Dissertation on

EFFECT OF INTRAVENOUS EPHEDRINE ON ONSET TIME AND INTUBATING CONDITIONS OF ROCURONIUM BROMIDE

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CERTIFICATE

This is to certify that the dissertation entitled, "**EFFECTS OF INTRAVENOUS EPHEDRINE ON ONSET TIME OF ROCURONIUM BROMIDE AND INTUBATING CONDITIONS"**

submitted by **Dr. S. JAGANATHAN** in partial fulfillment for the award of the degree of **Doctor of Medicine in anaesthesiology** by the Tamilnadu Dr. M.G.R. Medical University, Chennai is a bonafide record of the work done by him in the Institute of Anaesthesiology, Madras medical College, during the academic year 2008 - 2011.

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CONTENTS

INTRODUCTION

The introduction of d-tubocurarine - a neuromuscular blocking drug, by Griffith and Johnson[1] in 1942 revolutionized clinical anaesthesia. The use of muscle relaxants became a vitally important aspect of modern anaesthesia practice. In 1967, Baird and Reid[2] first reported on the clinical administration of the synthetic amino steroid pancuronium.

Development of the intermediate acting neuromuscular blockers was built on compound metabolism and resulted in the introduction of vecuronium, an aminosteroid,and atracurium, a benzylisoquinolium, in the 1980s. The lack of cardiovascular effects of vecuronium and degradation of atracurium by Hoffmann elimination, reduced the effects of biologic disorders such as advanced age or organ failure on the pattern of neuromuscular blockade. Despite the above mentioned neuromuscular blocking drugs, succinylcholine still remains the favorite for achieving rapid, evanescent relaxation despite its dangers of triggering malignant hyperthermia, producing hyperkalemia[3] in susceptible patients, raising intra ocular pressure,raising intra cranial pressure and muscle pains[4,5] in many.

Although succinylcholine is a reliable agent due to its rapid onset, its numerous side effects led to the search of newer muscle relaxants with a similar onset of action[6,7]. The technique of administering established non depolarizing muscle relaxants has been variously modified in an attempt to reduce its onset time.

Rocuronium is the first non-depolarizing relaxant considered to be an acceptable substitute for succinylcholine in facilitating rapid tracheal intubation[8,9,10]. Ephedrine is an sympathomimetic drug which acts on alpha1 and beta receptors.

It acts as agonist at these receptors and increases cardiac output and muscle blood flow.[11] It increases the oxygen consumption of tissues but cardiac output is also increased to meet the demand[12,13]

The onset time of muscle relaxants is partly determined by the speed with which these drugs reach the neuromuscular junction.

This concept is used in the present study in which the effect of Intravenous Ephedrine on the onset time and Intubating conditions of Rocuronium bromide was studied.

AIM OF THE STUDY

To compare the Effect of intravenous “Ephedrine” on the onset of action of Rocuronium and intubating conditions with a “placebo”.

ANATOMY OF NEUROMUSCULAR JUNCTION

Over a century ago, CLAUDE BERNARD inferred that excitation of the muscle was caused by a chemical transmitter at the neuromuscular junction. The Central nervous system controls muscle activity through its motor innervation, the connecting link between the two being the neuromuscular junction where the chemical signals from the nerve are converted into action potentials in the muscle.

MOTOR UNIT

Each motor neuron runs without interruption from the ventral horn of the spinal cord to the neuromuscular junction.A single anterior horn cell,its axon, the axonal branches and the group of muscle fibres innervated constitute a MOTOR UNIT.

THE END PLATE

The mammalian neuromuscular junction is compact and extends about 10 um above the muscle membrane. Macroscopically all the motor nerve pierce the muscle at a point between the origin and insertion- The Motor point. It then breaks up into the neurofibrils which innervate the muscle.Most muscle fibers in human beings are focally innervated (i.e.,) they receive innervation at the focal point-The motor

end plate. (EN Plaque endings). However tonic muscles such as the extra ocular muscles,the facial muscles and the intrinsic laryngeal muscles are multiply innervated with several motor end plates distributed over the muscle fibers (En Grappe endings).

