A COMPARATIVE STUDY TO FIND AN IDEAL INTUBATING DOSE OF INJ. ROCURONIUM BROMIDE USING INJ. VECURONIUM BROMIDE AS CONTROL.

Dissertation submitted

In partial fulfillment for the award of

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DECLARATION

I, Dr. D.Shunmuga Priya, solemnly declare that the dissertation, **"A COMPARATIVE STUDY TO FIND AN IDEAL INTUBATING DOSE OF INJ. ROCURONIUM BROMIDE USING INJ. VECURONIUM BROMIDE AS CONTROL"** is a bonafide work done by me in the Department of Anaesthesiology and Critical Care, Government Kilpauk, Medical College, Chennai under the able guidance of **Prof. Dr. P.S. Shanmugam, MD., DA.,** Professor and HOD, Department of Anaesthesiology and Critical Care, Government Kilpauk Medical College, Chennai.

Place : Chennai

Date :

(**Dr. D.SHUNMUGA PRIYA)**

CERTIFICATE

This is to certify that this dissertation titled "**A COMPARATIVE STUDY TO FIND AN IDEAL INTUBATING DOSE OF INJ. ROCURONIUM BROMIDE USING INJ. VECURONIUM BROMIDE AS CONTROL"** has been prepared by **Dr. D.SHUNMUGA PRIYA** under my supervision in the Department of Anaesthesiology and Critical Care, Government Kilpauk Medical College, Chennai during the academic period 2008-2011 and is being submitted to the Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the University regulation for the award of the Degree of Doctor of Medicine (MD Anaesthesiology and Critical Care) and her dissertation is a bonafide work.

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CONTENTS

INTRODUCTION

Endotracheal intubation is an integral part of administration of anaesthesia during surgical procedure.

Succinylcholine, a depolarizing muscle relaxant with rapid onset of action and short duration is still the relaxant of choice to facilitate tracheal intubation. But in addition to fasciculations, succinylcholine has many side effects such as bradycardia, dysrhythmias, increased release of potassium, postop myalgia, increased intra ocular pressure, intra cranial tension, intra gastric pressure, prolonged recovery in patients with pseudocholinesterase deficiency, masseter spasm and triggering malignant hyperthermia[1,2,3,4,6,7].

Since these side effects are due to depolarizing mechanism of action of Succinylcholine, search has been focused on to find an ideal non depolarizing muscle relaxant with rapid onset time and offering excellent intubating conditions and also lacking all the above mentioned side effects[5].

Pancuronium:

Pancuronium is a bisquaternary aminosteroid nondepolarizing neuromuscular-blocking drug with an ED_{95} of 70 μg/kg that has an onset of action in 3 to 5 minutes and a duration of neuromuscular blockade lasting 60 to 90 minutes. Respiratory acidosis enhances pancuronium–induced neuromuscular blockade and opposes its antagonism with neostigmine[8].

Doxacurium:

Doxacurium is a benzylisoquinolinium nondepolarizing neuromuscular blocking drug with an ED_{95} of 30 µg/kg that has an onset of action in 4 to 6 minutes and a duration of neuromuscular blockade lasting 60 to 90 minutes. The pharmacokinetics of doxacurium resemble pancuronium with respect to dependence on renal clearance[9,10].

Atracurium:

Atracurium is a bisquaternary benzylisoquinolinium non-depolarizing neuromuscular-blocking drug with an ED_{95} of 0.2 mg/kg that has an onset of action in 3 to 5 minutes and a duration of neuromuscular blockade lasting 20 to 35 minutes. Large bolus dose of 1.5mg/kg will allow intubation in 90 sec but has hypotension, tachycardia and histamine release as side effects[11].

Cisatracurium:

Cisatracurium is a benzylisoquinolinium nondepolarizing neuromuscular-blocking drug with an ED_{95} of 50 µg/kg that has onset of action in 3 to 5 minutes and duration of neuromuscular blockade lasting 20 to 35 minutes.

Vecuronium:

Vecuronium is a monoquaternary aminosteroid nondepolarizing neuromuscular - blocking drug with an ED_{95} of 50µg/kg that has an onset of action in 3 to 5 minutes and a duration of neuromuscular blockade lasting 20 to 35 minutes. This drug provides greater hemodynamic stability[12].

Rocuronium:

Rocuronium is a monoquaternary aminosteroid nondepolarizing neuromuscular-blocking drug with an ED_{95} of 0.3mg /kg with an onset of action in 1 to 2 minutes and a duration of neuromuscular blockade lasting 20 to 35 minutes. It has rapid onset with insignificant cardiovascular effects and ultimate safety profile[11,12].

An ideal muscle relaxant must have following properties :-

(i) Rapid onset of action
(ii) Minimal cardiovascular side effects
(iii) Less cumulative effects
(iv) Less dependence on hepatic or renal function for its metabolism and excretion
(v) No histamine release
(vi) Pharmacologically inactive metabolite.
(vii) Easily antagonized

Of all the available relaxants, ROCURONIUM and VECURONIUM retain the advantages while eliminating the disadvantages of other drugs. Among these two, rocuronium comes ahead because of its more rapid onset of action while retaining all the benefits of vecuronium. Hence these two drug were compared in this study.

AIM OF THE STUDY

The aim of the present study is to find an ideal intubating dose of Inj. Rocuronium bromide 0.6mg/kg (2 ED_{95}) and 0.9mg/kg (3 ED_{95}) comparing with Inj. Vecuronium bromide 0.1mg /kg (2 ED_{95}) as control with regards to

- Intubating conditions
- Onset of blockade or time to maximum blockade
- Duration of blockade
- Hemodynamic stability

HISTORY

1555 : Tracheal insufflations in animals was described by Andreas Vesalius of Padua.

1978 : William Mc Even of Glasgow passed a tube from mouth into trachea using finger as a guide in conscious patient.

1907 : Barthelemy and Dufour of Nancy, blew chloroform vapor and air from a Vernon Harcount inhaler and a rubber guided into the trachea by touch.

1928 : Magill published the results of blind nasal intubation with wide bore tube. The first blind nasal intubation was performed by Stanley Rowbotham. Use of muscle relaxant was pioneered by Bourne to facilitate intubation.

1850 : Claude Bernard showed Curare acts by paralyzing myo-neural junction .This led to his discovery of the concept of motor end plate.

1934 : Sir Henry Dale described the physiological actions of Acetylcholine and its association with neuromuscular transmission.

1935 : King isolated active compound from the Chondrodendron species and called it D-tubocurarine.

1938 : Richard Gill returned from Ecuador with 11 kg of dark tarlike paste, crude curare mixture.

1940 : Squibb and Sons, Inc., prepared Intocostrin from the dark tarlike paste.

1942 : Harold R.Griffith and Enid Johnson used curare to give relaxation during surgery on 23rd January in Montreal, Canada.

1949 : Daniel Bovet et al introduced Suxamethonium.

1951 : Suxamethonium was first used in anaesthesia by Otto Van Dardel in Stockholm and Otto Meyerhofer in Vienna.

1956 : W.D.M. Paton made the distinction between depolarizing and nondepolarizing muscle relaxants.

ANATOMY AND PHYSIOLOGY

Neuro Muscular Junction :

Neuro Muscular Junction is specialized on the nerve side and on the muscle side to transmit and receive chemical messages . Each motor neuron runs without interruption from ventral horn of the spinal cord to Neuro Muscular Junction as large myelinated axon. As it approaches the muscle, it repeatedly branches to contact many muscle cells.

Motor end plate:

The nerve axon with all the muscle fibers it innervates form the motor end plate.

The parts of Neuro Muscular Junction are,

Presynaptic Nerve terminal :

The architecture of nerve terminal is different from that of axon. As the nerve terminal reaches the muscle fibers, it loses its myelin to form a splay of terminal branches against the muscle surface. This is covered by Schwann cells. This is the synaptic area of muscle membrane. The vesicles containing acetylcholine are ordered in repeating clusters along active zones or release sites. The active zones are areas where vesicles attach and rupture.

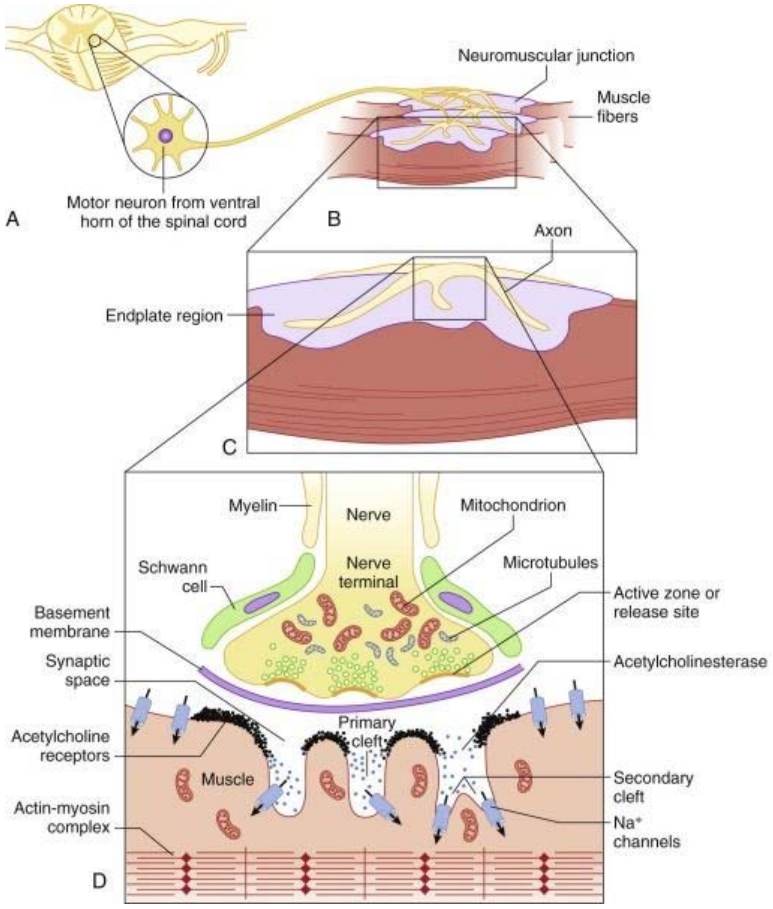
Synaptic cleft:

The nerve is separated from the surface of the muscle by a gap of 50nm, called the junctional cleft. The nerve and muscle are held tightly by

protein filaments called basal lamina, which spans the cleft between nerve and end plate[13].

Post synaptic muscle membrane:

The muscle surface is heavily corrugated with deep invaginations of the junctional cleft. They are the primary and secondary clefts between folds in the muscle membrane forming troughs and shoulders. This makes the end plate's total surface area very large. The shoulders of the fold are densely populated with acetylcholine receptors, about 5 million in each junction. The troughs have secondary clefts which contain sodium channels[14].



Contractile apparatus :

The contractile apparatus of the muscle is formed by the myofilament comprising of the thin actin filaments and thick myosin filaments along with tropomyosin, troponin I, T and C. Tropomyosin is attached to the myosin binding site of action.

The myofilaments combine to form myofibrils. The muscle plasma membrane, the sarcolemma, invaginates to form T-tubules which lie in close association with sarcoplasmic reticulum, which is a collection of sacs and tubules acting as a reservoir for calcium.

Perijunctional zone:

Area of muscle immediately beyond the junctional area is the perijunctional zone, and it is critical to the function of neuro muscular junction. This zone contains mixture of receptors, which include a small number of acetylcholine receptors and a large number of sodium channels. This mixture increases the response to depolarization produced by acetylcholine receptors and transduces it into wave of depolarization that travels along muscle to initiate muscle contraction.

Mechanism of Acetylcholine Release :

Quantal theory :

While observing the electrophysiologic activity of skeletal muscles, small spontaneous, depolarizing potentials at neuro muscular junction are seen. These potentials have only one hundredth the amplitude of the evoked end potential when the motor nerve is stimulated. These small amplitude potentials are called miniature end plate potential (MEPPs). MEPPs are

unitary responses and sizes of all MEPPs are equal to or multiples of the minimum size. MEPPs are produced in uniform sized packages called quanta. The stimulus evoked motor potential is the additive depolarization produced by synchronous discharge of quanta from several hundred vesicles[14,15].

Formation of Acetylcholine at nerve endings :

Choline, transported by a special system from the extra cellular fluid to the cytoplasm and acetate in the form of acetyl Co enzyme A combine in presence of acetyl transferase to form acetylcholine.

ECF	→	Choline	Acetyl	Acetyl
		+	→	
AcetylCoEA	→	Acetate	transferase	Choline

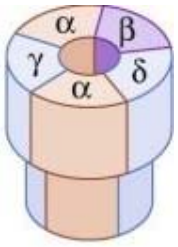
The acetylcholine is stored in cytoplasm and transported as vesicles during release[14,15].

