleast 70-80 percent of the receptors have to be occupied by an antagonist like a non-depolarising neuromuscular blocking agent before the response to nerve stimulation is affected. This is of great importance to the anaesthesiologist because when both clinical criteria and response to nerve stimulation may indicate sufficient recovery of neuromuscular function,70 – 80 percent receptors can still be occupied by the neuromuscular blocking drugs.

NEUROMUSCULAR BLOCKING DRUGS [23,24]

These drugs can be classified based on the mechanism of action into two groups depolarizing muscle relaxants and nondepolarizing muscle relaxants or on the basis of duration of action into short acting, intermediate acting and long acting.

DEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

Depolarizing muscle relaxants stimulate the effect of acetylcholine and are called as agonists in spite of them blocking the neurotransmission after initial stimulation. Succinylcholine is the only depolarising muscle relaxant in clinical use. It is two acetylcholine molecules joined through acetate methyl groups.

MECHANISM OF ACTION

Succinylcholine binds to the muscle type of nicotinic acetylcholine receptors, opens the channel and the current passes which depolarizes the end plate. Because of its rapid degradation by acetylcholinesterase, the response of acetylcholine is over in milliseconds and the end plate reverts to its resting state before another nerve impulse arrives. The depolarizing NMBs have a biphasic action on muscle. Initially the muscle fibre undergoes repetitive excitation known as fasciculations which is followed by relaxation lasting for minutes to hours where no excitation occurs, which results in paralysis. The depolarising NMBs, are not hydrolysed by acetylcholinesterase and are not eliminated from the synaptic cleft until after they are eliminated from the plasma. Thus, the time required to clear the drug from the body is the principal determinant of the duration of block.

PHASE Ⅰ AND PHASE Ⅱ BLOCK

After a depolarizing agent binds to the motor endplate receptor, the agent remains bound, and thus the endplate cannot repolarize. This is also known as a phase I block. It is during this depolarizing phase that transient muscle fasciculation occurs. Succinylcholine is metabolised by plasma cholinesterase. If there is prolonged exposure of succinylcholine at the neuromuscular junction either by administering relaxants in large or repeated doses or by infusion it can cause phase II block or the desensitizing phase in which the muscles are no longer responsive to acetylcholine released by the motor neurons. It is at this point that the depolarizing agent has fully achieved paralysis. This continuous depolarization of the endplate inactivates the voltage dependent sodium channels of the muscle membrane adjacent to the end plate thereby preventing depolarization of the muscle membrane and initiation of action potential. Thus, during phase Ⅱ block the original depolarizing block changes into non depolarizing like block characterised by tetanic fade, post tetanic facilitation and fade in the train of four response.

DESENSITIZATION BLOCK

Desensitization block is thought to be the primary mechanism responsible for phase Ⅱ block. Desensitization may occur when the receptors are no longer responsive to the presence of agonists on both alpha subunits, thus inactivating the receptors. Desensitization involves a conformational change in the structure of the receptor, preventing it from opening the channel normally. Desensitization block may be a safety mechanism which prevents overexcitation of the neuromuscular junction.

NONDEPOLARIZING NEUROMUSCULAR BLOCKING DRUGS

There are two broad categories of non-depolarizing muscle relaxants, Benzyl-iso-quinolines and amino-steroids.

Benzyl-iso-quinolines consist of two quaternary ammonium groups joined by a chain of methyl group. These drugs are more liable to breakdown in the plasma than the amino steroid compounds and are more likely to release histamine but lack any vagolytic effect. It includes compounds like Atracurium, Mivacurium, Doxacurium and Cisatracurium. Amino steroid compounds consist of an androstane skeleton to which acetylcholine like structures are introduced at the A ring and D ring. They do not cause histamine release. It includes compounds like Pancuronium, Vecuronium, Pipecuronium and Rocuronium.

MECHANISM OF ACTION:

Nondepolarizing neuromuscular blocking drugs are competitive antagonists of acetylcholine that is they block the postsynaptic acetylcholine receptor by binding to at least one of the two subunits, thus preventing access by acetylcholine. Unlike acetylcholine they do not cause any conformational change in the acetylcholine receptor. Under normal circumstances, only a small fraction of available receptors must bind to acetylcholine to produce sufficient depolarization to trigger a muscle contraction. Neuromuscular blocking drugs must be bound to a large number of receptors before any blockade is detectable.

The binding of these agents to receptors is dynamic that is the drug remains in contact with the receptor by associating and dissociating from it repeatedly. When fifty percent neuromuscular blockade is present at least 87 percent of the

postsynaptic acetylcholine receptors must be occupied and to produce 95 percent neuromuscular blockade 92 percent of the receptors should be occupied.

At normal conditions acetylcholinesterase enzyme destroys acetylcholine and therefore removes it from competition for a receptor, so that the non-depolarizing neuromuscular blocking drug has a better chance of inhibiting transmission. If acetylcholinesterase inhibitors such as neostigmine are added which overcome the neuromuscular paralysis produced by the non-depolarizing neuromuscular blocking drugs then acetylcholine is not destroyed by cholinesterase and the concentration of agonist will be high which shifts the competition between acetylcholine and non-depolarizing neuromuscular blocking drugs in favour of acetylcholine so that two acetylcholine molecules will bind to a receptor even in the presence of non-depolarizing neuromuscular blocking drugs.

Neuromuscular blocking drugs are known to have effects on the presynaptic and postsynaptic nACHRs, but recent studies show that they can react with nicotinic and muscarinic receptors which are present in the carotid body, vagus innervations of the heart, bronchial smooth muscle other than those at the neuromuscular junction.

PREJUNCTIONAL ACTION OF NON-DEPOLARIZING ANTAGONISTS

Acetylcholine acts on prejunctional nicotinic receptors in a positive feedback manner to increase its own release during high-frequency stimulation. Nondepolarizing neuromuscular blocking drugs by blocking presynaptic nicotinic receptors cause tetanic fade and TOF fade, in which there is a reduction in twitch height with successive stimuli as they result in failure of mobilization of Ach to keep pace with the demands of the stimulus frequency.

The release of acetylcholine normally decreases during high-frequency stimulation because the pool of readily releasable acetylcholine becomes depleted faster than it can be replenished. Under normal circumstances, the reduced amount released is well above what is required to produce muscle contraction because of the high margin of safety at the neuromuscular junction. However, during partial nondepolarizing blockade this decrease in transmitter output produces fade that is progressive decrease in muscle response with each stimulus.

Nondepolarizing agents have a greater affinity for presynaptic than postsynaptic receptors. Only small doses of nondepolarizing relaxants are needed to block presynaptic receptors. Neuromuscular blocking agents interfere with the action of acetylcholine at the interface between peripheral nerve and muscle. Their central effects are negligible. Nondepolarizing agents compete with acetylcholine for the same receptor sites but do not activate the receptor. Their effect can be antagonized by inhibitors of acetylcholinesterase, which increase the amount of acetylcholine available.

PRIMING

- The term "Priming" was given by Foldes.
- Priming principle was introduced in 1980.[25]
- It was initially described by Gergis and Hatton and was later popularised by Schwartz et.al. with his studies on priming.[27]
- This technique was introduced to fasten the onset of action of nondepolarizing drugs in which a small sub paralyzing dose is given followed 3 to 6 minutes later by the intubating dose of the same or other muscle relaxant.
- The phenomenon which leads to the decrease in the onset time after giving a small dose followed by intubating dose and attaining good conditions for intubation can be described by few theories.[26]
- One theory called as the post synaptic theory advocates that the small dose given as priming will occupy a part of post synaptic nicotinic receptors and reduces the safety margin present normally in neuromuscular transmission. Thus, the subsequent dose given after priming blocks the receptors more rapidly. In this theory, the time between priming and intubating dose as well as the size of the priming dose is important so as to occupy a certain quantity of receptors.
- The other theory advocates that the dose given for priming will block the presynaptic nicotinic receptors and reduces the acetylcholine release by which the onset time is decreased and muscle paralysis is achieved quickly.
- When priming principle is used for intubation then 2 to 3 times the ED95 of a nondepolarizing agent may be used.

- **ADVANTAGES**: Apart from decreasing the time of onset of non-depolarizing agents it also helps in decreasing the severity of dose related side effects like the release of histamine with atracurium can be reduced as the required initial dose is divided into two and the second dose is given after a time interval and also tachycardia seen with Pancuronium can be reduced. It also helps in knowing any unusual sensitivity to non-depolarizing agents thereby avoiding further effects.[26]

- **DISADVANTAGES**: This technique cannot be used in those with difficult airway and also in those who have more sensitivity to neuromuscular blocking drugs such as myasthenia gravis or who take drugs which interfere with neuromuscular function. Patient discomfort, risk of aspiration, difficulty in swallowing/coughing and diplopia may also be some of the unfavourable effects. Therefore, a smaller priming dose is usually preferable.[26]

CISATRACURIUM [28]

HISTORY:

Cisatracurium besylate was formerly called as 51W89, and its trade name,"Nimbex" stands for excellent Neuromuscular blocker. The generic name was given by combining the name "Atracurium" with "Cis" as it is one of the three *cis-cis* isomers of the ten isomers of the parent, Atracurium. Thus, in 1989, D A Hill and G L Turner at Burroughs, UK first synthesized Cisatracurium as an individual isomer molecule."

CHEMISTRY:

- Cisatracurium besylate is a non-depolarizing neuromuscular blocking agent for intravenous administration which belongs to the benzyl-iso quinolinium class.
- It binds to the nicotinic receptors at the NMJ and acts as a competitive acetylcholine antagonist.
- It has intermediate onset and duration of action.
- It is one of 10 isomers of atracurium and constitutes 15% of it.
- Its molecular formula is $C_{65}H_{82}N_2O_{18}S_2$ and molecular weight is 1243.49g.mol^{-1}.