JUNCTIONAL CLEFT

It is a gap of 20nm that separates the nerve from the surface of the muscle. The whole neuromuscular junction is surrounded by a membrane which is closely adherent to the nerve, termed the schwann cell membrane.It is this membrane that separates the synaptic cleft from the extracellular fluid. The muscle surface is heavily corrugated at the neuromuscular junction and the deep invaginations of the junctional cleft into the muscle. The secondary clefts are separated by the junctional folds on the surface. Thus the surface area of the junctional cleft is increased. Around the crest of the secondary cleft is a zone rich in cholinesterase. The shoulders of the fold are densely populated with choline receptors.Each neuromuscular end plate has 10^6 - 10^7 nicotinic receptors.

PERIJUNCTIONAL ZONE

It is a narrow transitional zone separating the membrane of the junction from the rest of the muscle .It is a critical area where the potential developed at the end plates is converted to an action potential that sweeps the muscle to initiate contraction.

THE VESICLES

These are synthesized in the cell bodies of the lower motor neurons in the spinal cord or the brain stem and reach the nerve terminal by axon transport. Acetylcholine is synthesized in the terminal axoplasm and loaded into these vesicles which are lined up along the synaptic cleft. Each of these vesicles contains 6000-8000 molecules of acetylcholine.

PREJUNCTIONAL RECEPTORS

They are cylindrical assemblages of protein sub units located in the nervous system. These receptors may be blocked by d-tubocurarine. They control an ion channel specific for sodium. The non depolarizing agents block the opened channels of these receptors.

POST JUNCTIONAL RECEPTORS

These are two types-junctional and extra junctional receptors.

JUNCTIONAL RECEPTORS

These are concentrated in the end plate on the shoulders of the junctional folds. The junctional receptors are found in the motor end plates of muscles in normal adults. They are generally assumed to be the receptors for acetylcholine. The receptor is a glycoprotein with a molecular weight of 2,50,000 and is made of (2:1:1:1) subunits. The five sub units are linear and arranged to form a potential tube or ion channel through the receptors. This channel is opened when two acetylcholine or other agonist molecules attach to the ACh binding sites on alpha units, and cause the subunits to rotate into a new conformation.

EXTRA JUNCTIONAL RECEPTORS

The subunit composition is α,β,γ and δ in a ratio of 2: 1: 1: 1. They are not usually present in muscles of normal adults. They are not restricted to the end plate, but spread over the entire surface of the muscle. They are more responsive to depolarizing agents and less responsive to non depolarizing agents.

THE MUSCLE

The contractile elements of the muscle cells are the myofilament- the thick myosin filaments and thin actin filaments with attached troponin and tropomyosin. These filaments interdigitate and slide over each other when the muscle contracts. The myofilamets are grouped into myofibrils. Surrounding the myofibrils is the sarcoplasmic reticulum, which acts as a reservoir for calcium. The sarcoplasmic reticulum comes into close proximity with the transverse tubules. These tubules convey the electrical impulse from the muscle into the sarcoplasmic reticulum, thereby triggering the liberation of calcium and the contraction of the myofilament.

PHYSIOLOGY OF NEUROMUSCULAR

TRANSMISSION

The transmission of impulses from the nerve to the muscle is mediated by acetylcholine,released by depolarization of the motor nerve terminal.

SYNTHESIS OF ACETYL CHOLINE

Acetylcholine is synthesized by a specific enzyme called choline acetyl transferase, from choline and acetylCoA. This enzyme is synthesized in the perikaryon and migrates along the cholinergic neurons to the nerve terminals.

The synthesis of acetylcholine requires the presence of choline, acetyl CoA, ATP,Glucose and calcium. Acetyl CoA and ATP are formed in the mitochondria and glucose is present in the cytoplasm. The choline necessary for this process is derived from the extra cellular fluid,from which it is transported to the nerve terminal by a specific carrier mediated transport system. This transport is inhibited by hemicholinium. The extra cellular choline is partly derived from hydrolysed acetyl choline and partly from the diet.

STORAGE OF ACETYL CHOLINE

Acetylcholine is stored in minute vesicles 30-60nm in diameter (quantals). These vesicles are present in large numbers in the nerve terminals near the synaptic surface. Each vesicle holds one quantum of transmitter, each having 6000-8000 molecules of acetylcholine.

There is always some free acetylcholine present in the cytoplasm (non quantal)

The quantal form could be in the reserve store (R-ACH) or as part of an immediate available source (IAS-ACH). Acetylcholine contained in the vesicle constitutes the releasable pool. Acetylcholine of the axoplasm is the non releasable or the stationary ACh.