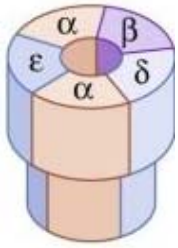
Binding of acetylcholine to receptor

The acetylcholine released from nerve diffuses across the junctional cleft and reacts with specialized receptor proteins in the end plate to initiate muscle contraction. Two isoforms of post junctional receptors exist, a junctional or mature and extrajunctional or immature receptor.

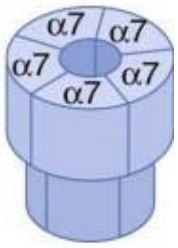
Acetylcholine receptors are synthesized in muscle cell and anchored to end plate membrane by 43 kd protein rapsyn in 1:1 ratio. These receptors have 5 subunits. The proteins are arranged like staves of a barrel with a

central pore for ion channeling. The receptor protein has a mass of 2,50,000 daltons. The 5 subunits are 2α, β,δ, ε or γ. Each subunit consists of 400-500 amino acids. The mass of each subunit is α :40000, β: 50000, δ:65000, ε:55000 and γ:60000 daltons[16]. The receptor protein complex passes through the membrane and protrudes beyond the surface of membrane into cytoplasm. The extrajunctional receptors have γ instead of δ as subunits. The acetylcholine binds to each of α subunits[17].





Immature Acetylcholine Receptor Mature Acetylcholine Receptor



Neuronal Acetylcholine Receptor

Acetylcholinesterase

Acetylcholine released from nerve diffuses across junctional cleft and reacts with specialized receptor protein to initiate muscle contraction. Transmitter molecules that do not react immediately with a receptor or

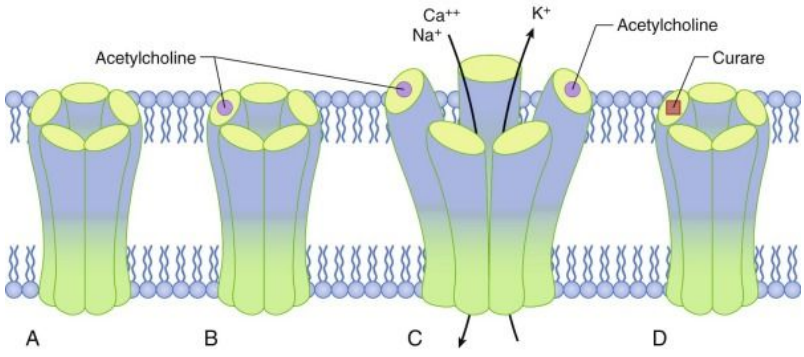
those relapsed after binding to the receptor are destroyed instantaneously by acetylcholinesterase in the junctional cleft[14,15,17]. Acetylcholinesterase is a type B carboxylesterase enzyme. Acetylcholine is a potent messenger but its actions are very short lived because it is destroyed in less than 1ms after release.

Extrajunctional nAChRs:

Normally these receptors are not present in large numbers since their synthesis is suppressed by neural activity. During conditions like trauma, skeletal denervation or burns these extrajunctional receptors proliferate rapidly. These receptors appear over the entire post junctional membrane rather than being confined to the area of neuromuscular junction[18].

Perijunctional nAChRs:

These receptors in motor nerve endings influence the release of neurotransmission. These prejunctional nAChRs are different from postjunctional nAChRs in their chemical binding characteristics, the nature of the ion channel they control and their preferential blockade during high frequency stimulation[18].



Basic Electrophysiology of Neurotransmission

The electrophysiology is studied by patch clamp test. The ion channel is inactive and does not open in absence of acetylcholine. Even binding of one α sub unit to acetylcholine does not open. Both α subunit must be occupied to cause conformational change to open the channel and allow sodium and calcium ions inside and potassium outside. When the one of two sites is occupied by antagonist like curare, the receptor will not open even if the other binding site is occupied by acetylcholine. The current carried by the ions depolarizes the adjacent membrane. The net depolarizing current causes the muscles to contract. The pulse stops when the channel closes and one or both agonist molecules detach from the receptor. Each burst of acetylcholine from the nerve normally opens about 5,00,000 channels causing depolarization and contraction[17,18].

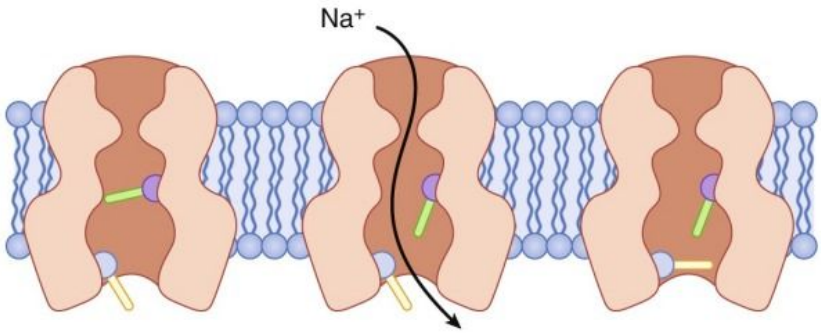
MECHANISM OF DEPOLARIZING BLOCKADE

Depolarizing relaxants, simulate the effects of acetylcholine and hence considered as agonists. Succinylcholine is two molecules of acetylcholine attached together. Succinylcholine or decamethonium can bind to one or both of α receptor, open the channel, pass current and depolarize the end plate. Depolarizing relaxants have biphasic action: an initial contraction followed by relaxation lasting from minutes to hours. Their action lasts till the depolarizing agents are cleared by plasma since they are not subject to hydrolysis by acetylcholinesterase.

Features of depolarizing blockade:

1. Decreased contraction in response to single twitch stimulation
2. Decreased amplitude but sustained response to continuous stimulation.
3. TOF ratio >0.7
4. Absence of post tetanic facilitation
5. Augmentation of neuro muscular blockade after administration of anticholinesterase drug
6. Onset of phase I blockade is accompanied by skeletal muscle fasciculation.

Sodium channels:



The quick shift from excitation of muscle contraction to blockade of transmission by depolarizing agents occurs because the end plate is continuously depolarized. This occurs because of ion channel, the sodium channel which does not respond to chemicals but opens when exposed to a transmembrane voltage change.

Sodium channel has two gates. In the resting state, the lower gate (time dependent or inactivation gate) is open but the upper gate (voltage dependant gate) is closed and sodium cannot pass.

During depolarization the top gate opens and because lower gate is also open, sodium flows through the channel. This stays open as long as the molecule is subject to depolarization. But shortly after this the voltage dependant gate remains open but the bottom gate is closed. This cuts off ion flow and time dependant gate does not open until voltage dependent gate closes. When depolarization stops, the voltage dependant gate closes, time dependant gate opens and sodium channel comes to a resting state[19].

Phase I block

The succinylcholine molecule is attached to one or both α subunit of acetylcholine receptor, depolarizing the postjunctional membrane. But since hydrolysis of succinylcholine is slow there is sustained depolarization called phase I blockade.

Phase II block

A complex phenomenon which occurs on continuous exposure to depolarizing agent or when large dose of succinylcholine (>2mg / kg IV) is given as infusion. The postjunctional membrane does not respond to acetylcholine even after depolarization. Resembles block produced by non depolarizing muscle relaxants. But reversal with cholinesterase inhibitors is not attempted.

In depolarizing block, muscle membrane is divided into 3 zones.

- End plate : Depolarized by succinylcholine
- Post junctional membrane: Sodium channels are frozen in an activated state.
- Rest of muscle membrane : Sodium channels are in resting excitable state.

This phenomenon is called as accommodation where synapse is unexcitable through the nerve (transmitter) but direct electrical stimulation of muscle will cause muscle contraction since sodium channels beyond the junctional area are in resting state. Accommodation does not occur in extra ocular muscle.

MECHANISM OF NON DEPOLARIZING BLOCKADE:

These act by combining with nicotinic acetylcholine receptors without causing any activation of these ion receptor channels. These drugs can act competitively with acetylcholine on α subunit of post junctional receptors without causing a change in the configuration of these receptor.

Features of non depolarizing muscle relaxants:

(i) Decreased twitch response to single stimulus
(ii) Unsustained response (fade) during continuous stimulation
(iii) TOF ratio <0.7
(iv) Post tetanic potentiation
(v) Potentiation of other non depolarizing muscle relaxants
(vi) Antagonism by anticholinesterase drugs
(vii) No skeletal muscle fasciculation seen.

NEUROMUSCULAR MONITORING

Neuromuscular function is monitored by evaluating the muscular response to supra maximal stimulation of a peripheral motor nerve.

Types of Neuromuscular stimulation:

1. Electrical : Most commonly used
2. Magnetic: Less painful and does not need contact with the body. But equipment is very heavy, cannot be used for TOF stimulation and difficult to achieve supra maximal stimulation. Hence seldom used.

Principles of peripheral nerve stimulation

The reaction of a single muscle fiber to a stimulus follows an all or none pattern. If the nerve is stimulated with sufficient intensity, all muscle fibers supplied by that nerve will react and maximum response is obtained. The reduction in response during constant stimulus reflects neuromuscular blockade.

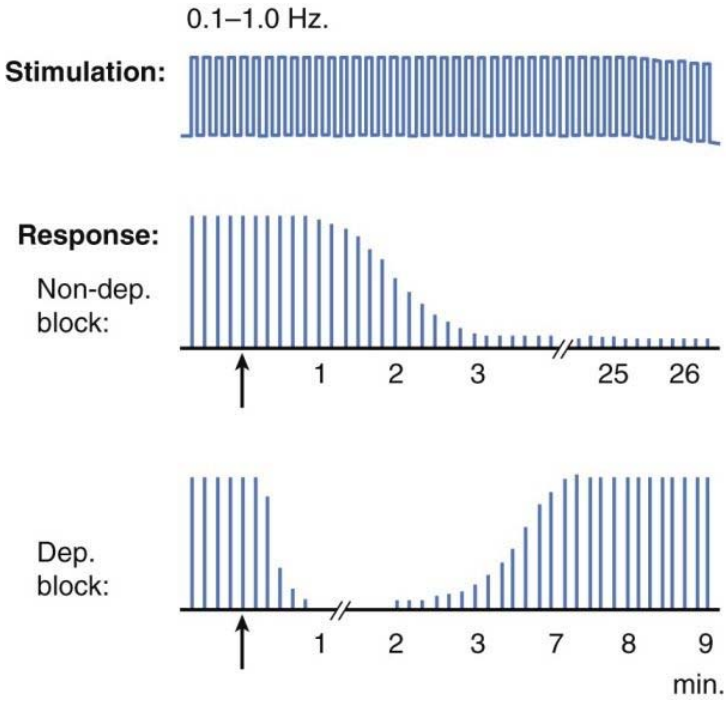
The stimulus is 20-25% above that needed for maximal response. Hence called as supramaximal.

Patterns of Neuromuscular stimulation

The most commonly used patterns of electrical nerve stimulation are single twitch, Train of four , tetanic count, post tetanic count and double burst stimulation[13,18].

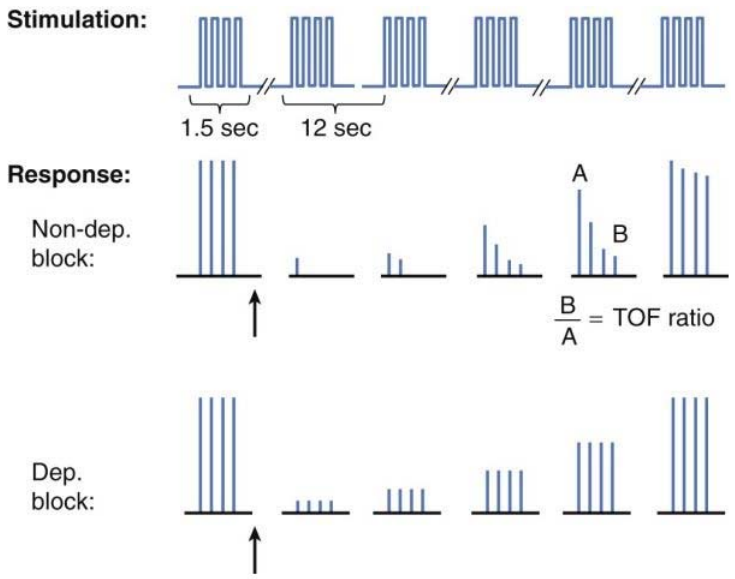
Single twitch stimulation:

Here single supramaximal electrical stimuli is applied to a peripheral motor nerve at frequencies from 1.0Hz (once every sec) to 0.1 Hz (once every 10 sec) The response to single twitch depends on the frequency with which the individual stimuli are applied. A frequency of 0.1 Hz is generally used. 1Hz stimulation can be used during induction of anaesthesia.



Train of four stimulation:

Introduced by Ali and associates during early 1970s[20]. Here four supramaximal stimuli are given every 0.5 sec (2 Hz). Dividing the amplitude of 4th response by the amplitude of 1st response provides TOF ratio.



In control, before giving muscle relaxant, all four responses are same. TOF ratio is 1.0

Partial DP blockade : No fade occurs
TOF ratio is 1.0

Partial NDP blockade : Ratio decreases (fades) and is inversely proportional to the degree of blockade.