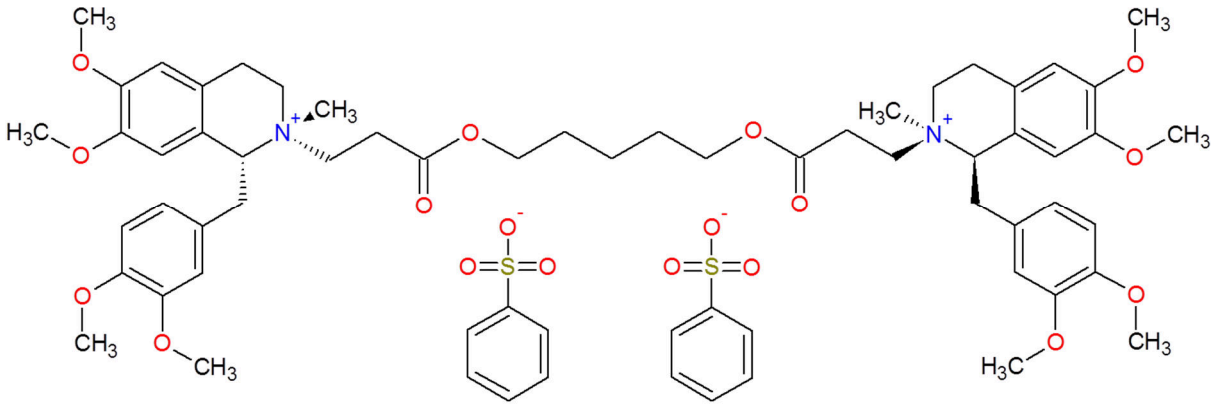


FIGURE 5: STRUCTURE OF CISATRACURIUM

AVAILABILITY AND STORAGE:

- Cisatracurium solution for injection is available in 10ml (20mg) and 5 ml(10mg) vials with 2mg/ml.
- Cisatracurium should be stored under refrigeration at 2 to 8 degrees Celsius and once removed from refrigeration to room temperature storage, it should be used within 21 days.
- It should be protected from light to preserve potency and the rate of loss of potency is 5% per month at 25 degrees Celsius.
- Diluted Cisatracurium is chemically and physically stable for at least 12 hours when stored in polyvinylchloride containers.

PHARMACOKINETICS:

- It undergoes Hofmann elimination (an organ independent elimination pathway occuring in plasma) which accounts for 77% of the overall elimination and ester hydrolysis and forms mono-quaternary acrylate and Laudanosine as metabolites.
- The mono-quaternary acrylate undergoes hydrolysis by non-specific plasma esterases to form the mono-quaternary alcohol metabolite which can also undergo Hofmann elimination but at a much slower rate than Cisatracurium.
- Laudanosine is further metabolized to des methyl metabolites which are conjugated with glucuronic acid and excreted in the urine.
- Therefore, neither of these by products has any neuromuscular blocking activity.
- The liver and kidney both play a minor role in the elimination of Cisatracurium but are primary pathways for the elimination of metabolites. Therefore, the half-life of metabolites is longer in patients with kidney or liver dysfunction.

- Hofmann elimination is a process dependent on pH and temperature. Therefore, the rate of degradation of Cisatracurium in vivo is highly influenced by body pH and temperature.
- Thus, an increase in body pH favors the elimination process, whereas a decrease in temperature slows down the process.

PHARMACOLOGY:[28]

- It binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in the blocking of neuromuscular transmission.
- The average ED95 (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of Cisatracurium is 0.05 mg/kg in adults.
- The typical dose for intubation is 0.15(3 × ED95) to 0.2 mg/kg (4 × ED95) after which ideal intubating conditions are generally achieved in between 1.5 and 2 minutes.
- The clinically effective duration of an intubating dose lasts 55 to 65 minutes.
- Maintenance dose: 0.02 mg/kg by bolus.
- Dose to maintain paralysis via infusion: 1 to 3 mcg/kg/min (although it is important to adjust the dosing based on peripheral nerve monitoring).
- The time to maximum block is about 1 minute slower in the elderly (>65 years).
- For children 2 to 12 years of age, dosage adjustment is required. The recommended dose is 0.10 mg/kg.
- The neuromuscular blocking potency of Cisatracurium is approximately three times that of Atracurium.

- Clinically the effective duration of action and rate of spontaneous recovery from equipotent doses of Cisatracurium and Atracurium are similar.
- Clinical duration of neuromuscular block after:
- Cisatracurium 0.1 mg/kg (2 × ED95) is 33 to 45 minutes and Cisatracurium 0.15 mg/kg (3 × ED95) is 55 minutes.
- Volume of distribution is limited by its large molecular weight and polarity. It is 145 ml/kg in healthy patients receiving opioid anaesthesia.
- Patients with hypothermia, which typically occurs in surgeries needing cardiopulmonary bypass and therapeutic hypothermia, may need a lower dose of Cisatracurium.
- A persistently febrile patient in ARDS on Cisatracurium drip may require higher doses of this medication.

CARDIOVASCULAR EFFECTS:

- It has no dose-related effects on mean arterial pressure (MAP) or heart rate (HR) following doses of Cisatracurium in the range of 2 to 8 times the ED95 in healthy patients or in patients with serious cardiovascular disease.

NEUROLOGIC EFFECTS:

- In patients with neuromuscular diseases such as myasthenia gravis or myasthenic (Eaton-Lambert) syndrome even small doses of non-depolarizing neuromuscular blocking agents may have profound effects.
- Therefore, in these patients and in patients where prolonged neuromuscular blockade can be seen as in patients with neuromuscular disease, carcinomatosis, severe cachexia etc, a peripheral nerve stimulator to assess the level of neuromuscular block and to monitor dosage requirements is needed.
- The first dose in these patients should not be more than 0.02mg/kg.

RENAL AND HEPATIC EFFECTS:

- Cisatracurium undergoes degradation in the body at physiological pH and temperature by organ independent Hofmann elimination to form Laudanosine and the mono-quaternary acrylate metabolite.
- The onset time was approximately 1 minute faster in patients with end-stage liver disease and approximately 1 minute slower in patients with renal dysfunction than in healthy adult patients.
- No clinically significant alterations in the recovery profile were observed in patients with renal impairment or hepatic impairment following a 0.1 mg/kg (2 x ED95) dose of Cisatracurium making it a good choice in a patient with either of these diseases.

USES:

- It is used as an adjunct to general anaesthesia in facilitating tracheal intubation and to provide skeletal muscle relaxation during surgery.
- It is also used to provide skeletal muscle relaxation to facilitate mechanical ventilation in an intensive care unit setting, but its use requires sedation.
- Laudanosine values are significantly lower in surgical patients who receive Cisatracurium infusions than in patients receiving infusions of atracurium, making it a better choice for long-term use in the ICU.

LIMITATION:

- Because of its intermediate onset of action Cisatracurium is not recommended for rapid sequence endotracheal intubation.

ADVERSE EFFECTS:

- Adverse effects are uncommon with the use of Cisatracurium.
- Adverse reactions are seen at a rate of less than 1% and include bradycardia, hypotension, bronchospasm, rash, anaphylaxis, prolonged neuromuscular blockade, and myopathy.

CONTRAINDICATIONS:

- Cisatracurium is acidic (pH 3-3.7) and should not be mixed with alkaline solutions having pH greater than 8.5.
- Cisatracurium contains benzyl alcohol as a preservative and is contraindicated in patients with known hypersensitivity to it.
- It is contraindicated in neonates and low birth weight infants.
- It should be used cautiously in patients with myasthenia gravis or myasthenic syndrome, as a profound effect may occur.
- It is also contraindicated in those patients with a history of prior anaphylactic reactions to neuromuscular blocking agents as there can be cross reactivity between these agents.
- Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents.
- The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of pre-eclampsia or eclampsia.
- Cisatracurium is hypotonic and therefore must not be administered into the infusion line of blood transfusion.

SPECIAL CONDITIONS:

- Patients with burns may develop resistance to non-depolarizing neuromuscular blocking agents and the extent of altered response depends upon the size of the burn and the time elapsed since the burn injury.
- Therefore, the dose must be increased in burn patients, because of increased protein binding and up-regulation of receptors, causing resistance at the endplate.
- In obese patients, the dose of Cisatracurium, as for all neuromuscular blocking agents, should be calculated based on lean body mass.
- It is a category B drug in pregnancy and should be used during pregnancy only if clearly needed.
- As it is not known whether it is excreted in human milk it should be used with caution in nursing woman.

MONITORING OF NEUROMUSCULAR TRANSMISSION

Whenever neuromuscular blockade is used, to improve the conditions of intubation and decrease airway injury the neuromuscular monitoring (NMT) can be used. NMT guides the clinical management of neuromuscular blockade by helping to know the onset of blockade and adequacy of intubating conditions and also to titrate the muscle relaxant dosage to the needs of the surgical procedure by avoiding overdosing or underdosing and thus help in using a minimum quantity of drug to achieve the desirable conditions and in minimising the incidence of postoperative residual muscle weakness.[29]

Previously, the level of neuromuscular blockade has been assessed on clinical tests which consisted of assessing the respiratory variables and muscle function like [31]:

- The occurrence of spontaneous muscular movements
- The feel of the anaesthetic reservoir bag
- The ability to open eyes
- To cough and to sustain a 5-s head lift
- Grip strength.

However, these tests are influenced by many factors apart from neuromuscular blockade and are unreliable and also require wakefulness and cooperation of the patient. When accurate information regarding neuromuscular functioning is needed then the muscle response to nerve stimulation should be evaluated which also considers the variation present in different individuals to the muscle relaxants.

In 2016, the Association of Anaesthetists of Great Britain and Ireland, asserted in their recommendations for standards of monitoring that

when neuromuscular blocking drugs are given it should be monitored by a peripheral nerve stimulator.

Two types of neuromuscular monitors can be used for monitoring in the perioperative period which are qualitative and quantitative monitors. Peripheral nerve stimulators are the qualitative monitoring devices which deliver a stimulus to a peripheral nerve, and the subsequent muscular response can be observed visually or tactilely whereas the quantitative monitors measure the strength of muscle contraction objectively and the results can be displayed on a screen (0-1.0 or 0% - 100%).

When the electrical stimulation is high enough to cause all the muscle fibres to contract maximal contraction is said to be done and this threshold is approximately 40 to 50 mA for the ulnar nerve in most of the patients. Therefore, a current 10%-20% above this threshold should be applied considering other factors which can change the skin resistance and is called as the supramaximal current. The Supramaximal current in the quantitative monitors can be determined by using the calibration mode whereas it should be set manually when using a qualitative monitor such as a peripheral nerve stimulator.