RELEASE OF ACETYL CHOLINE

Acetylcholine is released from the nerve terminal both spontaneously and as a result of depolarization. The random release of the transmitter from the motor nerve ending causes 1-2mv depolarization of the motor end plate. This causes the 'miniature end plate potentials' (MEPPS). As the MEPPS are so small, they do not generate an action potential.

When the end plate potential reaches a certain critical magnitude, it depolarizes these surface membrane of the muscle fibre and sets up a propagated action potential. Calcium entry begins when the action potential approaches the maximum, and continues until the membrane potential is returned to normal by the outward flux of potassium.

REMOVAL OF ACETYL CHOLINE

This is brought out by:

1) DIFFUSION

Diffusion is almost rapid enough to account for the rapid rate of decay in the action of acetyl choline.

2) ACETYL CHOLINESTERASE

It is an asymmetric protein found in high concentrations in all post synaptic clefts related to cholinergic neurons. Each molecule of the enzyme is able to bind and hydrolyse several molecules of acetyl choline. The active site of this enzyme consists of an anionic subsite and an ester binding sub site. Hydrolysis of acetylcholine involves the formation of a reversible enzyme-substrate complex followed by the acetylation of the esteratic sub site and release of choline into solution.

3) REUPTAKE OF ACETYL CHOLINE

This is insignificant but choline uptake is essential for acetylcholine synthesis.

THE MEMBRANE POTENTIAL AND DEPOLARISATION

At rest the membrane potential of -90mv is maintained by the sodium-potassium adenosine phosphatase pump, which provides the energy necessary for the active transport mechanism. This resting membrane potential of -90 mv is the result of an excess of positively charged ions outside the cell relative to the inside of the cell. This uneven distribution is the consequence of the greater permeability of the potassium relative to sodium. Potassium tends to pass out of the cell along the concentration gradient in the resting state (l50mmol inside the cell to about 5 mmol outside). The binding of the two molecules of acetyl choline to the two a subuits of the cholinergic receptor induces a conformational change in the proteins of the receptor. This results in the opening of channels in the receptor complex which allows cations to flow through thr membrane along the concentration and electrical gradients.

Though all the cations sodium , potassium and calcium may pass through channel, the most important change is a net inward flow of sodium. As a result of this,the transmembrane potential changes from - 90 mv to 0 or + 10mv and the end plate potential is produced. When the magnitude of the depolarization exceeds the critical threshold level (40-45mv) a propagated action potential occurs.By the way of T - Tubules the action potential reaches the sarcoplasmic reticulum from which calcium is released and muscle contraction is initiated.

Towards the end of depolarization, potassium conductance increases as sodium conductance falls back to its resting level and an excess of intra cellular sodium is expelled by means of the sodium pump mechanism charged ions outside the cell relative to the inside of the cell. This uneven distribution is the consequence of the greater permeability of the potassium relative to sodium. Potassium tends to pass out of the cell along the concentration gradient in the resting state (l50mmol inside the cell to about 5 mmol outside). The binding of the two molecules of acetyl choline to the two a subuits of the cholinergic receptor induces a conformational change in the proteins of the receptor. This results in the opening of channels in the receptor complex which allows cations to flow through thr membrane along the concentration and electrical gradients.