When used continuously each set of stimuli is repeated every 10^{th} to 20^{th} second.

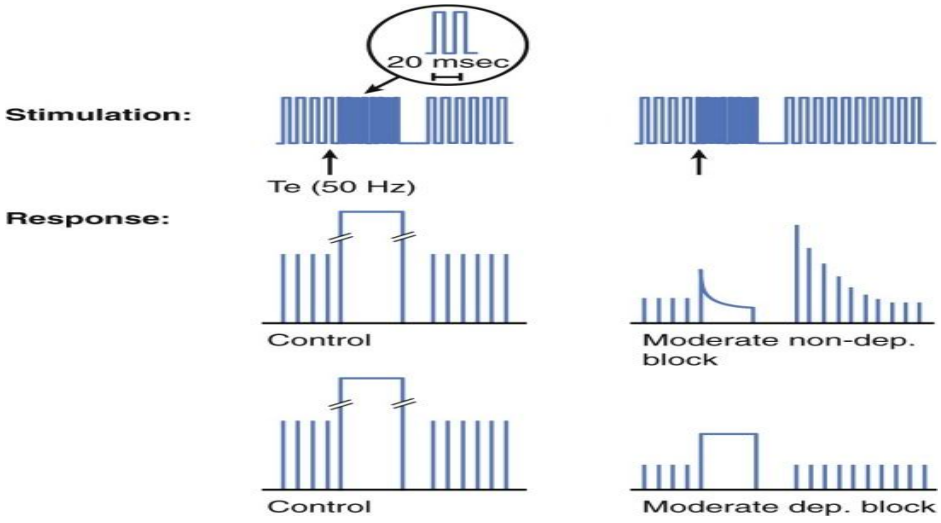
Loss of 4^{th} response : 70% blockade
Loss of 3^{rd} and 2^{nd} response : 80-90% blockade
All four twitches absent : 100% blockade

Tetanic stimulation:

Very rapid delivery (30, 50, or 100 Hz) of electrical stimuli. 50Hz stimulation given for 5 sec is the most commonly used pattern.

During normal neuromuscular transmission and depolarizing block, the muscle response is sustained. There is no post tetanic potentiation. During a NDP block and phase II block after succinylcholine, the responses will not be sustained (fade occurs). Potentiation of post tetanic twitch occurs.

Fade to tetanic stimulation is a presynaptic event. On application of tetanic stimulation, large amounts of acetylcholine is released from immediately available stores in nerve terminal.



As this stores become depleted, the rate of acetylcholine release decreases and reaches an equilibrium between mobilization and synthesis of acetylcholine.

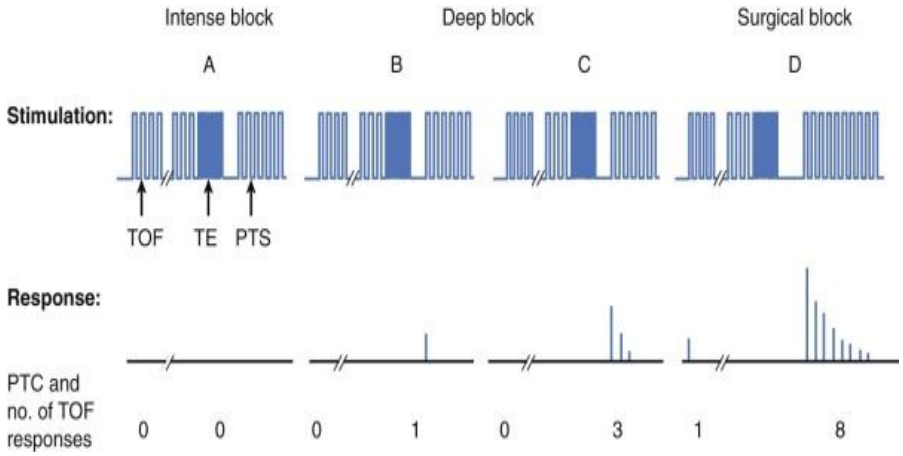
Repeated used of tetanic twitch may cause local reversal of block . It may also be painful in awake patients.

Post tetanic count stimulation

Intense neuromuscular blockade is quantified here. Tetanic stimulation (50Hz for 5 sec) is applied and post tetanic response to single twitch stimulation given at 1Hz starting 3 sec after end of tetanic stimulation is observed.

Usually 12 -20 counts detect first response.

Very intense blockade: No response to tetanic or post tetanic stimulation

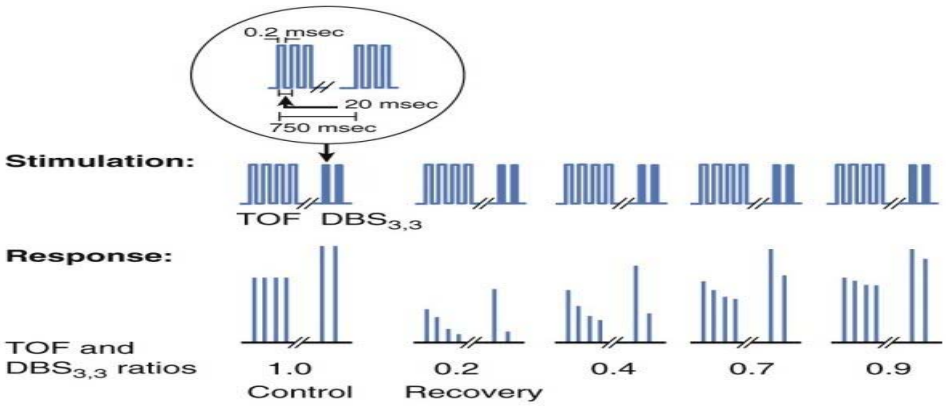


As intensity of block wears off the first response to post tetanic stimulation occurs, before response to TOF appears. As intense block wears off, more and more response to post tetanic stimulation occurs.

During surgical blockade : First TOF appears and post tetanic count increases further.

Double burst stimulation

This consists of two short bursts of 50Hz tetanic stimulation separated by 750msec. Duration of each square wave impulse in the burst is 0.2msec. DBS with three impulses in each of two tetanic burst is most commonly used.



Non paralyzed muscles **:** Two short muscle contractions of equal strength

Partly Paralyzed muscles **:** Second response is weaker than first (fade occurs)

DBS was developed with specific aim of allowing manual (tactile) detection of small amounts of residual blockade.

Peripheral Nerve stimulators:

Used to monitor transmissions across NMJ. The stimulus should produce a monophasic and rectangular wave form.

Electrodes:

Electrical impulses are transmitted from stimulator to nerve by means of surface or needle electrodes. Normally disposal pregelled silver or silver chloride surface electrodes are used. Conducting area is 7-8 diameter.

Skin is always cleaned properly and rubbed with abrasive before applying electrodes.

Needle should be placed subcutaneously but never in nerve. Length of pulse should not exceed 0.2 -0.3 msec. Nerve stimulator should be battery operated, generating 60-70 mA, not more than 80mA. Constant current is provided only when skin resistance ranges from 0Ω to 2.5 kΩ

Sites of nerve stimulation:

Any superficial peripheral motor nerve may be stimulated. Ulnar nerve is most commonly used. Median nerve, posterior tibial nerve, common peroneal and facial nerve are also used. In this study ulnar nerve was used . The electrodes were applied at volar side of wrist. Distal electrode is placed 1 cm proximal to the point at which proximal flexion crease of wrist crosses the radial side of tendon to flexor carpi ulnaris. Proximal electrode is placed 2-5 cm proximal to distal electrode.

The electrical stimulation elicits finger flexion and thumb adduction[12,13].

Recording of evoked responses :

Five methods of recording evoked response are

1. Mechanomyography MMG : Measuring evoked mechanical response of muscle.
2. Electromyography EMG : Measuring evoked electrical response of muscle.
3. Acceleromyograply AMG : Measuring acceleration of muscle response. This technique is based on Newton 's 2^{nd} law: force equals mass times acceleration . This is used in TOF watch SX 100, used in this study.
4. Piezoelectric NM monitor PzEMG : Measuring evoked electrical response in a piezoelectric fibro sensor.
5. Phonomyography PMG.

PHARMACOLOGY

ROCURONIUM BROMIDE (ORG 9426)

Rocuronium is a monoquaternary aminosteroid non depolarizing neuro muscular blocking drug with intermediate onset of action.

It is a 2- morpholino 3 desacetyl , 16 n –allyl pyrrolidino derivative of vecuronium.

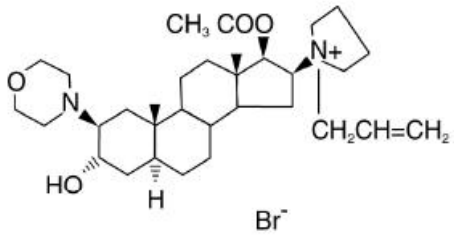
Structurally Roc resembles vecuronium except for the presence of a hydroxyl group rather than an acetyl group on the A- ring of steroid nucleus.

The presence of cyclic substituents other than piperidine at the 2 – and 16- positions resulted in a fast onset compound.

The methyl group attached to the quaternary N atom of vecuronium and pancuronium is replaced by allyl group, so it is 6 times less potent than vecuronium.

The replacement of acetyl ester attached to the A ring by a hydroxyl group has made Roc a stable solution[18,21].

Molecular structure:



Presentation:

A vial containing a clear, colourless to faintly yellow solution.

Available in two quantities : 50 mg and 100 mg

Product Esmeron contains 10mg /ml of Rocuronium bromide as active ingredient. It also contains

- Sodium acetate
- Sodium chloride
- Acetic acid
- Water for injection
- No preservative has been added.

Storage :

- ❖ Kept in refrigerator at 2-8 ° C and should not be frozen.
- ❖ Esmeron can be stored outside refrigerator at a temperature of 30°C for a maximum of 12 wks.
- ❖ Once kept outside it should not be placed back into the refrigerator.

Routes of administration :

- ❖ Intravenous bolus or infusion
- ❖ Intramuscular

PHARMACODYNAMICS

Dose:

IV:

ED 95	:	0.3 mg /kg
Intubation at 60-90 sec	:	0.6 - 0.9 mg /kg
Relaxation using (N_2O/O2)	:	0.3 -0.4 mg/kg
(Vaporizer)	:	0.15- 0.2 mg/kg
Maintenance	:	0.1-0.15 mg /kg
Maintenance Infusion	:	9-12 μg/kg/ min

IM:

Infant : 1mg/kg

Child : 1-8 mg/kg

Mechanism of action :

Rocuronium acts by combining with nAchRs without causing any activation of these ion receptor channels. It acts competitively with ACh at α subunits of postjunctional nAChRs without causing change in the configuration of these receptors. When large number of molecules of less potent Roc is used , greater number of molecules are available to diffuse into NMJ.

Onset of maximum single twitch depression after the administration of 3 or 4 ED95 of Roc resembles onset of action of SCh 1mg /kg IV.

Onset of action:

Onset is time from injection to onset of maximal single twitch depression[22].

IV:

With narcotic	2 ED 95: 1.5-2 min
With vaporizer	2 ED 95: 1.5 – 1.7 min
Vaporizer	3 ED 95 : 40 sec – 80 sec
	4 ED 95: 40 sec -70 sec

Duration of action :

Time from injection to return of single twitch height to 25% or 95% with 0.6 mg /kg is 25-35 min.

Clinical duration :

Time from injection to recovery of train of four ratio ≥ 0.7 to ≥ 0.9 for 0.6mg/kg is 55-80 min.

With narcotic: 0.6 mg /kg	:	36 min
With vaporizer 0.9mg/kg	:	50-55 min
With vaporizer 1.2mg/kg	:	70-80 min

Recovery index :

Time from 25% return of single twitch height to 75% return of single twitch height

For 0.6 mg /kg is 14 min

Maintenance dose:

Supplemental dose after intubation : 0.075 -0.15 mg / kg IV.

Continuous infusion:

For loading dose of 0.6mg/kg, infusion is 9-12 μg/kg /min

Infusion rate is adjusted to maintain 90-95% twitch inhibition under N_2O/O_2 anaesthesia or to maintain 1 – 2 response to TOF.

PHARMACOKINETICS

Distribution:

Neuromuscular blocking drugs due to their quaternary ammonium groups are highly ionized, water soluble compounds at physiological pH with limited lipid solubility. So volume of distribution is limited and similar to ECF volume (200 ml/kg). These do not easily cross lipid membrane barriers like blood brain barrier, renal tubular epithelium, GI epithelium or placenta.

So do not produce CNS effects, renal absorption is minimal, oral absorption ineffective and does not affect fetus.

Volume of distribution for Roc is 0.3 liters / kg

Metabolism:

Rocuronium is metabolized to 17 desacetyl Rocuronium and 16 n desallyl Rocuronium.