Ulnar nerve/adductor pollicis muscle and the facial nerve/orbicularis oculi or corrugator supercili muscle are the 2 most common sites for neuromuscular monitoring. A particular muscle which is monitored for the evoked response may not reflect onset or recovery of strength of other muscle groups which is due the different sensitivities of muscles to NMBAs, with the diaphragm exhibiting the lowest sensitivity and pharyngeal muscles demonstrating the greatest sensitivity.[32]

NERVES USED FOR STIMULATION:[30]

NERVE	SITE OF ELECTRODE	MUSCLE	RESPONSE SEEN
Ulnar nerve	Ulnar aspect of wrist	Adductor pollicis	Adduction of thumb
Median nerve	Elbow adjacent to brachial artery	Thenar muscles	Thumb adduction
Mandibular nerve	Beneath zygomatic arch	Masseter	Jaw contraction
Facial nerve	Laterally above zygomatic arch	Orbicularis oculi/corrugator supercili	Eye blink
Superficial peroneal nerve	Head of fibula	Tibialis anterior	Dorsiflexion of foot
Posterior tibial nerve	Behind lateral malleolus	Extensor hallucis	Dorsiflexion of great toe

PRINCIPLES OF PERIPHERAL NERVE STIMULATION:[32]

When a stimulus is given to a single muscle fibre it follows an all -or -none pattern and the whole muscle will respond depending on the number of muscle fibres activated. When sufficient intensity is used to stimulate a nerve, all the fibres supplied by the nerve will react, and the maximum response of the muscle will decrease in parallel to the number of fibres blocked. The degree of neuromuscular blockade is seen by the reduction in response when constant stimulation is provided. For this, the stimulus should be truly maximal throughout the monitoring period. Therefore, the electrical stimulus is applied which is not only needed for a maximum response but 20-25% above that needed for a maximal response. And this supramaximal stimulus may provide discomfort to the patient during recovery which might not be of much trouble during anaesthesia.

There are several patterns of nerve stimulation [33]

Single twitch stimulation

Tetanic stimulation

Post tetanic count

Double burst stimulation

Train -of -four-stimulation

TRAIN OF FOUR MONITORING

Train of four monitoring is considered to be one of the standard method for neuromuscular monitoring and it is simple and easy to use. In 1971, Ali et al. described the train of four monitoring in which four supramaximal stimuli are given every 0.5 seconds. The "train" i.e., each set of stimuli can be repeated every 15 or 20 seconds. Each stimulus causes the muscle to contract and the fade in the response is taken as the basis for evaluation in which the amplitude of fourth response is divided by the amplitude of first response to get the TOF ratio.[34]

Four muscle responses which are equal are seen in the absence of block and the T4/T1 ratio is 1. During a partial depolarising block, the twitch height is decreased to the same extent in all the four responses and there is no fade and TOF ratio is equal to one. If a phase 2 block develops after succinylcholine administration, TOF will show fade as now the depolarizing agent will exhibit features of a competitive blocker. During a partial non-depolarizing block, TOF will show fade which is inversely proportional to the degree of blockade.

To measure TOF two electrodes are needed to be placed along the nerve to pass current through it for stimulation of the nerve and these electrodes one positive and the other negative electrodes can be placed over the skin surface or percutaneously 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 the most superficial part of the nerve. Evaluation can be done subjectively either by looking at the evoked responses and assessing fade to TOF stimulation or by feeling the strength of contraction of muscles and assessing TOF.

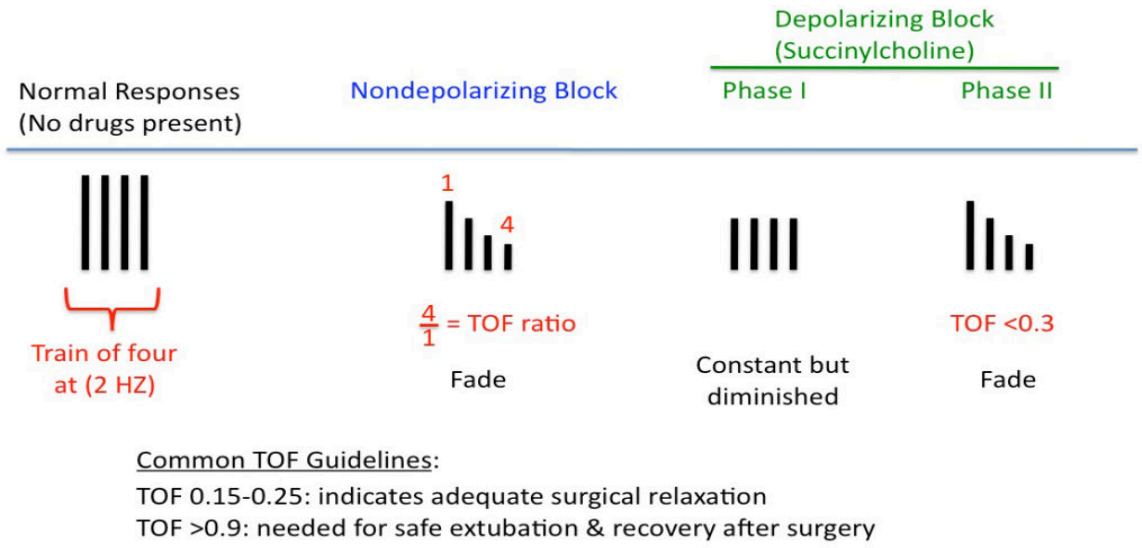


FIGURE 6: RESPONSE TO TRAIN OF FOUR STIMULATION BY DNMB AND NDNMB

Therefore, the train-of-four (TOF) test is a non-invasive peripheral nerve stimulator that shows the level of motor block of muscle relaxants which can be used to improve the quality of intubation and decrease airway injury.

USES AND ADVANTAGES [30]: It helps to assess the adequacy of neuromuscular blockade for intubation. It can also be used for maintenance of anesthesia by titrating the muscle relaxants. PTC and TOF monitoring are most useful during profound neuromuscular block. Intraoperatively it acts as a guide to muscle relaxant administration and is advantageous over DBS. Because in DBS when a response is present, fade is either present or absent, i.e. only two degrees of muscle relaxation may be distinguished. With TOF stimulation, when a response is present four degrees of relaxation may be distinguished, facilitating titration of muscle relaxant to a desired effect.

One of the main advantages of TOF stimulation is that it asses the degree of neuromuscular blockade without the necessity of control value in the unparalysed state. It causes less discomfort than the tetanic stimulation. It does not affect the amplitude of any subsequent response in contrast to tetanic stimulation. It is easy to use and can be used repeatedly.

TOF can be used for estimating onset of more profound NMB, the number of detectable responses is reduced progressively from four to none (TOF count). When intense block is achieved there is no response to either TOF or PTC stimulation. When moderate block is seen there may be one or two responses to TOF. It helps in measuring the degree of spontaneous recovery present prior to administration of reversal agents. Antagonism dosage and injection time can also be optimized by the proper monitoring of the neuromuscular blockade's depth. Reversal from muscle relaxant should have the presence of two responses and good recovery from NMB requires a TOF ratio >0.9.

NUMBER OF RESPONSES DETECTED	**DEGREE OF NEUROMUSCULAR BLOCKADE**
1	95%
2	90%
3	80%
4	75%

DISADVANTAGES: Poor performance at both extremes of neuromuscular block, deep relaxation or near complete recovery and tactile observation or visual observation of TOFR is of little value above a ratio of 0.4-0.5.

METHODOLOGY

MATERIALS & METHODS:

The present study titled "Comparative study of the onset time of Cisatracurium for tracheal intubation with and without priming dose of Cisatracurium in adult patients undergoing general anaesthesia " was conducted on 60 American society of Anaesthesiology Ⅰ - Ⅱ patients between the age group of 20-60 years of either gender posted for elective surgeries under general anaesthesia with tracheal intubation from January 2020 to December 2020 in the department of Anaesthesiology at KLE's Dr.Prabhakar Kore Hospital and Medical Research Centre.

METHOD OF COLLECTION OF DATA:

STUDY DESIGN: A one-year hospital based randomized controlled study.

RANDOMISATION: Patients were randomly divided into two groups based on computer generated randomization table.

GROUP A (n=30): Patients who received priming dose of 0.01mg/kg Cisatracurium diluted to 1 ml 3 minutes before intubating dose of 0.14mg/kg Cisatracurium.

GROUP B (n=30): Patients who received normal saline of 1 ml 3 minutes before intubating dose of 0.15mg/kg Cisatracurium.

The inclusion and exclusion criteria were as follows:

INCLUSION CRITERIA:

1. ASA physical status I and II.
2. Age between 20 to 60 years.
3. Patients undergoing elective surgeries under general anaesthesia.
4. Patients who provide consent.

EXCLUSION CRITERIA:

1. Patients undergoing emergency surgery.
2. Patients who are unable to give consent.
3. Patients requiring rapid sequence intubation.
4. Pregnant and lactating patients.
5. Patients with disorder of cardiovascular or neuromuscular systems.
6. Patients with airway problems suggesting difficult intubation.
7. Morbidly obese patients.

SAMPLE SIZE: A total of 60 adult patients divided into 2 groups.

SAMPLE SIZE CALCULATION: The minimum sample size formula based on mean and standard deviation was

$$n = \frac{(z_\alpha + z_\beta)^2 (s_1^2 + s_2^2)}{(\overline{X}_1 - \overline{X}_2)^2}$$

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.

Using results of previous studies and taking the clinical duration and recovery characteristics of Cisatracurium after priming with Cisatracurium as the criteria.

With $\overline{X}_1$ the mean of first group (12.2) and $\overline{X}_2$ the mean of second group (16.8) and S1 is the standard deviation of the onset time in the first group (5.40) and S2 is the standard deviation of the onset time in the second group (6.2).

With these values the minimum sample size obtained in each group was 25.

To make the study more confirmative, the sample size was raised to 60 with 30 in each group.

METHODOLOGY

After attaining the approval from the Institutional Ethical Committee and Review Board, written informed consent was obtained from 60 ASA Ⅰ -Ⅱ grade patients aged 20-60 years posted for elective surgical procedures under general anaesthesia. All the patients were evaluated preoperatively, routine investigations were done and advised NBM status for eight hours. In the preoperative room, an i.v line was secured.

In the operating room standard anaesthesia monitors including non-invasive blood pressure, pulse oximeter, electrocardiogram were attached, the neuromuscular monitor – Train of Four (TOF – Guard) acceleromyograph monitor was attached to the hand opposite to the hand where iv line was secured by placing two stimulating electrodes over the ulnar nerve at the wrist and attaching the acceleration transducer to the thumb with adhesive tape. Baseline blood pressure, heart rate and peripheral oxygen saturation were recorded.