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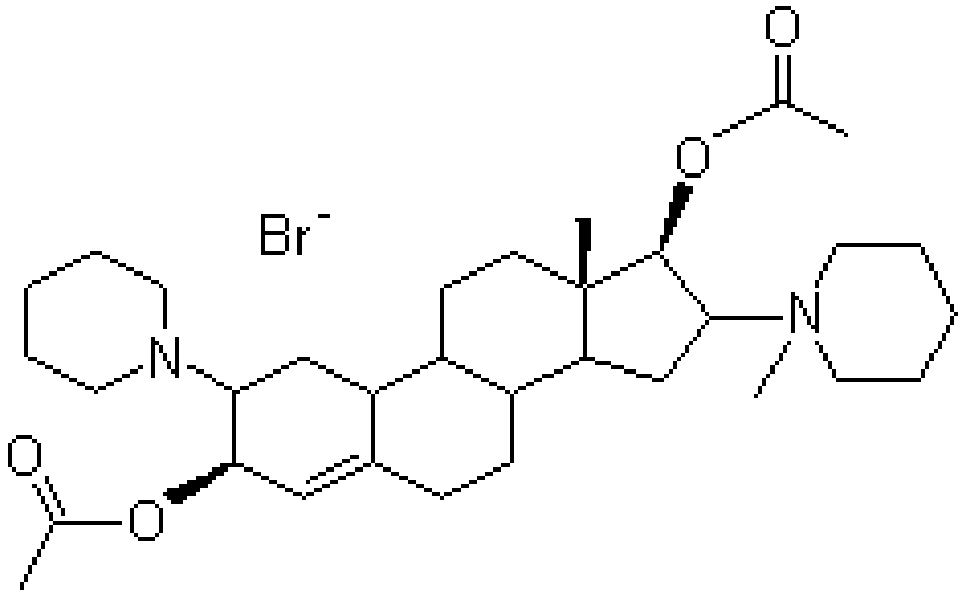
PHARMACOLOGY OF ROCURONIUM BROMIDE



Originally synthesized and studied in the Organon and Teknika laboratories as ORG 9426.Introduced into clinical practice in 1994. [14]

CHEMISTRY

Rocuronium is a steroidal muscle relaxant of intermediate duration of action. It is the 2-morpholino, 3-hydroxy, 16N - allyl -pyrrolidino derivative of vecuronium.l - [(2b,3a,5a,16b,17b)-17-- (acetyl oxy) -3-hydroxy-2- (4-morpholinyl)-androstan-16-yl (2propenyl) pyrrolidium bromide.

ROUTES OF ADMINISTRATION

Rocuronium can be administered by intravenous and intramuscular routes.

DOSES

ED95-0.3mg/kg

- Intubation at 60-90 sec-0.6-0.9mg/kg
- Relaxation (N20/02)-0.3-0Amg/kg
- Relaxation (inhalational agent)-0.2-0.3mg/kg ,
- Maintenance-0.1-0.15 mg/kg
- Infusion-8-12/kg/min

I.M

- Infants-l mg/kg
- Children-1.8mg/kg

MECHANISM OF ACTION

Rocuronium is a non-depolarizing neuromuscular blocking agent with a rapid onset of action, depending on dose. It has an intermediate duration of action. Rocuronium produces neuromuscular blockade by competing with acetylcholine for cholinergic receptors at the motor end plate. It is 7-8 times less potent than vecuronium.A greater number of drug molecules are able to reach junctional receptors within a fewer circulation times, enabling faster development of neuro muscular blockade. Low potency leads to a weaker binding to receptors and prevents buffered diffusion, a process that occurs with potent drugs, which causes repetitive binding and unbinding to receptors. Diffusion of less potent drugs away from the receptors very likely occurs much more readily, thereby helping to limit the duration of blocking effect. This is the most likely reason why the duration of action of rocuronium remains intermediate.

ONSET OF ACTION

ED90-is the dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve. With doses of 0.6 mg rocuronium per kg of body weight administered over 5

sec; effective intubating conditions are achieved within 60 to 90 seconds.[7,8] Onset of action of rocuronium may be delayed in patients with conditions such as cardiovascular disease and advanced age, which are associated with a slowed circulation. The onset of action is faster in infants and children than in adults.

When i.m. route is chosen in infants and in children, tracheal intubation can be performed in 2.5-3 mins with a duration of action of 2 hours.

TIME TO PEAK EFFECT

The time to peak effect is depend on dosage, the age of the patient, and the anaesthetic administered concurrently. The median times to maximum block are given below.

Adults 18-64 yrs of age under opioid-nitrous oxide-oxygen anaesthesia

0.4mg/kg:3 minutes (range,1.3-8.2)

0.6mg/kg:1.8 minutes (range,0.6-13)0.9mg/kg: 1.4 minutes (range,0.8-6.2)

1.2mg/kg:1 minute (range,0.6-4.7)

DURATION OF ACTION

The clinical duration of action (the duration until spontaneous recovery to 25% of control twitch height) with 0.6 mg/kg is 30-40min.

The total duration (time until spontaneous recovery to 90% of control twitch height) is 50 min.