Clearance:

Roc is 4ml/kg /min

Elimination:

Normal t ½ : 87 min

Roc is largely excreted unchanged in bile

Biliary excretion: 50-70% unchanged

Renal excretion: 10-25% unchanged

Influence of age:

Age may affect pharmacokinetics of rocuronium since total body water and function of organs involved in elimination of drugs diminish with increasing age.

In neonates and children, volume of distribution is increased and plasma clearance unchanged, causing longer elimination half life.

In children, volume of distribution is unchanged but clearance is increased, resulting in shorter half life and mean residual time[23].

Elderly:

Duration prolonged due to decreased hepatic clearance

Influence of obesity:

Rocuronium onset time is shorter and duration is prolonged in overweight patients when compared to normal and underweight people[24].

Hepatic diseases :

Increased volume of distribution of Roc, and results in longer duration of action of drug with t ½ 97min[25].

Renal failure:

Modest prolongation of action t ½ 97 min[26]

Autonomic effect

Autonomic ganglia : No effect

Cardiac muscarinic receptor : Blocks moderately

Hisamine release : None

Safety profile

1. Cardiovascular effects:

   Like Vec, Roc at standard dose of 0.6 mg/kg does not produce significant changes in HR or MAP[27].

2. Histamine release :

   Roc does not produce significant histamine related symptoms with upto 4 times ED_{95} dose[27,12]

3. Anaphylaxis / anaphylactoid reaction:

   Has low risk of anaphylactoid reaction manifested as cutaneous erythema, hypotension, tachycardia. Bronchospasm may occur occasionally.

4. Cholinesterase inhibition

   Lower than that of vec

Drug interactions :

Volatiles:

Enflurane and isoflurane potentiate the effects of Roc. Halothane has less potentiation. N_2O does not have any effect on depth of block[28,29].

IV Anaesthetics:

Interactions have been reported when other NDNM blocking drugs are used. Roc with mivacurium results in synergistic activity. Studies suggest using subparalyzing dose of Roc before SCh to reduce fasciculation.

IV Antibiotics:

NM blockade is prolonged when, Roc is used with amino glycosides, bacitracin, colistin, polymyxin, tetracycline and vancomycin[30].

Anticonvulsants :

Chronic phenytoin therapy causes resistance to neuromuscular blockade activity probably due to receptor up regulation. Magnesium salts prolong NM blockade.

Reversibility

TOF ratio of 0.6-0.7 show adequate recovery of neuromuscular strength

Block is antagonized with

Neostigmine 0.04-0.07μg/kg or sugammadex ORG 25969 2-8 mg/kg[31]

VECURONIUM BROMIDE

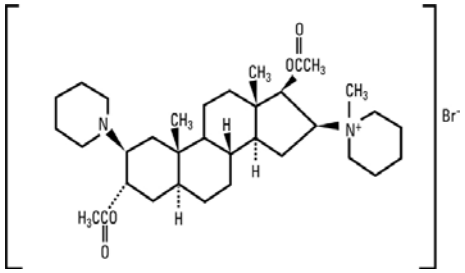
Structure:

Vecuronium is an N-demethylated derivative of pancuronium in which 2 piperidne substituent is not methylated.

Vec is a monoquaternary aminosteroid non depolarizing NMBD with intermediate duration of action . At physiologic pH, the tertiary amine is largely protonated similar to dTc.

This modification causes slight change in potency, a marked reduction in vagolytic properties, molecular instability in solution causing short duration of action than pancuronium and increased lipid solubility causing greater elimination than pancuronium[18].

Molecular structure:



Presentation :

Vec is unstable is solution so supplied as a sterile, non pyrogenic, freeze dried, lyophilized powder which is dissolved in sterile water before its use. Addition of 1ml water for injection results in clear to almost clear

isotonic solution with pH of approximately 4 containing 4mg Vecuronium Bromide per ml.

Reconstituted solution can be stored for 24hrs at room temperature 15°C to 25°C in daylight.

Solution can be prepared with :

- 5% glucose solution
- 0.9% NaCl
- RL solution
- 5% glucose in RL solution
- 5% glucose in 0.9% NaCl solution
- Water for injection

Packages :

- ❖ Vecuronium bromide 4mg
  Package of 5 ampoules of each containing 4mg vec bromide

- ❖ Vecuronium bromide 10mg
  Package of 5 vials of each containing 10mg vec bromide
  Vecuronium bromide is supplied in a citrate phosphate buffered freeze dried form containing mannitol for tonicity adjustment

- ❖ No preservative has been added

Routes of administration :

IV bolus or infusion

PHARMACODYNAMICS

Dose :

IV :

ED_{95}	: 0.05 mg /kg
Intubation dose	: 0.1-0.2 mg/kg
Relaxation (N_2O /O_2)	: 0.05mg /kg
(Vaporizer)	: 0.03mg/kg
Maintenance	: 0.02 -0.03 mg /kg
Infusion	: 0.8 to 1µg/kg/min

Mechanism of Action :

Vecuronium acts by combining with nAchRs without causing any activation of these ion receptor channels. It acts competitively with Ach at α subunits of postjunctional nAchRs without causing change in the configuration of these receptors.

Onset of action :

Onset is time from injection to onset of maximal single twitch depression[32]

IV:

With narcotic 2 ED_{95}	: 3-5 min
With vaporizer 2 ED_{95}	: 2-4 min

Duration of action

Time from injection to return of single twitch height to 25% or 95% with 0.1mg /kg it is 25-35 min[32].

Clinical duration :

Time from injection to recovery of TOF ratio to ≥ 0.7 or ≥ 0.9 for 0.1mg/kg is 40-80 min

With narcotic 0.1mg/kg : 41 min

With vaporizer 0.1 mg/kg : 44min

Recovery index:

Time from 25% return of single twitch height to 75% return of single twitch height 0.1mg/kg is 13 min.

Maintenance dose :

Supplemental dose after intubation 0.02mg/kg IV

Continuous infusion :

For a loading dose of 0.1 mg /kg , infusion is 0.8 -1 μg/kg /min.
Infusion rate is adjusted to maintain 90-95% twitch inhibition under N2O/O2 anaesthesia or to maintain 1-2 response to TOF.

PHARMACOKINETICS

Distribution:

NMBDs due to their quaternary ammonium groups and other linkage and methoxy groups have high degree of water solubility and slight lipid

solubility. Vecuronium is more lipid soluble than pancuronium due to absence of quaternizing methyl group at 2 position.

Volume of distribution of vec is 0.27 liter /kg

Metabolism :

Vecuronium is more lipid soluble than pancuronium. It undergoes metabolism 2-3 times more than Pan. Vec is taken up by liver by carrier mediated transport system and is desacetylated at 3- position by liver microsomes.

12% of vec is cleared as 3- desacetyl vec.

30-40% cleared in bile as parent compound.

Other metabolites are.

17 desacetyl vec and

3,17 desacetyl vec

Principal metabolite 3- desacetyl vec is a potent NMBD, about 80% of vecuronium. 3- desacetyl vec has lower plasma clearance and longer duration than vec.

Clearance :

Vecuronium is 3-6 ml/kg /min

3 desacetyl vec is 3.5ml/kg /min

Elimination:

- Normal elimination t ½ 50-110 min
- 40-75 % excreted unchanged in bile
- 15-25% excreted unchanged in urine
- 20-30% hepatic degradation

Hepatic disease :

Prolonged elimination half life and increased duration of action. Elimination t ½ 49-192 min.

Renal failure :

Elimination half life of both vecuronium and 3- desacetyl vecuronium is prolonged leading to decreased clearance of drug. Increased plasma concentration of 3 desacetyl vec contributes to prolonged skeletal muscle paralysis after prolonged infusion in renal failure patient.

Elimination of t ½ = 80-150 min[33].

Cumulative effects :

Vec has large volume of distribution and tissue uptake. After a single dose of vecuronium, the plasma concentration decreases rapidly due to redistribution from central to peripheral compartment. With subsequent doses, the vecuronium present in peripheral tissue compartment limits the distribution and also the rate of decrease in plasma concentration of drug causing a cumulative effect.

Autonomic effects :

Autonomic ganglia : None

Cardiac muscarinic receptors : None

Histamine release : None

Pediatric patients:

Onset in more rapid in infants than adults. Duration of action is longest in infants and shortest in children[34].

Vec mg/kg		Onset of action (min)	Duration Min
Infants	0.07	1.5	73
Children	0.07	2.4	35
Adults	0.07	2.9	54

High cardiac output in infants speeds onset of Vec and immature enzyme system prolongs the duration of action[36].

Elderly patients:

Prolonged duration of blockade

Volume of distribution and plasma clearances are decreased.

Pregnancy:

Insufficient amount of drug cross placenta to produce significant effects in fetus. Clearance of Vec is accelerated during late pregnancy due to stimulation of hepatic enzymes by progesterone and large fluid shift during pregnancy. Duration of action is prolonged in immediate post partum period.

Obesity

Duration of action of Vec is prolonged in obese patients[35]

Safety profile :

1. Cardio vascular system:

Vec at doses of 0.1 - 0.15 mg /kg does not produce any significant changes in heart rate or MAP[37,38].

2. Histamine release :

Administration of clinical doses of vec does not produce any significant histamine release[27].

3. Anaphylactic / Anaphylactoid reactions:

Rare instances of hypersensitivity reactions may occur like bronchospasm, hypotension, tachycardia with erythema or utricaria.

Drug interactions:

Inhalational anaesthetics :

Volatiles like enflurane, isoflurane and halothane enhance Vec induced NM blockade. Potentiation is more prominent with enflurane and isoflurane[39].

IV Anaesthetics:

Use of other NDNM blocking agents like pancuronium, metocurine along with Vecuronium may show additive effect. Use of sub paralyzing dose of vec before succinlycholine, to attenuate some side effects of succinylcholine have not been sufficiently studied.

IV Antibiotics :

NM blockade of Vec is prolonged when drugs like aminoglycosides, tetracycline, bacitracin, polymyxin B, colistin are used[30].

Others:

Electrolyte imbalance, adrenocortical insufficiency alter Vec induced NM blockade. Magnesium salts prolong Vec blockade.

Reversibility:

Vec induced NM blockade can be reversed with use of neostigmine, physostigmine or edrophonium along with glycopyrrolate or atropine.

REVIEW LITERATURE

1. Lin PL, Liu CC, Fan SZ, Chao A, Shin SC, Tai YT et al., in Acta Anesthesiol Sin. 1997 have compared the neuromuscular action of Rocuronium with Vecuronium, and concluded that Rocuronium 0.6mg/kg provides more rapid onset of action than that of vecuronium 0.1mg /kg and also provides good to excellent intubation conditions.

2. England AJ, Margarson MP, Feldman SA et al., in Anesthesia 1997 have studied the tracheal intubation 1min after giving Rocuronium and vecuronium. The patients received twice ED_{95} or equipotent mixture of both vecuronium, alone and in combination. The intubating conditions in Rocuronium and the mixture groups were similar and both groups significantly better than vecuronium group.

3. Magorian T, Flannery KB, Miller RD et al., of Department of Anesthesia, University of California have compared three doses of Rocuronium (0.6, 0.9 and 1.2 mg/kg), Vecuronium (0.1 mg/kg) and Succinylcholine (1.0mg/kg).They found that onset time of patients receiving 0.9mg /kg and 1.2mg /kg and Sch (1.0mg /kg) were similar. Onset time for groups Roc 0.6mg /kg and Vec 0.1 µg/kg were significantly longer. Clinical duration was prolonged with 0.9µg/kg and 1.2µg/kg groups. It was concluded that there is a dose dependent decrease in onset time with Rocuronium

4. Smith I, Saad RS et al., Keele University, in Br. J Anaesth, 1998 have compared intubating conditions after Rocuronium or Vecuronium, with the timing of intubation judged by clinical criteria.

They found that Rocuronium 0.6mg/kg resulted in significantly better intubating conditions compared with Vecuronium 0.1mg with no significant reduction in the hemodynamic response. They also concluded that earlier intubation should be possible by careful timing or by neuromuscular monitoring.

5. Shingu K, Masuzawa M, Omote K, Namiki A et al., of Department of Anesthesiology, Kansai Medical University in Masui 2006 have done a comparative study between Rocuronium 0.6mg /kg and 0.9 mg/kg with Vecuronium 0.1mg/kg in Japanese patients. The onset time of 0.6 and 0.9 mg/kg were 84.6 and 77.1 sec respectively which showed a significant difference from that of Vecuronium 0.1mg /kg 125.7 sec. Clinical duration of 0.6, 0.9 mg/kg of Roc and 0.1mg /kg of Vec were 53.4 , 73.4 and 59.9min. It was concluded that Org 9426 showed more rapid onset time than Vecuronium, and similar clinical duration for equipotent doses in Japanese patients.