Premedication of all the patients in both the groups was done with injection Glycopyrrolate 0.005mg/kg, Midazolam 0.05mg/kg, Fentanyl 2mcg/kg. Pre-oxygenation was performed for 3 minutes, and anesthesia induction was done with i.v Propofol 2mg/kg till the disappearance of the eyelash reflex. Oxygen and Nitrogen in the ratio of 4:6 and Isoflurane 1% was started for the maintenance of anesthesia with closed circuit. A supramaximal stimulus with TOF was applied to the ulnar nerve at the wrist through two surface electrodes after automatic calibration. Baseline TOF ratio percentage was noted.

In group A, priming dose of 0.01mg/kg Cisatracurium diluted to 1ml with normal saline was given. After 3 minutes of priming interval, intubating dose of 0.14mg/kg Cisatracurium was given and the iv line was flushed by rapid flow of fluid for 15 seconds. TOF was recorded every 10 seconds till complete loss of T1. The time was noted and at this point intubation was performed.

In group B, 1 ml of normal saline was given and after 3 minutes, intubating dose of Cisatracurium 0.15mg/kg was given which was flushed by rapid flow of fluid for 15 seconds. TOF was recorded every 10 seconds till complete loss of T1. The time was noted and intubation was performed.

The time from administration of intubating dose of Cisatracurium till TOF count reached zero was taken as onset time.

The following parameters were recorded and noted

1. The time of onset of neuromuscular blockade (Intubation time).
2. The intubating conditions.

Intubating conditions are assessed by:

VARIABLE	**EXCELLENT**	**GOOD**	**POOR**
Laryngoscopy	Easy	Fair	Difficult
Vocal cord position	abducted	Intermediate/moving	Closed
Reaction to insertion of tracheal tube and cuff inflation (diaphragmatic movement /coughing)	None	Slight (1- 2 weak contractions or movement for <5 sec)	Vigorous/sustained (more than 2 contractions and or movement for longer than 5 sec)

Type of Laryngoscopy was graded as follows

• Easy: Jaw relaxed, no resistance to blade insertion.

• Fair: Jaw not fully relaxed slight resistance to blade insertion.

• Difficult: Poor jaw relaxation, active resistance of the patient to laryngoscopy.

Intubating Conditions were scored as follows

• Excellent: All variables were excellent.

• Good: Atleast two variables being good or excellent with no poor variable.

• Poor: The presence of single variable listed under "poor."

Excellent and good intubating conditions were considered to be clinically acceptable. Poor conditions were considered as not clinically acceptable.

The patients were also monitored for hemodynamic variations and side effects if any like bradycardia, hypotension etc and treated accordingly. At the end of surgical procedure, patients were reversed with injection Glycopyrrolate 0.01mg/kg and Neostigmine 0.05mg/kg and trachea extubated after complete neuromuscular recovery.

RESULTS

In the present study titled "**Comparative study of the onset time of Cisatracurium for tracheal intubation with and without priming dose of Cisatracurium in adult patients undergoing general anaesthesia"** the patients were randomized into two groups.

In "Group A" - priming was done with 0.01mg/kg of Cisatracurium followed by an intubating dose of 0.14mg/kg of Cisatracurium.

In "Group B" – priming was done with 1ml of normal saline followed by an intubating dose of 0.15mg/kg of Cisatracurium.

The results obtained were analyzed and are tabulated as follows.

TABLE 1: GENDER DISTRIBUTION

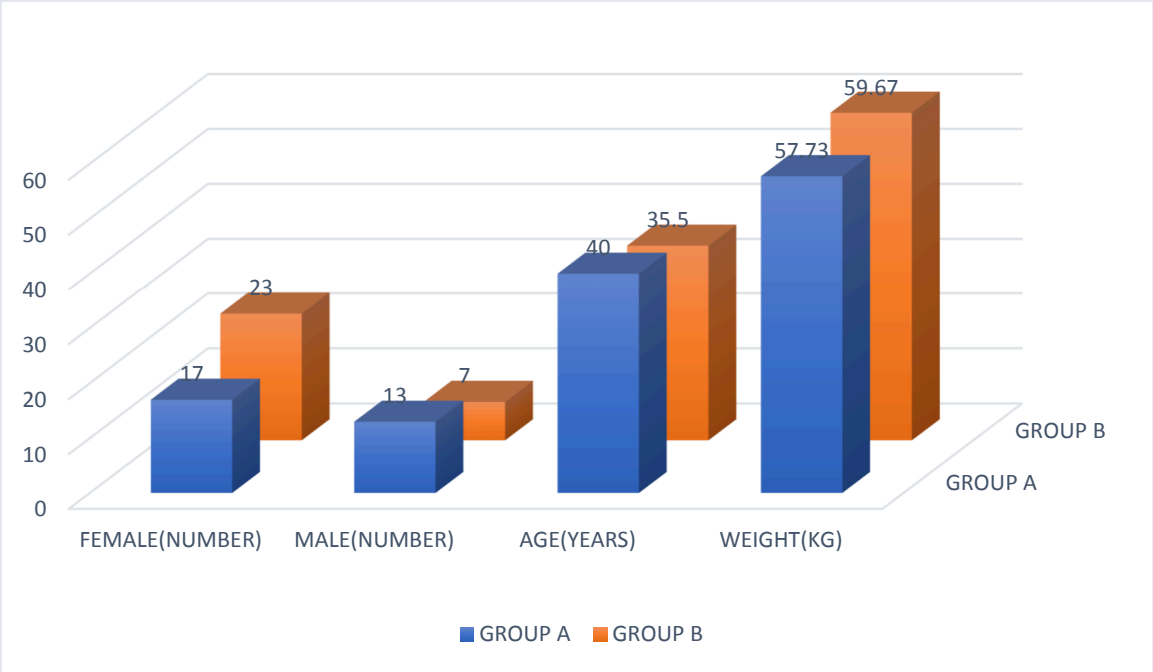
GENDER	GROUP A	GROUP B	TOTAL
FEMALE	17	23	40
MALE	13	7	20
TOTAL	30	30	60

In this study, group A had 17 female and 13 male patients and group B had 23 female and 7 male patients, sex distribution did not account to statistical difference. [P VALUE = 0.100 (NS)]

TABLE 2: AGE AND WEIGHT DISTRIBUTION

VARIABLE	AGE(YEARS)		WEIGHT(KG)	
	GROUP A	GROUP B	GROUP A	GROUP B
MEAN	40.00	35.50	57.73	59.67
STANDARD DEVIATION	12.376	11.147	8.308	5.973
P VALUE	0.144(NS)		0.305(NS)	

GRAPH 1: GENDER, AGE AND WEIGHT DISTRIBUTION

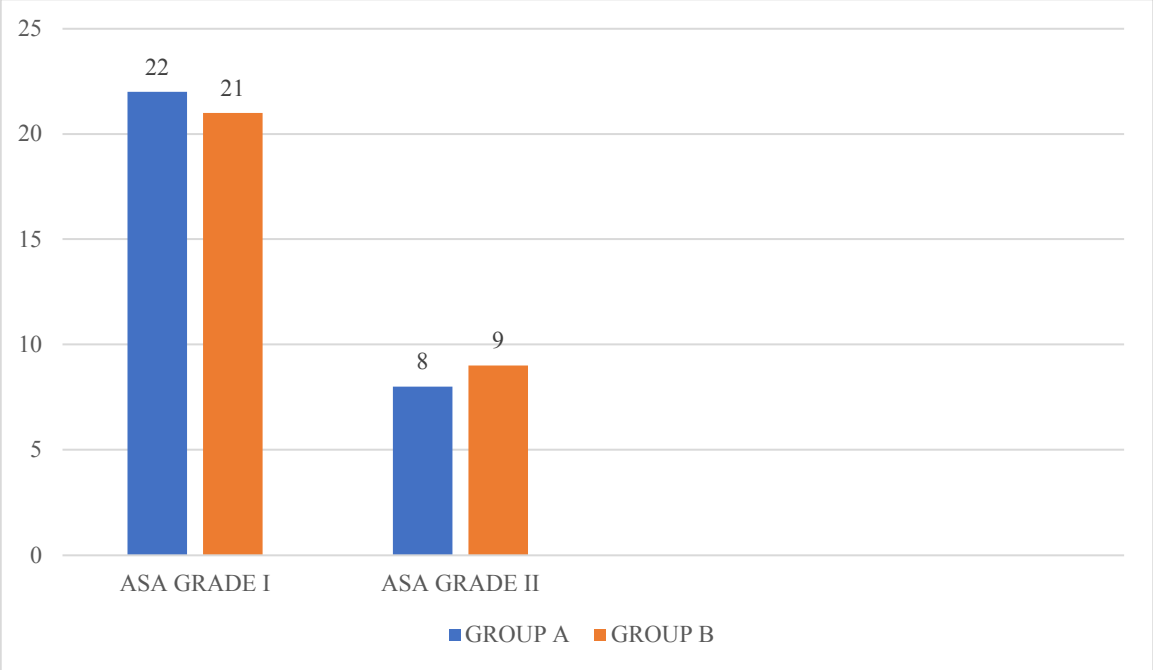


In this study, 40 ± 12.37 years was the mean age in group A and 35.5 ± 11.14 years in group B. There was no statistical difference between the two groups in terms of age and the mean weight of group A was 57.73 ± 8.3 kg and mean weight of group B was 59.67 ± 5.97kg with no statistical difference between the two groups in terms of weight.