The mean time of spontaneous recovery of twitch response from 25%-75% (recovery index) after a bolus dose of 0.6mg/kg is 14min.As the dose is increased,the recovery slows. The duration of action is also limited by avid liver uptake and elimination into bile, due to an increase in the lipophilic nature of the molecule with respect to vecuronium. Duration of clinical effect (the time until spontaneous return of the twitch response to 250/0 of control value is determined using a peripheral nerve stimulator) is dependent on dosage. Median time to spontaneous recovery from 250/0 to 75% of the control value is 13 min in adults. During rapid sequence induction of anaesthesia under propofol or fentanyl/thiopental anaesthesia, adequate intubating conditions are achieved with in 60 secs, in 96% of the patients, following a dose of 1 mg/kg of rocuronium bromide.Of these 70% are rated excellent.

Following a dose of 0.6mg/kg , adequate intubating conditions are achieved with in 60 seconds, in 81 % and 75% of the patients during a rapid sequence induction techniques with propofol or fentanyl / thiopentone respectively.

The clinical duration of action is shorter in childrens than in adults.

With doses higher than 1 mg/kg, intubating conditions will not improve appreciably. However the duration of action will be prolonged.

Adults 18 to 64 years of age-

- 0.45 mg/kg- 22 minutes (12-31)
- 0.6 mg/kg -31 minutes (15-85)
- 0.9 mg/kg-58 minutes (27-111)
- 1.2 mg/kg-67 minutes (38-160)

MAINTENANCE DOSE

0.075-0.15 mg/kg give when the twitch height has recovered to 25% of control twitch height, or when 2 or 3 responses to TOF is present. No cumulation of effect with repetitive maintenance dosing at the recommended level has been observed.

CONTINUOUS INFUSION

A loading dose of 0.6 mg/kg is administered, and the infusion is started at 0.3-0.6 mg/kg/hr, when the neuromuscular function starts to recover. The infusion rate should be adjusted to maintain the twitch response at 10% control twitch height or to maintain 1 or 2 responses to TOF.

DISTRIBUTION

Rocuronium has a biphasic distribution . The rapid distribution half life is 1-2 minutes and the slower distribution half life is 14-18 minutes. Approximately 80% of the initial rocuronium dose is redistributed. As administration of rocuronium continues, tissue compartments filled with in 4-8 hours, less rocuronium is redistributed away from the site of action, and the dosage required to maintain neuromuscular blockade via continuous infusion falls to about 20% of the initial infusion rate.

- Volume of distribution -203 ml/kg (193-214)
- Clearance -3.71 ml/kg/min (3.5-3.9)
- Plasma half life-73 min (66-80)

PROTEIN BINDING

Low (30%)

BIOTRANSFORMATION

Deacetylated in the liver to 17 - desacetyl - rocuronium (ORG 9943) and 16 N desallyl rocuronium (ORG 20860), these are usually not detectable in plasma and therefore not expected to contribute significantly to pharmacodynamic effects of rocuronium.

ELIMINATION

Rocuronium is primarily eliminated by the liver, with the small fraction (10%) eliminated by the kidneys. It is taken up in to the liver by a carrier mediated active transport system. Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% with in 12-24 hours

HEPATIC DISEASE

In hepatic disease (most commonly cirrhosis) the volume of distribution of rocuronium is increased and clearance is decreased. The duration of action is prolonged and the onset may be prolonged. Consequently dose in patients with hepatic disease should be conservative and guided by careful monitoring of neuromuscular functions.

Adult and geriatric patients with normal hepatic functions:

1.4 ±0.04 hrs during opiod- nitrous oxide- oxygen anaesthesia and 2.4±0.08 hrs during isoflurane anaesthesia.

Adults and geriatric patients with hepatic function impairment:

4.3±6hrs during isoflurane anaestheia.

RENAL FAILURE

In patients with renal failure, the plasma clearance of rocuronium may be decreased and its volume of distribution is increased. The duration of action of single and repeated dose is not significantly affected. In the elderly the clearance is decreased and the volume of distribution is increased with a consequent prolongation in duration of action.