6. Shorten GD, Uppington J, Comunale ME, of Department of Anesthesia and Critical Care, Beth Israel hospital, Boston in Eur. J Anesthesia, 1998 had studied the changes in plasma concentration of catecholamines and hemodynamic effects of Rocuronium and Vecuronium in elderly patients. The study was compared after administration of Roc 0.9mg/kg and Vecuronium 0.12mg/kg in elderly patients. It was found that BP and HR were similar in two groups throughout the study. There was no significant change in either plasma noradrenaline or adrenaline concentration is either groups after muscle relaxant or during tracheal intubation.

7. Bartkowski RR, Witkowski TA, Azad S et al, of Department of Anethesiology, Thomas Jefferson University, Philadelphia, had compared the onset, maximal neuromuscular block and duration of Rocuronium with Vecuronium, and Atracurium during enflurane anaesthesia. 60 patients received 80,100,120 or 160, mcg/kg Rocuronium. Rocuronium's onset time was significantly faster than either of the other two muscle relaxants. Time to 90% of final block was 1.35 min for Roc, 3.06 min for Atracurium and 3.7 min for Vecuronium. The speed of onset was inversely related to their potency.

8. Smith CE, Kovach B, Polk JD et al., of Metro Health Medical Centre, Cleveland in Air Med J.2002 had studied prehospital tracheal intubating conditions during rapid emergency intubation using Rocuronium and Vecuronium. In this study patients received equipotent doses of Roc 1.0mg/kg and Vec 0.15mg /kg. They concluded that no cardiovascular differences occurred between groups after intubation. Tracheal intubating conditions and clinical evidence of complete neuromuscular blockade was better in Roc 1.0mg /kg than Vec 0.15mg /kg .

9. Naguib M, Samarkandi AH, Bakhamees HS et al., Department of Anesthesia, King Saud University, Riyadh in Br J Anaesth. 1995 had studied histamine-release hemodynamic changes produced by Rocuronium 0.6mg /kg, Vecuronium 0.1mg/kg, Mivacurium 0.2mg /kg, Atracurium 0.6mg/kg, and Tubocurarine 0.5mg/kg. Venous blood samples were obtained 1 min before and after induction and 1, 3, 5 min after giving the NM blocking drug. Mivacurium,

Atracurium and Tubocurarine caused 370%, 234% and 252% at 1min and 223%, 148% and 157% at 3min increase in plasma histamine concentrations respectively. Rocuronium and Vecuronium groups had no significant changes in either plasma histamine concentrations or hemodynamic variables.

10. McCoy EP, Maddineni VR, Elliott P et al., Department of Anesthesia, Queen's University, Northern Ireland compared the hemodynamic effects of Rocuronium 0.6mg/kg and Vecuronium 0.08mg/kg during fentanyl anaesthesia in elective CABG patients. They observed that changes in heart rate, mean arterial pressure, systemic vascular resistance, mean pulmonary artery pressure in both Rocuronium and Vecuronium groups were insignificant ($p<0.05$). The absolute values of all variables were within acceptable clinical limits. They also observed no evidence of histamine release in any patient.

11. Booth MG, Marsh B, Bryden FM et al., of Division of Anesthesia, Royal Infirmary, Glasgow had compared the pharmacodynamics of Rocuronium 0.6mg /kg and Vecuronium 0.1mg /kg during halothane anesthesia. The onset time, duration 25, duration 75 and TOF 70 were measured. The onset of neuromuscular blockade following Rocuronium was more rapid than Vecuronium (P=0.0001). All other pharmacodynamic parameters were similar.

12. B.B.Kushwaha, B.K.Behary, P.Rajan et al., in Journal of Anesthesiology Clinical Pharmacology 2008 ; had compared the intubating conditions and cardiovascular effects after administration of Rocuronium and Vecuronium in children. Patients were randomly

allotted into three groups each receiving Group I Vecuronium 0.1mg/kg, group II Rocuronium 0.6mg/kg and group III Rocuronium 0.9 mg/kg. They had found that Vecuronium 0.1/kg has onset time of 120 seconds. 0.9 mg/kg Rocuronium provides excellent intubating conditions at 60 seconds than 0.6mg /kg at 90 seconds. They also concluded that hemodynamic parameters remained in clinically acceptable limits in all three groups.

13. De Mey JC, Debrock M, Rolly G. et al., Department of Anesthesiology, University Hospital, Belgium had studied the evaluation of the onset and intubating conditions of Rocuronium bromide. Patients received three doses of Rocuronium 0.6, 0.75 and 0.9 mg/kg after supramaximal TOF stimulation of the ulnar nerve, and intubation conditions, onset time, recovery to 25% were determined. They concluded that in general, intubation conditions were excellent or good. They also concluded that onset time was longer ($P<0.01$) in 0.6mg/kg group compared to 0.9mg/kg group. The recovery to 25% was shorter in the 0.6mg/kg group ($P<0.01$)

14. Cooper RA, Mirakhur RK, Maddineni VR et al, of Department of Anesthetics, Queen's University of Belfast, had studied the neuromuscular effects of Rocuronium bromide (ORG 9426) 0.6mg/kg and 0.9mg/kg during fentanyl and halothane anesthesia. Neuromuscular block was monitored using mechanomyography and train of four stimulation. They found that mean onset time for 0.6mg/kg in fentanyl and halothane groups were 58 sec and 59 sec. Onset time for 0.9mg/kg on were 47 sec and 44 sec for fentanyl and halothane group. The time to recovery of TOF to 0.7 were 83 min

and 93 min in 0.9 mg /kg fentanyl and halothane groups, and in 0.6mg /kg groups were 55 min and 60 min.

15. Bencini A, Newton DE et al., is Br Jr Anaesth had studied the rate of onset of good intubating conditions, respiratory depression and hand muscle paralysis after Vecuronium. They had observed the NM blockade of adductor pollicis muscle following 0.1, 0.15 and 0.2mg/kg and compared with the intubating conditions and respiratory paralysis. Ideal intubating conditions were attained 3.5 min and 2.5min after injection of Vec 0.1 mg/kg and 0.2mg/kg respectively. They had concluded that increasing the dose of Vecuronium form 0.1mg/kg to 0.2mg/kg prolonged the duration of action significantly from 21 to 48 min but did not shorten the onset of time significantly nor prolong the rate of recovery.

16. Andrews JI, Kumar N, van den Brom RH, et al., of Department of Anesthesia, University of Newcastle had conducted a large randomized trial of Rocuronium with Succinylcholine in rapid sequence induction of anaesthesia along with propofol. 349 patients were randomized to receive Rocuronium 0.6 or 1mg /kg or succinylcholine 1.0mg/kg. They had observed that Rocuronium 1.0 mg/kg provided superior intubating conditions compared with Rocuronium 0.6mg/kg and the incidence of clinically acceptable intubating condition with Rocuronium 1.0mg/kg and succinylcholine 1.0mg/kg was 93.2% and 97.1% respectively. They had concluded that Rocuronium 1.0mg/kg given along with propofol in a rapid sequence induction is clinically equivalent to succinylcholine 1.0mg /kg.

17. McCourt KC. Salmela L, Mirakhur RK, et al., of Department of Anaesthetics, Queen's University of Belfast, UK had compared Rocuronium and suxamethonium for use during rapid sequence induction of anaesthesia. Patients were randomized to receive Rocuronium 0.6 or 1.0mg/kg and Suxamethonium 1.0 mg/1kg. The results showed that the intubating conditions were significantly superior with Roc 1.0mg/kg than Roc 0.6mg/kg ($p<0.01$). The comparison between Rocuronium 1.0mg/kg and Suxamethonium 1.0 mg/kg showed no significant difference in incidence of intubation (96% and 97%) respectively. They thus concluded that Rocuronium 1.0mg/kg can be used as an alternative to Suxamethonium 1.0mg/kg but the clinical duration of Rocuronium is 50-60 min.

18. Wierda JM, Hommes FD, Nap HJ, van den Broek L, et al., of Department of Anesthesiology, University Hospital of Groningen, The Netherlands had studied the time course of action and intubating conditions following Vecuronium, Rocuronium and Mivacurium. The patients randomly received 2 x ED 95 of either Vecuronium, Rocuronium or Mivacurium. Average onset time of Rocuronium (172 sec) and Vecuronium (192 sec) were significantly shorter than Mivacurium (229 sec). The clinical duration for Mivacurium (13 min) was significantly shorter than Vecuronium (33 min) or Rocuronium (28 min).

MATERIALS AND METHODOLOGY

Adult patients of both sexes in the age group of 15-50 yrs belonging to ASA I / II category and their weight ranging 40-80 kg posted for various surgeries requiring general anaesthesia at Department of General Surgery, Department of Surgical Gastroenterology, Department of Plastic Surgery, Department of Urology and Department of Eye, Nose and Throat, Govt. KMCH, formed the study group.

This study was designed as randomized, prospective study. The study was performed after obtaining the institutional ethical committee approval. Pre study assessment was done, procedure explained and informed consent obtained and patients were randomly allocated into 3 groups requiring GA.

Groups :

1. Group I :15 patients receiving Inj. Rocuronium Bromide 0.6 mg/kg
2. Group II :15 patients receiving Inj. Rocuronium Bromide 0.9 mg/kg
3. Group III :15 patients receiving Inj. Vecuronium bromide 0.1 mg/kg

Patient Selection :

Inclusion Criteria :

- 45 patients of ASA grade I & II
- Age 15-50 yrs
- Both sex
- Requiring General Anaesthesia with Endotracheal Intubation.
- Elective Surgery
- Without any comorbid illness.

Exclusion criteria:

- Having any allergy to narcotics or neuromuscular blocking drug.
- Patients on any other treatment which might interfere with action of NM blocking drugs
- Pregnant patients
- Having neuro muscular diseases
- Having preop airway or intubation problems.

Drug Treatment:

Group A : ROC 0.6 mg /kg

Group B: ROC 0.9 mg /kg

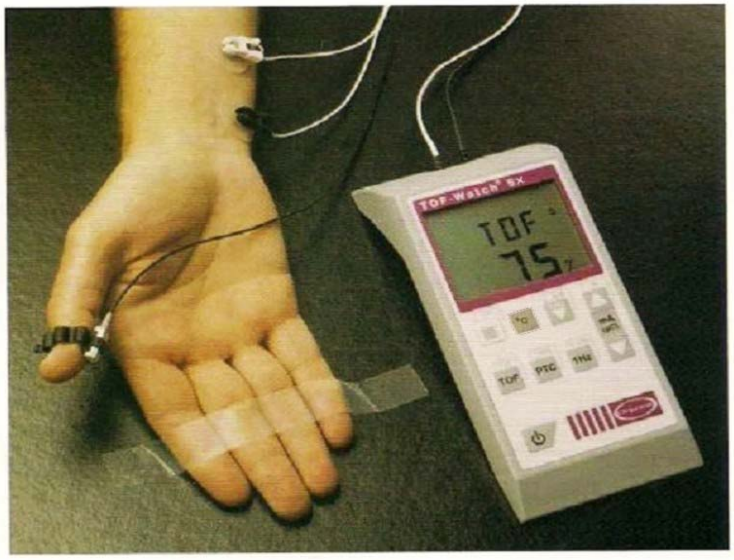
Group C: VEC 0.1 mg/kg

Monitoring :

- Pulse oximetry
- NIBP
- ECG
- TOF-WATCH SX 100
- Temperature Monitor

TOF WATCH SX :

- Has two optional calibration modes.
- Acceleration transducer, temperature sensor and cable for surface electrodes present.
- Nerve stimulation attained at low current
- Display of data in computers.
- Train of four with programmable repetition time.



Methodology

- 45 patients were randomized into three groups of 15 each.
- Premedication :

  Patients premedicated with Inj. Glycopyrrolate 0.2 mg IV, Inj. Fentanyl 2 mcg/kg IV 15 min before induction.
- Preoxygenation :

  Done with 100% O2 for 3 min

Preinduction :

PR, BP, ECG monitors connected

IV line started

TOF – WATCH SX 100 nerve stimulator attached.

Induction :

- Pt. induced with Inj. Propofol 1.5mg/kg IV
- Loss of eyelash reflex observed.

- TOF WATCH SX turned on. Once the current and twitch height were standardized, instrument switched to TOF mode where supra maximal TOF stimuli is applied to ulnar nerve every 15 sec.
- Calibration and baseline responses obtained before administering NM blocking drug.

Muscle Relaxation & Intubation :

Group I : Received Inj. Rocuronium 0.6mg/kg

Group II : Received Inj. Rocuronium 0.9 mg/kg

Group III : Received Inj. Vecuronium 0.1 mg/kg

- Bolus dose given as IV over 5 sec in rapidly running IV line and time noted
- TOF WATCH SX showed TOF ratio as percentage and results recorded at 30 sec interval.