TABLE 3: ASA DISTRIBUTION

	GROUP A	GROUP B	TOTAL
ASA GRADE I	22	21	43
ASA GRADE II	8	9	17
TOTAL	30	30	60

GRAPH 2: ASA GRADE DISTRIBUTION

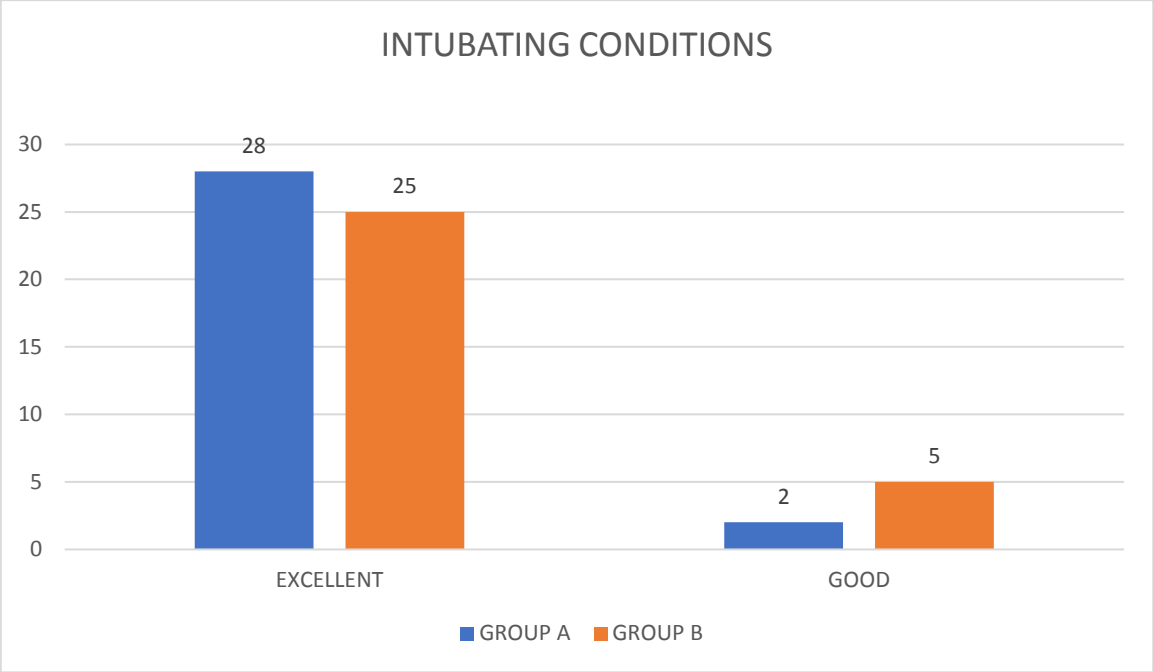


The number of patients who were posted for elective surgeries and belonging to ASA grade I in group A was 22(73.3%) and group B was 21(70%) and the number of patients belonging to ASA grade II in group A was 8(26.7%) and group B was 9(30%).The P VALUE = 0.774 (NS) which states that there was no statistical difference between the two groups.

TABLE 4: INTUBATING CONDITIONS

INTUBATING CONDITIONS	GROUP A	GROUP B	TOTAL
EXCELLENT	28	25	53
GOOD	2	5	7
TOTAL	30	30	60

GRAPH 3: INTER GROUP COMPARISION OF INTUBATING CONDITIONS

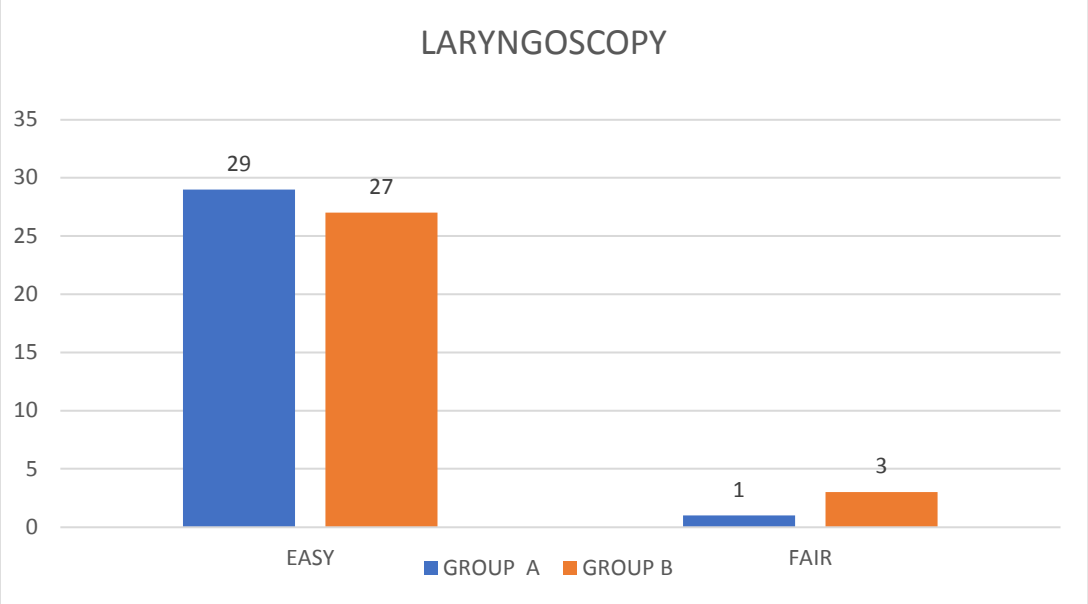


The Intubating conditions were excellent in 28(93.3%) patients in group A and 25(83.3%) patients in group B. Good intubating conditions were seen in 2(6.7%) patients in group A and 5(16.7%) patients in group B. The p value using chi square test was 0.421 which states that there was no statistical difference in the intubating conditions in both the groups. Poor intubating conditions were not seen in any patients in both the groups.

TABLE 5: TYPE OF LARYNGOSCOPY

LARYNGOSCOPY	GROUP A	GROUP B	TOTAL
EASY	29	27	56
FAIR	1	3	4
TOTAL	30	30	60

GRAPH 4: INTER GROUP COMPARISION OF TYPE OF LARYNGOSCOPY

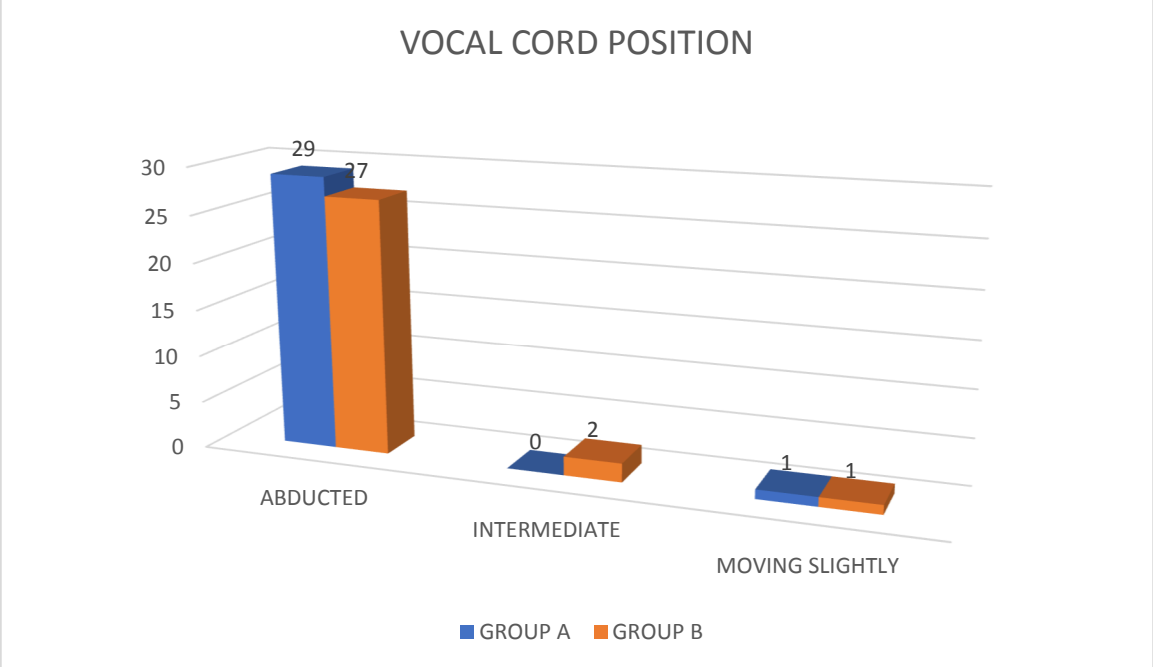


In our study laryngoscopy was easy in 29 patients in group A and 27 patients in group B. Fair conditions were seen in 1 patient in group A and 3 patients in group B. The p value was 0.605 which shows no statistical significance between the two groups.

TABLE 6: POSITION OF VOCAL CORD

VOCAL CORD POSITION	GROUP A	GROUP B	TOTAL
ABDUCTED	29	27	56
INTERMEDIATE	0	2	2
MOVING SLIGHTLY	1	1	2
TOTAL	30	30	60

GRAPH 5: INTER GROUP COMPARISION OF VOCAL CORD POSITION

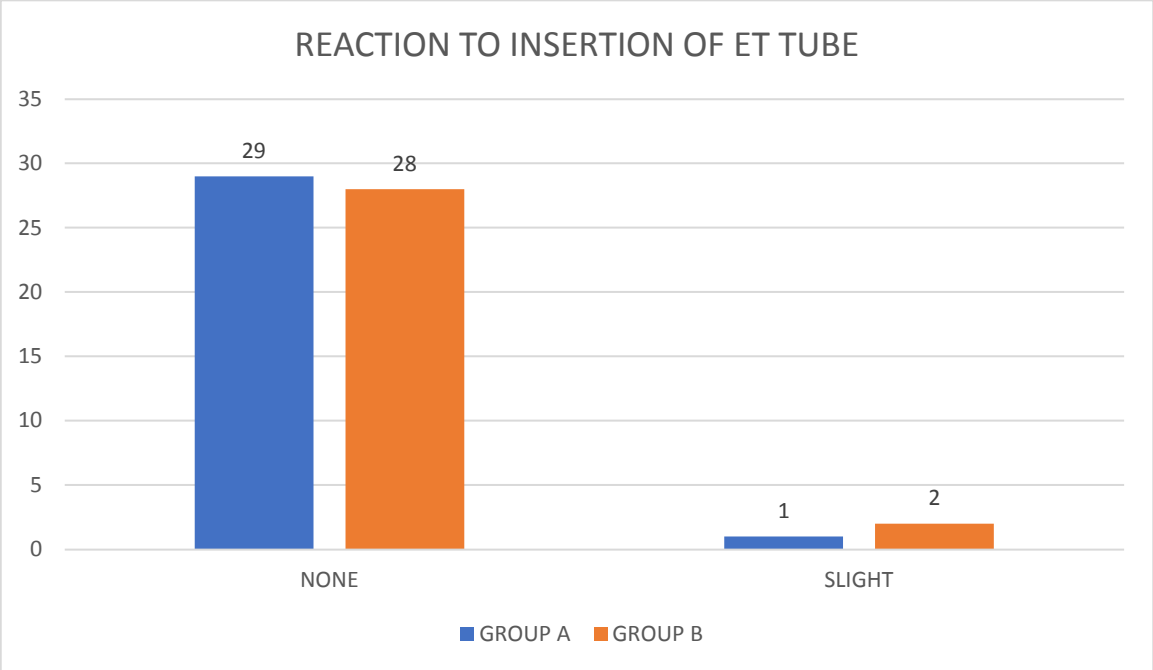


The vocal cord position was abducted in 29 patients and moving slightly in 1 patient in group A. In group B the vocal cord position was abducted in 27 patients, intermediate in 2 patients and moving slightly in 1 patient. P value was 0.355 and it was not statistically significant.