CARDIOVASCULAR EFFECTS

The cardiovascular effects of muscle relaxants may be produced by

1. Muscarinic receptor block
2. Ganglionic block
3. Increased noradrenaline release
4. Blockade of noradrenaline reuptake
5. Histamine liberation

Initial animal studies with rocuronium suggested the occurrence of muscarinic receptor and ganglionic blocking effects only with the doses that are much higher than the dose required for neuromuscular blockade. Further studies in dogs conformed that cardiovascular effects were minimal with the doses of up to 3xED 95, although heart rate tended to increase with the doses greater than 5xED 95.

Routine measurements of heart rate and the arterial pressure during neuromuscular studies showed that rocuronium had minimal effects on these variables with the dose of 2-3 ED 95.

The autonomic margin of safety for vagal block (3.0-5.0) is about 10 times less than that of vecuronium. In equipotent doses (2xED 95) the administration of rocuronium was associated with small increase in heart rate of 7% (not statistically significant). However, there was increase in cardiac index of about 11 % (statistically significant) There was little change in MAP.

Rocuronium causes increase in heart rate of over 30% of baseline in some patients .While the etiology of tachycardia is believed to be multifactorial, pain on injection or vagal blockade may contribute to tachycardia. Rocuronium is more likely than vecuronium less likely than pancuronium to cause tachycardia.

HISTAMINE RELEASE

Rocuronium may cause histamine release. In a study of histamine release, 1 of 88 (1.1 %) patients receiving rocuronium has clinically significant concentration of histamine. In pre marketing clinical trials, rocuronium administration was accompanied by clinical signs of histamine release (eg, flushing, rash or bronchospasm) in 9 of 1137 (0.8%) patients. No clinical evidence of histamine release was observed in 45 patients enrolled in one study designed to provoke mine release by the rapid injection on rocuronium. No significant mine release with the dose of rocuronium up to 3xED95.

CUMULATION

Lack of cumulation has also been demonstrated by the absence of significant change in the dosage of rocuronium required to maintain stable relaxation with infusion lasting for over 2 hrs.

VERSIBILITY AND POSTOPERATIVE CURARIZATION

When adequate spontaneous recovery (an average of >TI of 25%) has occurred, the neuromuscular block induced with rocuronium can be antagonized by edrophonium or neostigmine.

APHYLACTIC/ANAPHYLACTOID REACTION

No such anaphylactic/anaphylactoid reactions has so far been reported following administration of rocuronium.

CENTRAL NERVOUS SYSTEM

It has no effect as it does not cross the blood brain barrier. No effect on intracranial pressure.

INTRAOCULAR PRESSURE

It produces minimal change in intraocular pressure and appears to be safe for use in rapid sequence induction of anaesthesia for penetrating eye injuries.

CENTAL TRANSFER

Rocuronium does not cross placenta in significant amounts.

PSEUDOCHOLINE ESTERASE INHIBITION

This may result in the prolongation of action of drugs that dependent on cholinesterase for their metabolism like succinyl choline and mivacurium. The anticholinesterase activity of rocuronium is less than that of vecuronium.