Time to Maximum Blockade

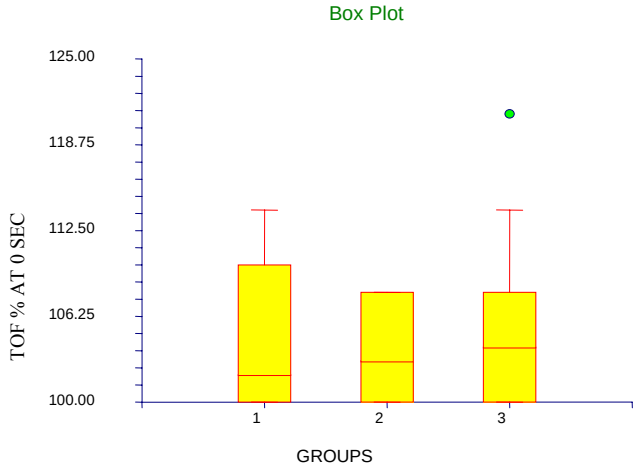
- Time interval between administration of dose of relaxant and disappearance of all four twitches in TOF monitor.
- Intubation was done when TOF ratio was 0%.
- Anaesthesia maintained with O_2 :N_2O and 0.8% Isoflurane
- The intubating conditions and degree of neuro muscular blockade assessed at 1,2,3 and 4 min with 30 sec interval.
- Time to maximum blockade and duration of action were also assessed.

OBSERVATION

TOF % at '0' sec

S.No	N	Mean	Std. Deviation	Std. Error
1	15	104.73	5.365	1.385
2	15	103.40	3.225	.833
3	15	105.27	5.958	1.538

P =0.577 Not significant

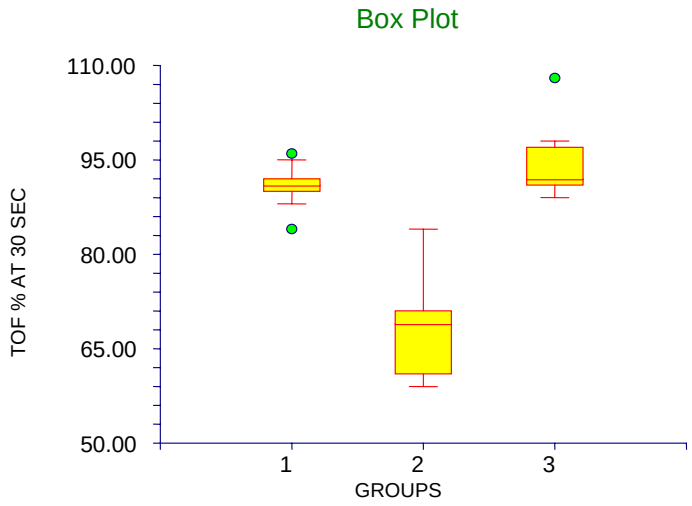


Using ANOVA, TOF % at '0' sec was not significant in any group.

TOF % at '30' sec

S.No	N	Mean	Std. Deviation	Std. Error
1	15	91.00	2.903	.750
2	15	68.67	8.006	2.067
3	15	94.00	4.943	1.276

P= 0.0000 <0.005 Significant

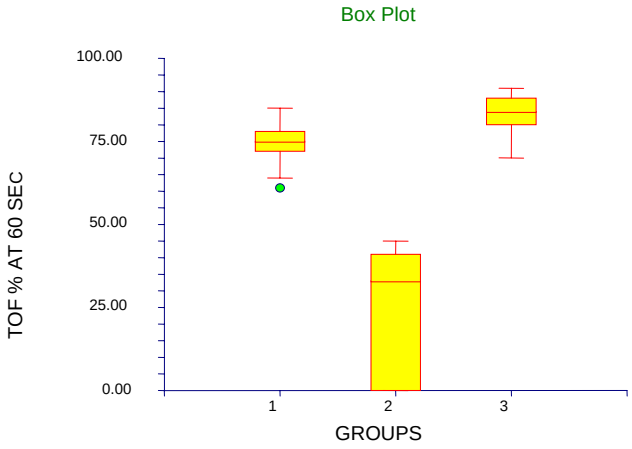


Using ANOVA, TOF % at '30' sec was found to be significant in group 2 than other two groups.

TOF % at '60' sec

S.No	N	Mean	Std. Deviation	Std. Error
1	15	74.67	6.008	1.551
2	15	23.40	20.170	5.208
3	15	83.40	5.488	1.417

P: 0.0000 <0.005 Significant

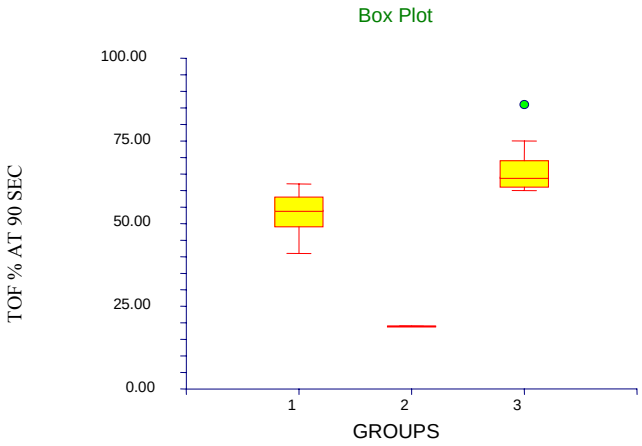


Using ANOVA, TOF% at 60 sec was found to be significant in group 2 than other two groups.

TOF % at '90' sec

S.No	N	Mean	Std. Deviation	Std. Error
1	15	53.20	6.930	1.789
2	1 14	19.00 0.00	.	.
3	15	66.33	7.228	1.866

P: 0.000 <0.005 Significant

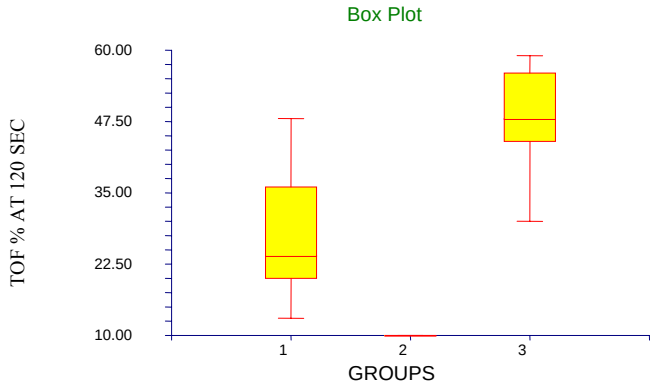


Using ANOVA, TOF% at 90 sec was found to be significant in group 2 than other two groups.

TOF % at '120' sec

S.No	N	Mean	Std. Deviation	Std. Error
1	15	27.73	10.257	2.648
2	1 14	10.00 0.00	.	.
3	15	47.20	8.954	2.312

P: 0.000 <0.005 Significant

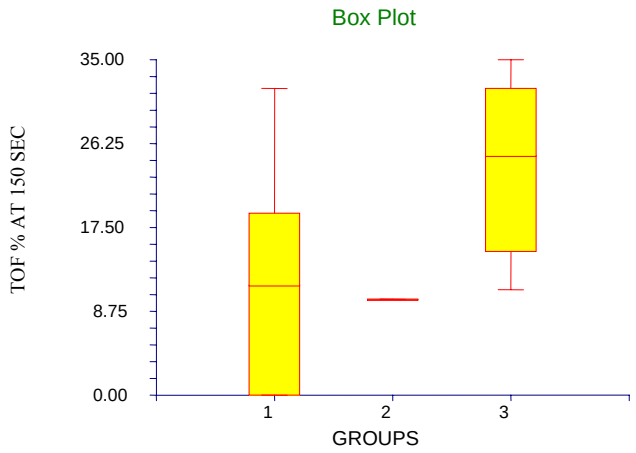


Using ANOVA, TOF% at 120 sec was found to be significant in group 2 than other two groups.

TOF % at '150' sec

S.No	N	Mean	Std. Deviation	Std. Error
1	14 1	11.29 0.00	9.809	2.622
2	1 14	10.00 0.00	.	.
3	15	24.27	8.489	2.192

P: 0.0002 <0.005 Significant

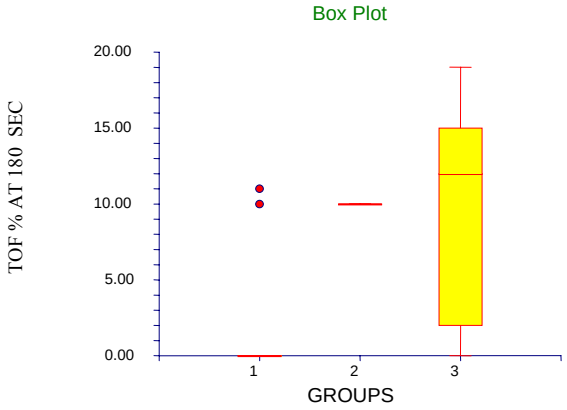


Using ANOVA, TOF% at 150 sec was found to be significant in group 2 than other two groups.

TOF % at '180' sec

S.No	N	Mean	Std. Deviation	Std. Error
1	13 1 1	1.62 10.00 0.00	3.948	1.095
2	1 14	10.00 0.00	.	.
3	13 2	10.00 0.00	6.904	1.915

P: 0.003 <0.005 Significant

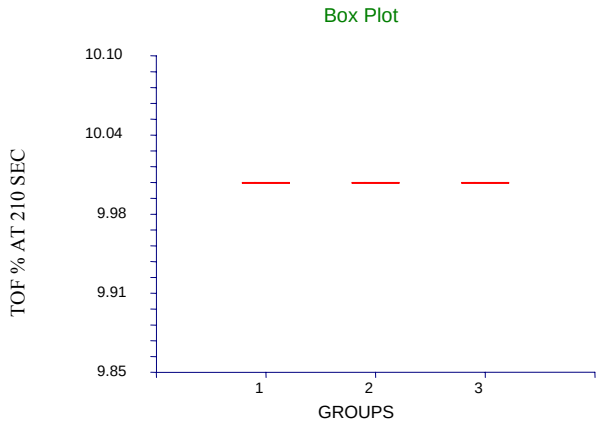


Using ANOVA, TOF% at 180 sec was found to be significant in group 2 than other two groups.

TOF % at '210' sec

S.No	N	Mean	Std. Deviation	Std. Error
1	1 14	10.00 0.00	.	.
2	1 14	10.00 0.00	.	.
3	1 14	10.00 0.00	.	.

P: 0.637 > 0.005 Not Significant

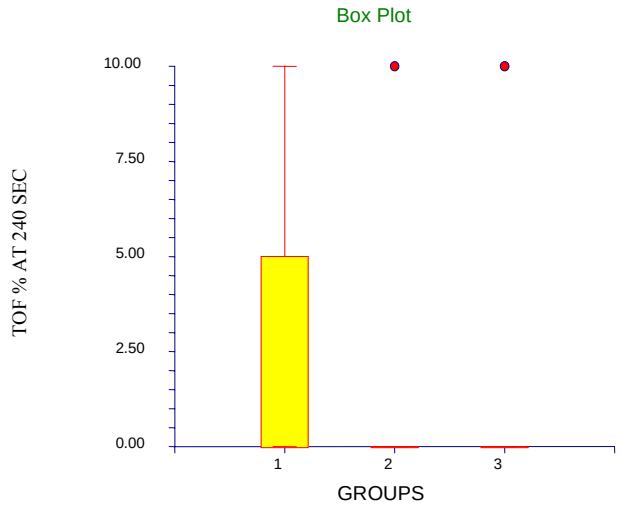


Using ANOVA, TOF% at 210 sec was found to be 'o' in all three group and hence not significant.

TOF % at '240' sec

S.No	N	Mean	Std. Deviation	Std. Error
1	5 10	2.00 0.00	4.472	2.000
2	15	.67	2.582	.667
3	15	.67	2.582	.667

P: 0.637 >0.005 Not Significant

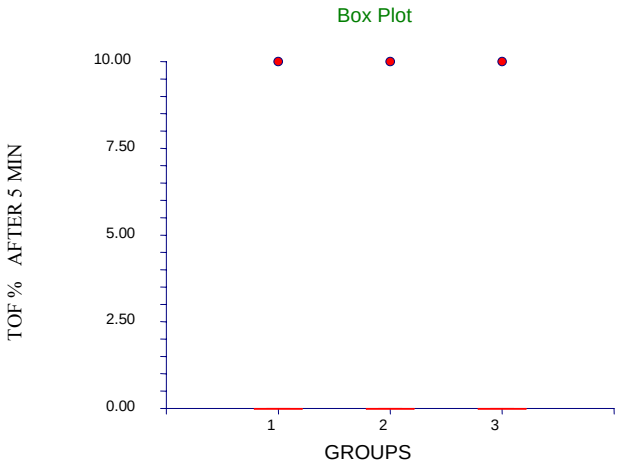


Using ANOVA, TOF% at 240 sec was found to be 'o' in all three group and hence not significant.