TABLE 7: REACTION TO INSERTION OF ET TUBE

REACTION TO INSERTION OF ET TUBE	GROUP A	GROUP B	TOTAL
NONE	29	28	57
SLIGHT	1	2	3
TOTAL	30	30	60

GRAPH 6: INTERGROUP COMPARISION OF REACTION TO ET TUBE INSERTION

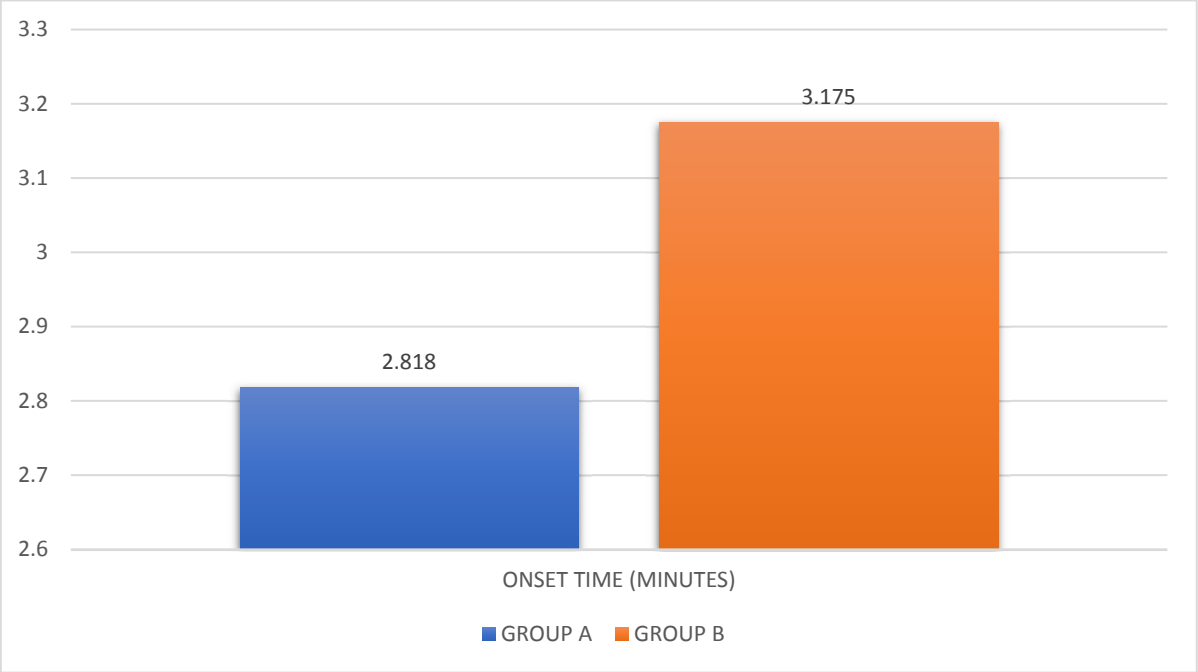


There was no reaction to insertion of ET tube in 29 patients in group A and 28 patients in group B. There was slight movement to insertion of ET tube in 1 patient in group A and 2 patients in group B.The P value was 1.000 which was not significant.

TABLE 8: ONSET TIME

ONSET TIME (MINUTES)	GROUP A	GROUP B
MEAN	2.8180	3.1750
STANDARD DEVIATION	0.10848	0.11802
P VALUE	0.001(HS)	

GRAPH 7: INTER GROUP COMPARISION OF ONSET TIME



In our study the mean onset time in group A where priming was done with Cisatracurium was 2.818 ± 0.108 minutes and in group B where priming was done with normal saline was 3.175 ± 0.118 minutes. The p value was 0.001 which shows that the difference in onset time in the two groups was significant.

DISCUSSION

Endotracheal intubation is essential to secure the airway to provide oxygenation and ventilation. Non depolarizing muscle relaxants (NDMR) are commonly used for intubation especially when depolarising drugs are contraindicated. However, the onset time for nondepolarizing agents is not as fast as Succinylcholine. Therefore, various methods to decrease this time has been tried which includes combination of neuromuscular drugs, using timing and priming technique or using initial large doses. In priming technique, a small dose of NDMR is given three minutes before the intubating dose.

This study was done by using priming principle with Cisatracurium to know the onset of neuromuscular block with Cisatracurium.

In our study the patients mean age in group A was 40 ± 12.376 years and 35 ± 11.147 years in group B, with no statistical significance between the two groups. The gender distribution of the patients in the two groups was comparable. There were a total of 40 female and 20 male patients in the study with 17 female patients in group A and 23 in group B and 13 male patients in group A and 7 in group B. The mean weight of patients was 57.73± 8.308 kg in group A and 59.69± 5.973 kg in group B. The two groups did not differ significantly with respect to their weight.73.3% patients in group A were scheduled for surgery with ASA grade Ⅰ and 26.7% with ASA grade Ⅱ compared to 70% patients with ASA grade Ⅰ in group B and 30% patients with ASA grade Ⅱ.

There was no significant change in the vital parameters like pulse rate and blood pressure in both the groups. The demographic data of age, gender, weight and ASA status were comparable and not significant in both the groups.

In our study the onset time was 2.818 ± 0.108 minutes in group A and 3.175 ± 0.11 minutes in group B. This was found to be statistically significant as the p value was < 0.001, indicating that the onset time was reduced when priming was done with Cis atracurium as compared to normal saline. In a study performed by Shih-pin Lin et al who observed the onset time of Cisatracurium with priming to be 2.51 ± 37.5 minutes as compared to normal saline as 3.68 ± 36.6 minutes, which was similar to the findings of our study [11]. In another study conducted by Ki Tae Jung et al, where time of onset of Cisatracurium was compared with priming and normal saline, the onset time with normal saline was more as compared with priming with Cisatracurium(2.026 ± 27.8 minutes vs 1.846 ± 45.6 minutes).[16]These results were similar to the observations in our study.

These observations are due to the fact that when the initial priming dose is given it occupies most of the post synaptic nicotinic receptors and when the intubating dose is given then it blocks the other receptors more rapidly which decreases the onset time.

The intubating conditions were assessed using three variables namely laryngoscopy, the position of vocal cords and the reaction to tracheal tube insertion and labelled as excellent, good and poor. In our study laryngoscopy was easy in 29 patients (96.7%), vocal cord abducted in 29 patients (96.7%), intermediate in none of the patients and moving slightly in 1 patient (3.3%) and after laryngoscopy no reaction to insertion of tube was seen in 29 patients (96.7%) and slight movement was seen in 1 patient (3.3%) in group A. In group B, laryngoscopy was easy in 27 patients (90%) and in 3 patients (10%) it was fair and the vocal cord position was abducted in 27 patients (90%) and it was intermediate in 2 patients (6.7%) and slightly moving in 1 patient (3.3%) and 28 patients (93.3%) had no reaction to insertion of tube and 2 patients (6.7%) had slight movement.

Excellent conditions of intubation were seen in 28 patients (93.3%) in group A and 25 patients (83.3%) in group B and good conditions were seen in 2 patients (6.7%) in group A where priming with Cisatracurium was done and 5 patients (16.7%) in group B where priming with normal saline was done. There was no statistical significance in terms of intubating conditions between both of the groups.

All the patients in our study had clinically acceptable conditions which might be because we used adductor pollicis muscle for train of four monitoring in all the patients as it has slower onset time when compared with central muscles like orbicularis oculi and adequate time given for optimal relaxation.

These results are consistent with the observations of Krishna Prasad Deepika et al. who studied the effect of priming technique on the intubating conditions using different doses of Cisatracurium and observed that priming Cisatracurium with 0.01mg/kg and using intubating dose of 0.14mg/kg provides excellent to good conditions of intubation in all the patients [6]. In another study Johann Motsch et al also found that the intubating conditions were excellent to good in all the patients irrespective of priming with saline or Cisatracurium which was similar to the result of our study.[17]

CONCLUSION

To conclude, from our study the priming dose of Cisatracurium (0.01 mg/kg) accelerates the onset time of neuromuscular blockade with intubating dose of 0.14mg/kg Cisatracurium and also provides excellent intubating conditions compared to 0.15mg/kg Cisatracurium without the priming dose.

SUMMARY

The present study “Comparision of onset time of Cisatracurium for tracheal intubation with and without priming dose of Cisatracurium in adult patients undergoing general anaesthesia ‘’ was conducted at KLES Dr. Prabhakar kore hospital and medical research center. The objectives were to determine the effect of the priming technique on the onset time for intubation and the intubating conditions.

Sixty patients posted for elective surgeries under general anaesthesia were randomised into two groups with 30 patients in each group. After premedication, induction and priming, train of four monitoring was done every 10 seconds till complete loss of T1. Group A patients received priming by using 0.01mg/kg Cisatracurium as priming dose and 0.14mg/kg Cisatracurium as intubating dose and group B patients received normal saline of 1 ml and 0.15mg/kg Cisatracurium as intubating dose and the time from administration of intubating dose till TOF count reached zero was taken as onset time and intubation was done at that time.

In our study the mean onset time in group A was 2.818 ± 0.108 minutes and in group B was 3.175 ± 0.118 minutes which shows that the difference in onset time in the two groups was significant.

In this study the intubating conditions were graded according to 3 parameters. The intubating conditions were assessed by laryngoscopy, position of vocal cords and the reaction to tracheal tube insertion.

In our study laryngoscopy was easy in 29 patients (96.7%) and in 1 patient (3.3%) it was fair in group A. In group B, laryngoscopy was easy in 27 patients (90%) and in 3 patients (10%) it was fair.

The vocal cord position was abducted in 29 patients (96.7%), intermediate in none of the patients and moving slightly in 1 patient (3.3%) in group A. In group B the vocal cord position was abducted in 27 patients (90%) and it was intermediate in 2 patients (6.7%) and slightly moving in 1 patient (3.3%).

After laryngoscopy no reaction to insertion of tube was seen in 29 patients (96.7%), slight movement was seen in 1 patient (3.3%) in group A and 28 patients (93.3%) had no reaction to insertion of tube and 2 patients (6.7%) had slight movement in group B.