TOF % after '5' min

S.No	N	Mean	Std. Deviation	Std. Error
1	15	.67	2.582	.667
2	15	.67	2.582	.667
3	15	.67	2.582	.667

P: 1.000 > 0.005 Not significant

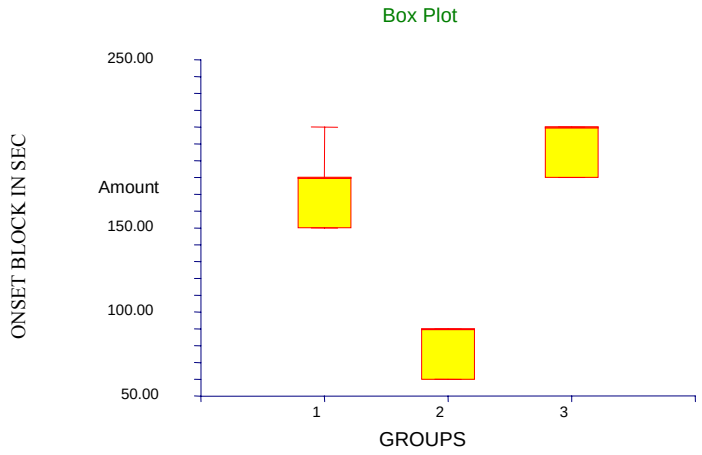


Using ANOVA, TOF% after 5 min was found to be 'o' in all three groups and hence not significant.

Time to maximum blockade

S.No	N	Mean	Std. Deviation	Std. Error
1	14	171.43	18.337	4.901
2	14	77.14	15.407	4.118
3	14	199.29	14.917	3.987

P: 0.000 <0.005 Significant

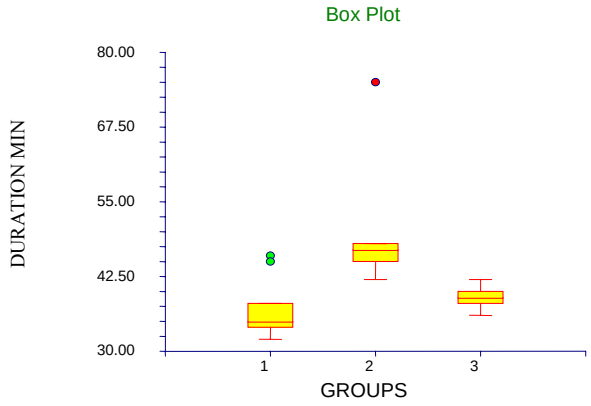


Using ANOVA, time to maximum blockade or onset of action was found to be significant in group 2 than other two groups

Duration of Action

S.No	N	Mean	Std. Deviation	Std. Error
1	15	36.60	4.014	1.036
2	15	48.20	7.608	1.964
3	15	38.93	1.580	.408

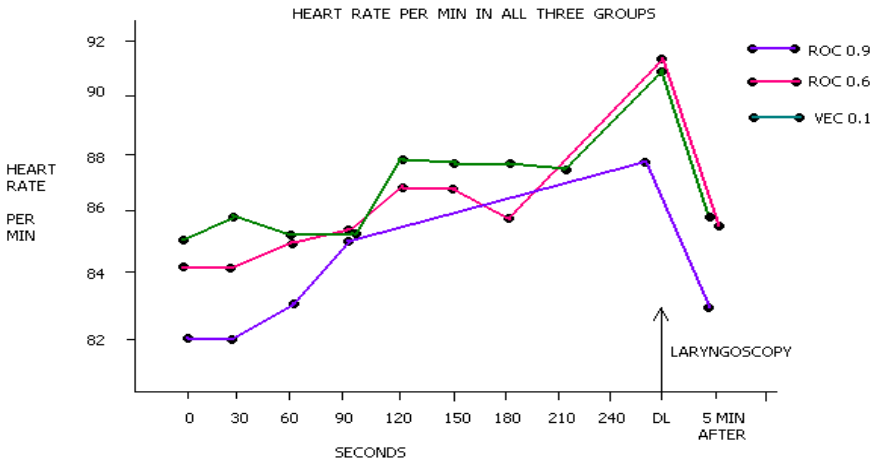
P: 0.000 <0.005 Significant



Using ANOVA, duration of action was found to be significant in Group 2 than other two groups.

OBSERVATIONS OF HEART RATE

	MEAN HEART RATE PER MIN		
SEC	**GROUP I ROC 0.6**	**GROUP II ROC 0.9**	**GROUP III VEC 0.1**
0	84.60	82.40	85.47
30	84.67	82.40	86.13
60	85.13	83.13	85.67
90	85.93	85.44	85.93
120	87.13	87.32	88.20
150	87.27	87.22	88.20
180	86.10	83.15	88.20
210	81.00	83.13	88.60
240	81.00	83.12	88.60
DL	92.60	88.13	91.67
After 5 min	86.07	83.47	86.33



P>0.005 in all three groups

Hence heart rate changes are Not Significant.

OBSERVATIONS OF MEAN SYSTOLIC BP

	MEAN SYSTOLIC BP mm Hg			
SEC	**GROUP I ROC 0.6**	**GROUP II ROC 0.9**	**GROUP III VEC 0.1**	**SIGNIFICANCE**
0	120.80	119.33	119.60	
30	120.80	119.33	119.60	0.876
60	121.00	120.53	119.60	0.895
90	122.80	121.78	119.67	0.526
120	124.07		119.67	0.171
150	124.73		121.20	0.307
180	125.80		121.27	0.243
210	122.50		121.50	0.580
240			110.00	
DL	129.33	125.40	125.00	0.320
AFTER 5 MIN	122.53	120.73	120.40	0.748

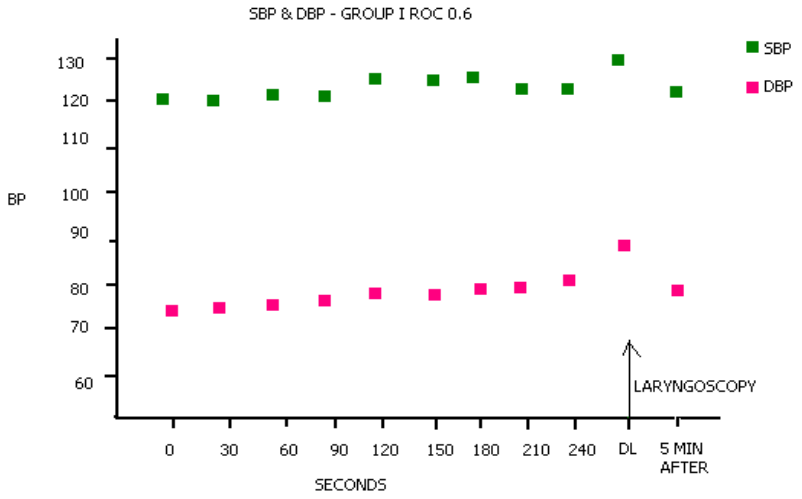
P >0.005 Not Significant

OBSERVATIONS OF MEAN DIASTOLIC BP

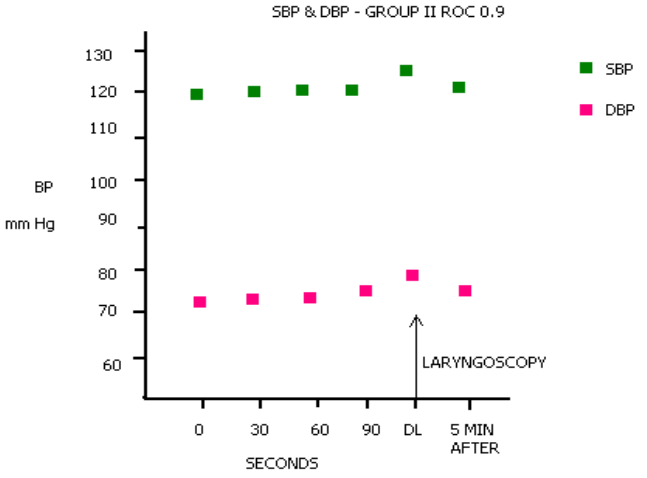
	MEAN DIASTOLIC BP mm Hg			
SEC	**GROUP I ROC 0.6**	**GROUP II ROC 0.9**	**GROUP III VEC 0.1**	**SIGNIFICANCE**
0	74.26	74.67	73.33	0.886
30	74.27	74.67	73.33	0.886
60	74.33	75.33	73.33	0.775
90	75.93	78.89	74.07	0.234
120	77.33		76.33	0.728
150	77.47		76.40	0.720
180	78.60		76.40	0.647
210	78.60		77.40	0.506
240	78.60		77.40	
DL	83.20	79.47	80.27	0.407
AFTER 5 MIN	76.93	75.73	74.33	0.640

P >0.005 Not Significant

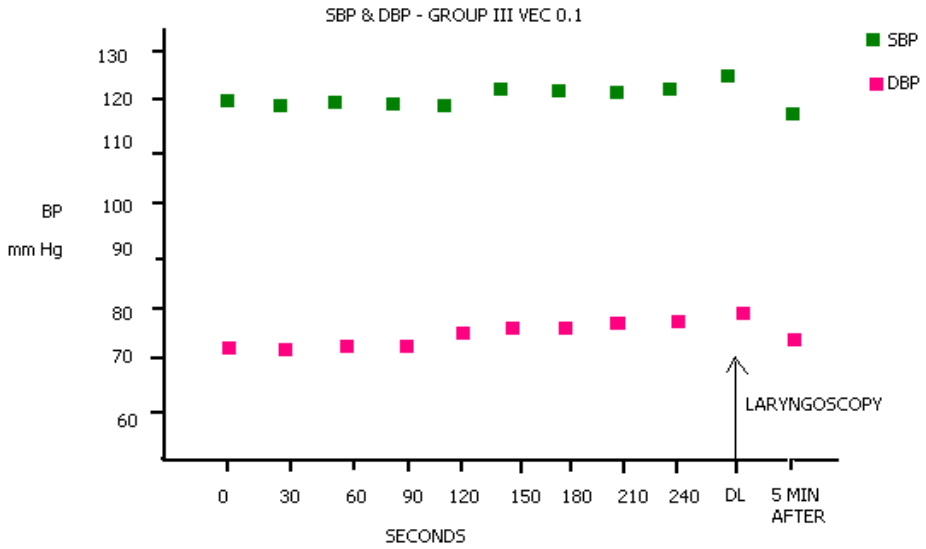
SBP & DBP – OF GROUP I ROC 0.6



SBP & DBP – OF GROUP II ROC 0.9



SBP & DBP – OF GROUP III VEC 0.1



Systolic and diastolic BP variations before giving drug, at the time of giving drug, during laryngoscopy and 5 min after laryngoscopy were not significant in all three groups.

DISCUSSION

The use of neuromuscular blocking drugs has its origin in South American Indian's arrow poison or curares. Initially d-tubocurarine was used but increased mortality led to the search of other neuromuscular blocking drugs. Succinylcholine introduced by Theselff and Foldes in 1952 has changed the anaesthetic practice due to its rapid onset and short duration facilitating rapid tracheal intubation.

Later in 1967, Baird and Reid first reported the use of aminosteroid Pancuronium which lacked ganglionic blocking and histamine releasing properties and also was vagolytic. Since then numerous non depolarizing muscle relaxants like pipecurium, doxacurium, atracurium, cis atracurium, rapacuronium, vecuronium and rocuronium were introduced, each with an advancement over their predecessor.

In this study, non depolarizing, intermediate acting, steroidal compounds Rocuronium and Vecuronium were chosen which provide rapid onset, better cardiovascular stability, nil histamine release, and their neuromuscular function was monitored using TOF-WATCH SX 100.

Rocuronium, a non depolarizing, aminosteroid has rapid onset with intermediate duration of action[41,42,43,44]. The changes in the steroid nucleus has made it a more stable solution and 6-10 times less potent than Vecuronium. The speed of onset is inversely proportional to the potency of non depolarizing neuromuscular blockers[53]. The onset time or time to maximum blockade of 3 ED95 (0.9 mg/kg) and 4 ED95 (1.2mg/kg) of Rocuronium are 1.3 min and 0.9 min respectively[47,49]. High dose regime

also increases the duration of action from 53 min (0.9mg/kg) to 73 min (1.2mg/kg) [42,51].

Low potency neuromuscular blockers like Rocuronium have more molecules to diffuse from central compartment into the effect compartment, where they act promptly. Weaker binding of low potency drugs to receptors prevent buffered diffusion and more molecules occupy receptors causing rapid onset. Potent drugs undergo buffered diffusion causing repetitive binding and unbinding to receptors, so onset time is prolonged[53]. Rocuronium 0.9mg/kg provides excellent intubating conditions and rapid tracheal intubation, and 0.6mg/kg is the intubating dose, hence these two doses were used in this study[42].

The onset of blockade is much more rapid in laryngeal adductors, diaphragm and masseter than in adductor pollicis. The pattern of blockade in orbicularis oculi is similar to that in larynx. But since adductor pollicis is most commonly used to monitor neuromuscular blockade, Ulnar Nerve was used to monitor in this study[54].

Vecuronium is a demethylated derivative of Pancuronium having slight change in potency, marked reduction in vagolytic properties, not stable in solution and increased lipid solubility. The onset of action of 2 ED95 (0.1mg/kg) is 3-5 min and the duration of action is 25-35 min. Since studies have shown that increasing the dose of Vecuronium does not significantly shorten the onset of action, only 2 ED95 (0.1mg/kg) dose is used in this study[32,52].

Shingu et al have studied that the onset time of 0.6, 0.9 mg/kg of Roc, and 0.1 mg/kg of Vec were 84.6 sec, 77.1 sec and 125.7 sec

respectively. The clinical duration of 0.6, 0.9 mg/kg of Roc and 0.1 mg/kg of Vec were 53.4, 73.4 and 59.9 min respectively.

Magorian et al have studied and concluded that onset time of patients receiving Roc 0.9 mg/kg, 1.2 mg/kg and Succinylcholine 1.0mg/kg were similar whereas the onset time of Roc 0.6 mg/kg and Vec 0.1 mg/kg were significantly longer. The clinical duration was longest in Roc 0.9 mg/kg and 1.2 mg/kg groups.

Andrews et al had studied the effects of Roc 0.6 mg/kg, 1 mg/kg and Succinylcholine 1 mg/kg and concluded that Roc 1mg/kg along with propofol provided superior intubating conditions and clinically equivalent to Sch 1.0 mg/kg.

Bencini et al had studied the effects of Vecuronium 0.1, 0.15 and 0.2 mg/kg and found that onset time for 0.1 and 0.2 mg/kg were 3.5 min and 2.5 min. They concluded that increasing the dose of Vec from 0.1 to 0.2 mg/kg prolonged the dration of action significantly from 21 to 48 min, but did not shorten the onset time significantly.

Shorten et al had studied the plasma concentration of catecholamines and hemodynamic effects of patients receiving Roc 0.9mg/kg and Vec 0.1 mg/kg. They concluded that hemodynamic variables were similar in both groups and no significant change in plasma catecholamine concentration in any group.

In this prospective, randomized, comparative study, 45 patients satisfying selection criteria underwent general anesthesia using Roc 0.6,

Roc 0.9 and Vec 0.1 mg/kg. The onset of action, which was the disappearance of all four twitches and TOF ratio 0 %, the duration of action and hemodynamic variables were assessed.

The onset of action or the time to maximum blockade was significantly faster in Group II (Roc 0.9mg/kg) than Group I (Roc 0.6mg/kg) or Group III (Vec 0.1mg/kg). The onset of action was 60-90 sec in Group II, 150-180 sec for Group I and 180-210 sec for group III as shown by Bartkowski et al, B.B.Kushwaha et al and Magorian et al.

TOF % was between 0-20% at 60-90 sec in Group II (Roc 0.9mg/kg); 11% at 150-180 sec in Group I (Roc 0.6mg/kg) and 0-1% in all the groups at 180-210 sec. This shows that the speed of onset is inversely proportional to the potency. So large dose of a low potent drug, Rocuronium 0.9mg/kg provides faster onset than other two groups.

The duration of blockade was significantly longer in Group II (Roc 0.9mg/kg) 48.20 min than Group I (Roc 0.6mg/kg) 36.6 min and Group III (Vec 0.1mg/kg) 38.93 min. These results were consistent with the studies done by Shingu et al, Cooper et al, McCourt et al.

The hemodynamic variables like pulse rate, systolic and diastolic BP were not significantly altered in all the three groups. There were no significant changes in the hemodynamic variables during preop, at the time of injecting the drug, during laryngoscopy and 5 min after laryngoscopy in all the three groups (Roc 0.6, Roc 0.9 and Vec 0.1 mg/kg) as shown by Shorten et al and Naguib et al.

No adverse reaction or complication occurred in any of the three groups.

SUMMARY

1. Group II patients receiving Inj.Roc 0.9 mg/kg showed excellent intubating conditions between 60 – 90 sec.
2. Group I patients receiving Inj.Roc 0.6 mg/kg had maximum blockade between 150–180 sec and Group III patients receiving Inj.Vec 0.1 mg/kg had maximum blockade between 180-210 sec.
3. The mean duration of action in Group II (Inj.Roc 0.9) was 48 min.
4. The mean duration of action in Group I (Inj.Roc 0.6) was 37 min and in Group III (Inj.Vec 0.1) was 39 min.
5. There were no significant changes in hemodynamic variables in all three groups.

CONCLUSION

In conclusion, Roc 0.9 mg/kg provides excellent intubating conditions with rapid onset of action, with longer duration of action and no significant hemodynamic changes when compared with Roc 0.6 mg/kg and Vec 0.1mg/kg and hence can be used as an ideal intubating dose. From the above mentioned study it can also be concluded that Roc 0.9mg/kg can be used for rapid sequence intubation in the place of depolarizing muscle relaxants like succinylcholine.

PROFORMA

NAME: AGE/SEX: IP NO.

DATE: Wt: GROUP:

DIAGNOSIS:

SURGERY:

BRIEF HISTORY:

COEXISTING ILLNESS:

EXAMINATION:

PR: CVS:

BP: RS:

RR: AIRWAY:

INVESTIGATIONS:

Hb: BLOOD UREA:

URINE ALB: SUGAR:

SUGAR: Sr. CREATININE:

ELECTROLYTES Na: K:

INTUBATION DETAILS:

Premedication:

Preoxygenation:

Induction:

Muscle Relaxant:

Intubation Score:

Confirmation of ETT:

No. of attempts at intubation:

	PREOP	DRUG VEC0.1	BLOCKADE								MAX. BLOCK	AT DL	5MIN AFTER INTUB
TIME			30S	1MIN	1MIN 30 S	2MIN	2MIN 30 S	3MIN	3MIN 30S	4MIN			
PR													
BP													
TOF RATIO													

MAXIMUM BLOCK:

DURATION:

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S NO	GROUP	NAME	AGE	SEX	IP NO.	WEIGHT	DIAGNOSIS / TREATMENT	60S HR	60S SBP	60S DBP	60S TOF%	90S HR	90S SBP	90S DBP	90S TOF%	120S HR	120S SBP	120S DBP	120S TOF%
1	1	MR ELUMALAI	45	M	11956	75	LT PYELOLITHOTOMY	88	114	70	74	88	118	76	58	91	118	76	22
2	1	MRS PARVATHY	32	F	14002	50	LAP CHOLECYSTECTOMY	85	124	72	72	85	124	72	56	88	129	76	13
3	1	MRS RADHA	30	F	12408	50	PB CONTRACTURE RELEASE & SSG	94	126	70	75	93	128	72	49	93	128	72	26
4	1	MR VINAYAGAM	45	M	12945	80	TRANS HIATAL ESOPHAGECTOMY	76	106	69	78	78	108	72	49	78	108	72	20
5	1	MRS SAROJA	50	F	10152	60	SUBTOTAL GASTRECTOMY WITH GJ	70	132	92	85	71	132	92	61	72	134	94	42
6	1	MR MUJBUR RAHMAN	18	M	17731	45	TONSIL ENUCLEATION & CURRETAGE	102	124	80	64	102	124	80	52	104	128	82	21
7	1	MR ANTHONY	35	M	17315	47	TONSILLECTOMY	85	114	68	80	86	118	68	62	86	118	68	36
8	1	MR SATHISHKUMAR	20	M	16188	51	NASAL POLYP FESS	91	122	72	61	93	124	74	43	93	124	74	20
9	1	MR KOTTI	24	M	12252	51	BILATERAL GYNAECOMASTIA REPAIR	93	128	84	78	93	128	84	56	95	130	88	24
10	1	MR SOLAI	25	M	17146	49	LT MASTOIDECTOMY & MYRINGOPLASTY	82	123	70	75	85	126	74	43	85	126	74	19
11	1	MR KATHIRVEL	36	M	13564	58	RT PYELOLITHOTOMY	91	132	82	74	93	134	82	54	93	134	84	39
12	1	MRS KRISHNAVENI	43	F	16282	50	RT DACROCYSTORHINOSTOMY	76	116	64	76	76	116	64	58	78	118	66	36
13	1	MR MANICKAM	35	M	11006	67	ETHMOIDAL POLYP FESS	64	104	68	80	62	108	71	62	67	108	72	48
14	1	MR RAJA	50	M	11843	64	BIL HERNIOPLASTY & BIL EVERSION OF SAC	91	130	84	76	93	130	84	54	93	134	88	31
15	1	MRS KAMALA	44	F	14321	51	LAP CHOLECYSTECTOMY	89	120	70	72	91	124	74	41	91	124	74	19
16	2	MRS POORNIMA	41	F	10036	45	RT MOD RADICAL MASTECTOMY	70	112	68	0				0				0
17	2	MR RAMAN	42	M	19947	44	REC CA COLON LAPROTOMY & PROCEED	98	120	68	0				0				0
18	2	MR JAINUL ABDEEN	54	M	23303	56	LAP/OPEN CHOLECYSTECTOMY	76	114	78	42	76	114	78	0				0
19	2	MR VENKATESAN	28	M	22827	60	POST BURNS: FOREHEAD FLAP COVER	114	132	90	33	114	132	90	0				0
20	2	MRS MANIMEGALAI	50	F	11487	55	OPEN CHOLECYSTECTOMY	69	116	76	30	71	116	76	2			76	0
21	2	MRS SARASU	42	F	21276	45	LAP/OPEN CHOLECYSTECTOMY	93	124	74	41	93	124	74	0				0
22	2	MR CHANDRAMOHAN	15	M	19691	45	TONSILLECTOMY	118	130	86	35	118	130	86	0				0
23	2	MR KARTHIKEYAN	30	M	12634	53	BIL INGUINAL HERNIOPLASTY	74	130	80	40	74	130	80	19	75	132	82	10
24	2	MRS MOHANA	50	F	18171	50	LT MOD RADICAL MASTECTOMY	87	132	90	0				0				0
25	2	MR KUMAR	21	M	18148	44	LAP APPENDICECTOMY	91	118	70	0				0				0
26	2	MR RAJA	31	M	17413	55	LT GYNAECOMASTIA REPAIR	75	130	64	0				0				0
27	2	MRS SUJATHA	35	F	10342	51	SUBTOTAL THYROIDECTOMY	62	118	70	45	63	118	70	0				0
28	2	MS ALAMELU	17	F	10531	40	LAP APPENDICECTOMY	62	104	62	0				0				0
29	2	MRS FATHIMA	46	F	10642	55	LAP CHOLECYSTECTOMY	72	114	80	45	73	116	80	0				0
30	2	MR RAJENDRAN	39	M	10145	60	BIL INGUINAL HERNIOPLASTY	86	114	74	40	87	116	76	0				0
31	3	MS PRIYA	16	F	24554	40	OPEN APPENDICECTOMY	99	109	74	91	99	109	74	64	103	109	78	48
32	3	MRS RAJAMMAL	48	F	22104	45	RT MOD RADICAL MASTECTOMY	70	118	70	85	70	118	70	62	72	118	72	44
33	3	MRS SAROJA	36	F	24512	53	LAP CHOLECYSTECTOMY	92	120	68	80	92	120	69	68	95	120	69	59
34	3	MR KANNIAPPAN	43	M	22140	50	SUBTOTAL GASTRECTOMY WITH GJ	82	116	84	78	82	116	84	64	83	116	86	35
35	3	MR ABDULLAH	36	M	27135	55	PARIETAL WALL TUMOR EXCISION	64	110	72	85	64	110	72	61	67	110	74	44
36	3	MRS RAJI	42	F	22245	55	LT HEMITHYROIDECTOMY	75	114	70	79	75	114	70	61	79	114	73	47
37	3	ME VELU	41	M	22017	59	RT PYELOLITHOTOMY WITH PUJ STENTING	83	132	72	70	85	133	74	60	85	133	74	51
38	3	MRS SHARMILA	29	F	24054	58	OPEN CHOLECYSTECTOMY	101	130	76	89	104	130	76	64	104	130	78	30
39	3	MRS JAYA	50	F	29095	50	RT PYELOLITHOTOMY WITH PUJ STENTING	78	128	82	82	75	126	84	74	79	126	84	56
40	3	MRS JAYA	45	F	23314	49	CHOLECYSTECTOMY WITH CBD EXPL	87	126	72	88	89	128	78	69	89	128	78	58
41	3	MS SANDHYA	18	F	14897	38	TONSILLECTOMY	107	112	70	91	107	112	70	86	109	112	74	54
42	3	MS ROSY	23	F	24053	40	TONSILLECTOMY	95	120	64	82	95	120	64	75	98	120	66	56
43	3	MRS RUKMANI	50	F	24426	55	LT MOD RADICAL MASTECTOMY	91	125	74	82	91	125	74	66	93	125	80	34
44	3	MRS VALARMATHI	34	F	22921	60	INCISIONAL HERNIA ANATOMICAL REPAIR	75	112	68	85	75	112	68	60	78	112	71	44
45	3	MR RAJENDRAN	38	M	24251	62	BIL HERNIOPLASTY & RT EVERSION OF SAC	86	122	84	84	86	122	84	61	89	122	88	48