Excellent conditions of intubation were seen in 28 patients (93.3%) and good conditions were seen in 2 patients (6.7%) in group A and 25 patients (83.3%) had excellent conditions of intubation and 5 patients (16.7%) had good conditions in group B.

There was no significant change in the vital parameters like pulse rate and blood pressure in both the groups. These vital parameters were comparable in both the groups.

In conclusion the priming dose of Cisatracurium of 0.01 mg/kg accelerates the onset time of neuromuscular blockade with 0.14mg/kg of intubating dose of Cisatracurium and also provides good intubating conditions compared to 0.15mg/kg dose of Cisatracurium.

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ANNEXURE I

INFORMED CONSENT FOR PARTICIPATION IN RESEARCH STUDY

- **OBJECTIVE/PURPOSE OF THE STUDY:**

We are requesting you to enroll in the study titled **"COMPARATIVE STUDY OF THE ONSET TIME OF CISATRACURIUM FOR TRACHEAL INTUBATION WITH AND WITHOUT PRIMING DOSE OF CISATRACURIUM IN ADULT PATIENTS UNDERGOING GENERAL ANAESTHESIA": A ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL TRIAL.**

This study will be conducted by Post graduate in M.D. Anaesthesiology Head, Department of Anaesthesiology, J.N. Medical College, Belagavi under KAHER, Belagavi.

Respected Sir/Madam, we request you to participate in our study as you are eligible for the same. Your participation in this research is voluntary. Your decision whether or not to participate in the study will not affect your relationship with J. N. Medical College or KLEH. If you decide not to participate you are free to withdraw at any time.

- **PROCEDURE INVOLVED:**

On the day of study, the volunteer will be brought to the operation theatre and placed in supine position on the operating table. Patient will be again explained about the procedure. He/she will be randomised into one of the two groups on computer - based randomisation table and intravenous access will be secured using 18G or 20 G iv cannula and iv fluids will be started. The priming and intubation doses of the drugs will be diluted to volumes of 1ml and 10ml respectively.

In the operating room, standard monitoring devices will be attached before induction of anaesthesia, including noninvasive blood pressure, heart rate, ECG and oxygen saturation and two stimulating electrodes will be placed over the ulnar nerve at the wrist and acceleration transducer will be attached to the thumb with adhesive tape. Baseline heart rate, blood pressure (BP), and oxygen saturation will be recorded.

All patients will be premedicated with inj. Midazolam 0.05mg/kg, inj. Glycopyrrolate 0.005mg/kg, and inj. Fentanyl 2µg/kg. After preoxygenation with 100% oxygen, anaesthesia will be induced with inj. Propofol 2mg/kg. After loss of eyelash reflex, O2-N2O in the ratio of 4:6 and Isoflurane 1% started for maintenance of anaesthesia using closed circuit. Neuromuscular function will be assessed with train of four (TOF) stimuli after induction of anaesthesia to prevent patient's discomfort. Supramaximal stimulus will be given (2hertz for 2 sec) through nerve stimulator. Baseline train of four will be recorded. T4/T1 percentage i.e., the percentage between the fourth and first twitch will be recorded and then Priming dose of Cisatracurium (0.01 mg/kg IV diluted to 1 ml with 0.9% normal saline) will be given to group A patients and group B patients will receive1 ml of 0.9% of normal saline. After 3 min of priming interval, intubating dose of Cisatracurium0.14 mg/kg (diluted to 10ml) will be given to patients in group A and Cisatracurium0.15 mg/kg (diluted to 10ml) to patients in group B. The intravenous line will be flushed by rapid flow of fluid for 15 s. TOF will be recorded every 10 s till complete loss of T1. At this point, intubation will be attempted by the anesthesiologist. The time from the end of Cisatracurium injection till TOF count reached zero will be measured as onset time (OT).

- **RISKS:**

There is almost no risk involved with Cisatracurium.

- **BENEFITS:**

Cisatracurium is more potent than atracurium and it undergoes Hoffmann elimination which is an organ independent degenerative mechanism and is safe in patients with renal and hepatic diseases

- **ALTERNATIVES:**

Even if you decline your participation in the study, the course of your treatment will not be affected. You are free to withdraw from the study at any point of time. Everything about the study will be explained in detail to you before giving consent for the same.

- **PRIVACY AND CONFIDENTIALITY:**

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:

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

- **INSTITUTIONAL POLICY:**

In the event of injury related to the study, treatment will be made available through KLES' Hospital & MRC, Belagavi. There is no compensation or payment for such medical treatment by law.

- **FINANCIAL INCENTIVES FOR PARTICIPATION:**

No financial incentives are being offered to enrolled patients. It is purely being done with the idea of research and all the cost of the study will be borne by the investigator.

- **AUTHORISATION 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 your identity remaining confidential.

- **CONSENT STATEMENT:**

Mode of communication of consent form: Verbal / Written

Contents: Self read/ readout by investigator

Participant's awareness regarding voluntary withdrawal from study: Yes / No

Investigator's decision to remove participants from study: Yes / No

Awareness regarding voluntary participation: Yes/ No

Adequate time given to clarify any doubts about the study or rights of a

study participant: Yes/ No

In case of any questions related to the study, in future or in case of study related injury or illness, you can contact Department of Anaesthesiology, KLE'S Hospital and MRC, Belagavi.

Signature or left thumb print of participant or legally authorized representative

_____Participant's name _____Participant's signature/thumb print

_____Experimenters' name _____Experimenters' signature

_____ Witness' name _____Witness' signature

_____ Date

ANNEXURE II

PROFORMA

"COMPARATIVE STUDY OF THE ONSET TIME OF CISATRACURIUM FOR TRACHEAL INTUBATION WITH AND WITHOUT PRIMING DOSE OF CISATRACURIUM IN ADULT PATIENTS UNDERGOING GENERAL ANAESTHESIA": A ONE YEAR HOSPITAL BASED RANDOMISED CLINICAL TRIAL.

Name : I.P. No. :

Age : Gender :

Date of operation : Address :

Surgeon : Anaesthesiologist :

PRE ANAESTHETIC EVALUATION:

Chief complaints:

HOPI:

Past History:

- H/o HTN / DM/ Asthma/TB/Thyroid disease/ Cardiac illness/ Neurological disease/ Any other illness.
- H/o previous anaesthetic procedure / previous surgeries.

Family History*:*

General physical examination

PR : BP :

RR : SPO2 :

Weight (Kg) : Temperature (^{0}F) :

Systemic examination:

RS : CNS :

CVS : GIT :

Airway Assessment:

Teeth: Jaw movements:

MPG grading:

Spine:

Investigations:

Hb% : Platelet:

Serum creatinine : FBS :

CXR : ECG :

Diagnosis:

Proposed Surgery:

Preoperative physical status: ASA Grade I II III IV V

Groups –

Group A – Priming with cisatracurium	
Group B – Priming with NS	

Characteristics of the patient:

Group	A	B
Age		
Weight		
Sex		

Intubating conditions will be assessed by:

Variable	Excellent	Good	Poor
Laryngoscopy	Easy	Fair	Difficult
Vocal cord position	abducted	Intermediate/Moving	Closed
Reaction to insertion of tracheal tube and cuff inflation (diaphragmatic movement /coughing)	None	Slight (1- 2 weak contractions or movement for <5 sec)	Vigorous/sustained(more than 2contractions and or movement for longer than 5 sec)

Type of Laryngoscopy

• Easy: Jaw relaxed, no resistance to blade insertion,

• Fair: Jaw not fully relaxed slight resistance to blade insertion,

• Difficult: Poor jaw relaxation, active resistance of the patient to laryngoscopy.

From above-mentioned Intubating Conditions

• Excellent: All variables are excellent.

• Good: Atleast two variables are either excellent or good with no poor variable.

• Poor: The presence of single variable listed under "poor."

Excellent and good intubating conditions will be considered to be clinically acceptable. Poor conditions will be considered as clinically not acceptable.

	Group A	**Group B**
Onset time		
spo2		
Heart rate		
Systolic bp		
Diastolic bp		
Mean bp		
Intubating conditions		

SIGNATURE OF THE ANAESTHESIOLOGIST - _____

SIGNATURE OF THE WITNESS - _____

SIGNATURE OF THE PRINCIPAL INVESTIGATOR - _____

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/ 173 **Date: 24/12/2019**

To,

BA0119007
PG student in Anaesthesiology,
J.N.Medical College,
BELAGAVI.

Sub: Institutional Ethical Clearance for the study.

With reference to the above, we wish to inform you that your proposed research project titled **"COMPARATIVE STUDY OF THE ONSET TIME OF CISATRACURIUM FOR TRACHEAL INTUBATION WITH AND WITHOUT PRIMING DOSE OF CISATRACURIUM IN ADULT PATIENTS UNDERGOING GENERAL ANAESTHESIA: A ONE YEAR RANDOMISED CLINICAL TRIAL "**, is ethical and justifiable. The proposed research project has been cleared by the JNMC Institutional Ethics Committee on Human Subjects Research.

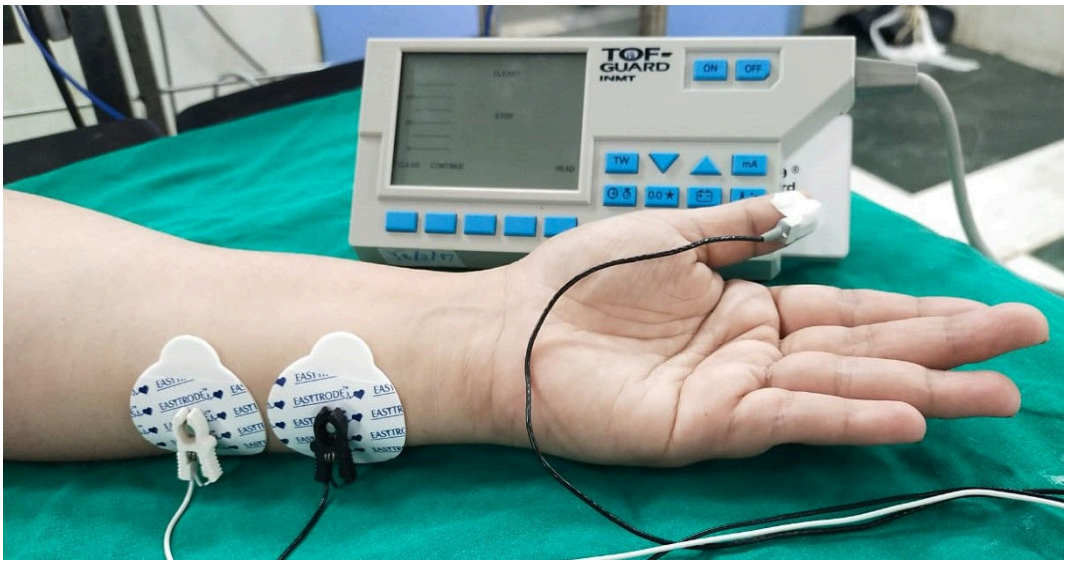
(Dr. Anita Dalal)
Member Secretary
JNMC Institutional Ethics Committee
on Human Subjects Research,
J.N.Medical College, Belagavi.

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

ANNEXURE IV: PHOTOGRAPHS

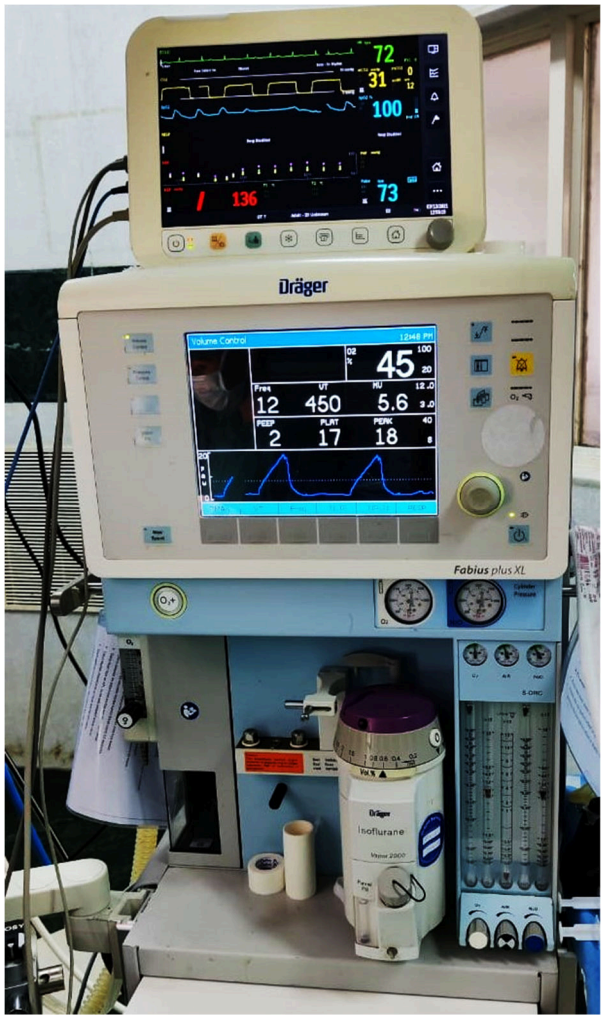
Photograph 1: Train of Four (TOF – Guard) Acceleromyograph

(Organon – Teknika, Belgium)



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

Photograph 3: Cisatracurium



Photograph 4: Anaesthesia work station (Drager fabius plus)

ANNEXURE-V

KEY TO MASTER CHART

ASA – American Society of Anaesthesiologists

DBP – Diastolic Blood Pressure

F – Female

HR – Heart Rate

KG – Kilogram

MPG – Mallampati Grade

M – Male

MAP – Mean Arterial Pressure

SBP – Systolic Blood Pressure

ANNEXURE-VI MASTER CHART

GROUP - A

S.no.	IP number	Age(years)	Gender	Weight(kg)	Asa grade	Onset time(minutes)	spo2	heart rate	systolic bp	diastolic bp	mean bp	Intubating conditions	Laryngoscopy	vocal cord position	reaction to insertion
1	996884	45	M	65	1	2.8	100	86	130	80	80	EXCELLENT	easy	abducted	none
2	998602	45	M	68	1	2.86	100	78	140	80	92	EXCELLENT	easy	abducted	none
3	1001520	45	F	58	1	2.88	100	78	110	80	70	EXCELLENT	easy	abducted	none
4	1002430	54	M	59	2	2.9	100	76	135	78	96	EXCELLENT	easy	abducted	none
5	1014963	24	F	45	1	2.85	100	86	110	75	86	EXCELLENT	easy	abducted	none
6	1015420	32	F	62	1	2.76	100	80	126	82	88	EXCELLENT	easy	abducted	none
7	1014291	59	M	67	2	2.96	100	65	110	80	70	GOOD	fair	moving slight	none
8	1015506	30	M	57	1	2.88	100	94	130	80	90	EXCELLENT	easy	abducted	none
9	1015673	22	M	64	1	3	100	82	110	80	85	EXCELLENT	easy	abducted	none
10	1016212	35	F	65	1	2.72	100	76	125	67	86	EXCELLENT	easy	abducted	none
11	1017626	38	F	47	1	2.68	100	76	130	90	100	EXCELLENT	easy	abducted	none
12	1022735	51	F	68	1	2.88	100	86	132	76	82	EXCELLENT	easy	abducted	none
13	1022912	60	F	58	2	2.8	100	73	130	70	100	EXCELLENT	easy	abducted	none
14	1023540	25	F	40	1	2.72	100	86	110	80	80	EXCELLENT	easy	abducted	none
15	1024041	18	F	45	1	2.65	100	92	130	80	70	EXCELLENT	easy	abducted	none
16	1024597	31	F	53	1	2.7	100	82	130	80	90	EXCELLENT	easy	abducted	none
17	1025040	33	M	62	1	2.68	100	92	128	76	78	EXCELLENT	easy	abducted	none
18	1025128	45	M	48	2	2.6	100	82	110	80	80	EXCELLENT	easy	abducted	none
19	1025343	34	F	70	1	2.86	100	72	130	80	80	EXCELLENT	easy	abducted	none
20	1025347	60	M	68	2	2.69	100	82	140	80	90	EXCELLENT	easy	abducted	none
21	1025227	47	F	68	2	2.72	100	72	140	80	100	GOOD	easy	abducted	slight
22	1026806	58	M	58	2	2.9	100	72	130	80	100	EXCELLENT	easy	abducted	none
23	1026403	47	F	46	1	2.98	100	82	110	70	90	EXCELLENT	easy	abducted	none
24	1026816	47	F	55	1	3.01	100	68	100	65	77	EXCELLENT	easy	abducted	none
25	1026967	29	M	55	1	2.9	100	72	110	80	85	EXCELLENT	easy	abducted	none
26	1027356	35	F	59	1	2.85	100	82	130	80	90	EXCELLENT	easy	abducted	none
27	1028521	31	F	50	1	2.8	100	72	110	70	80	EXCELLENT	easy	abducted	none
28	1028613	22	F	56	1	2.89	100	82	126	82	80	EXCELLENT	easy	abducted	none
29	1030583	45	M	64	2	2.76	100	86	140	80	86	EXCELLENT	easy	abducted	none
30	1031285	53	M	52	1	2.86	100	78	120	80	70	EXCELLENT	easy	abducted	none

GROUP - B

S.no.	IP number	Age(years)	Gender	Weight(kg)	Asa grade	Onset time(minutes)	spo2	heart rate	systolic bp	diastolic bp	mean bp	Intubating conditions	Laryngoscopy	vocal cord position	reaction to insertion
31	995768	21	F	50	1	3.2	100	78	120	80	75	EXCELLENT	easy	abducted	none
32	1000012	21	M	56	1	3.3	100	65	120	80	75	EXCELLENT	easy	abducted	none
33	1001526	23	M	52	1	3.25	100	68	120	80	70	EXCELLENT	easy	abducted	none
34	1003101	48	F	58	2	3.15	100	82	140	80	100	GOOD	fair	abducted	none
35	1002292	56	F	65	2	3.17	100	72	140	80	96	GOOD	easy	moving slight	none
36	1005559	28	F	52	1	3.16	100	82	120	80	70	EXCELLENT	easy	abducted	none
37	1007516	55	F	62	1	2.8	100	72	110	80	90	EXCELLENT	easy	abducted	none
38	1014840	34	F	55	1	3.28	100	68	120	80	80	EXCELLENT	easy	abducted	none
39	1014913	22	F	47	1	3.15	100	72	110	76	82	GOOD	easy	internediate	none
40	1014875	20	F	59	1	3.14	100	70	110	70	80	EXCELLENT	easy	abducted	none
41	1015647	42	F	62	1	3.17	100	72	127	82	86	EXCELLENT	easy	abducted	none
42	1016155	35	F	65	1	3.16	100	86	130	80	82	EXCELLENT	easy	abducted	none
43	1025060	39	F	68	1	2.98	100	76	128	82	90	EXCELLENT	easy	abducted	none
44	1027371	27	M	56	1	3.32	100	72	130	92	100	GOOD	fair	internediate	slight
45	1028373	40	M	65	2	3.23	100	92	138	82	100	EXCELLENT	easy	abducted	none
46	1029926	39	M	66	2	3.26	100	68	140	70	86	EXCELLENT	easy	abducted	none
47	1030502	40	F	56	2	3.34	100	72	140	80	86	EXCELLENT	easy	abducted	none
48	1030008	35	F	68	1	3.08	100	76	110	70	72	EXCELLENT	easy	abducted	none
49	1030158	35	F	64	1	3.12	100	88	120	80	72	EXCELLENT	easy	abducted	none
50	1030080	42	F	62	2	3.22	100	70	150	82	88	GOOD	fair	abducted	slight
51	1030788	22	F	58	1	3.28	100	88	128	72	88	EXCELLENT	easy	abducted	none
52	1030955	37	F	62	1	3.32	100	82	130	70	82	EXCELLENT	easy	abducted	none
53	1031089	57	F	65	2	3.06	100	72	110	80	70	EXCELLENT	easy	abducted	none
54	1032382	22	F	53	1	3.26	100	92	120	70	76	EXCELLENT	easy	abducted	none
55	1032099	31	M	67	1	3.11	100	86	110	80	72	EXCELLENT	easy	abducted	none
56	1032679	30	M	60	1	3.2	100	80	130	80	82	EXCELLENT	easy	abducted	none
57	1033137	55	F	60	1	3.14	100	82	130	80	88	EXCELLENT	easy	abducted	none
58	1033696	41	F	59	2	3.02	100	78	136	82	88	EXCELLENT	easy	abducted	none
59	1034142	40	F	68	1	3.32	100	80	140	80	86	EXCELLENT	easy	abducted	none
60	1034292	28	F	50	2	3.06	100	72	110	80	72	EXCELLENT	easy	abducted	none