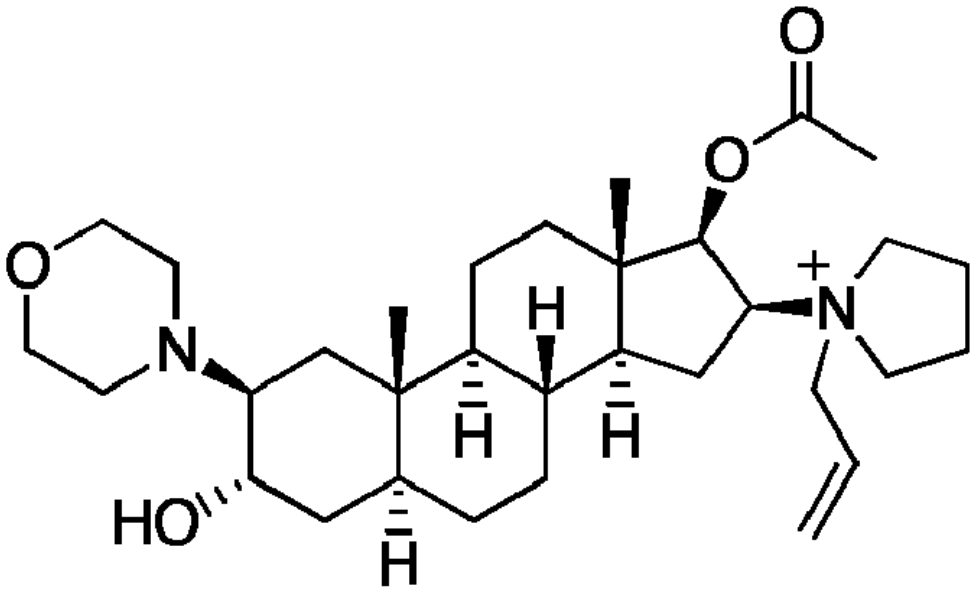
SIDE/ADVERSE EFFECTS

Pain on injection[15]- especially when the patient has not been completely lost consciousness and when propofol is used as an inducing agent in RSI. Hiccups, nausea, vomiting, aspiration,hypertension, hypotension, arrhythmias, bronchospasm, pruritus, rhonchi, skin rash, swelling at the injection site, tachycardia, wheezing.[16,17]

PRESENTATION

As a clear, colourless solution containg 10 mg/ml of rocuronium bromide. It is available in 5 ml and 10 ml vials.

PHARMACOLOGY OF EPHEDRINE



Ephedrine is a synthetic non catecholamine.[18,19]

It is an indirectly acting sympathomimetic drug. It is derived from Beta Phenylethlamine.[18,19]

Ephedrine has OH group at the beta carbon of Beta Phenylethylamine. It does not cross the Blood Brain Barrier.

MECHANISM OF ACTION :

It acts by evoking the release of the endogenous neurotransmitter norepinephrine from Post-ganglionic sympathetic nerve endings.[21]

Denervation (or) depletion of neurotransmitter, as with repeated does of a sympathomimetic, blunts the pharmacologic responses normally evoked by the drug.

It acts on $\alpha 1$ and β receptors

CLINICAL EFFECTS :

Cardiovascular System :

Increases Heart rate and Cardiac output.[22]

Increases Peripheral Vascular resistance and Mean arterial pressure. Uterine blood flow is not greatly altered when Ephedrine is administered.

Repeated does of Ephedrine produces a less intense response than the first dose. This Phenomenon known as tachyphylaxis[22] which represents a persistent blockade of adrenergic receptors by the previously administered Ephedrine.

DOSAGE AND ROUTES OF ADMINISTRATION :

Orally administered for decongesant effect.

Intravenous does 10 to 25 mg IV for adults[23]

Ephedrine 0.5 mg/kg IM has an entiemetic effect similar to that of droperidol but with less sedation.

Intra muscular and subcutaneous dose 25 to 50 mg

USES:

It is used as a pressor agent particularly after spinal hypotension[20,23]

In Strokes – Adams syndrome with complete heart block it has a role similar to epinephrine

Used as a central nervous stimulant in narcolepsy and depression

It is also used in mayasthenia gravis

Orally used as nasal decongestant[20]

SIDE EFFECTS:

With large doses headache,vertigo,tachycardia,palpitation and swetting can occur.[19,21]

Urinary retention can occur in larger doses[19]

Prolonged drug abuse with ephedrine sulphate injection can lead to symptoms similar to paranoid schizophrenia.[19]

DRUG INTERACTIONS:

Concurrent use of ephedrine with general anaesthetics cyclopropane , halogenated compounds and digitalis can cause cardiac arrhythmias as these medications can sensitize the myocardium to the effects of ephedrine sulphate.

Can block the effects of antihypertensives.

REVIEW OF LITERATURE

1. Hernan R. Munoz, Alenjandro G. Gonzale etal., in 1997[24], compared the effects of a single dose of Ephedrine, given at the moment of induction, on the onset time of rocuronium and on blood pressure and heart rate with placebo.

Patients were randomly assigned to receive either Ephedrine 70 mg/kg (or) Saline 5ml (Group II - n=30) before thiopentone. Rocuronium 0.6 mg/kg was administered and tracheal intubation performed.

Heart rate and blood pressure was measured prior to and 1, 3, and 5 min after tracheal intubation. They found that the onset time of Rocuronium was 72 $\pm$ 19S in group receiving Ephedrine and 98 $\pm$ 31 in group receiving placebo.

They also concluded that intubating conditions was either good (or) excellent and haemodynamic profile was similar in both groups and no patient presented arrythmias during study.

2. Peter szmuk, Tibriu Ezri, et al.[25,26], compared the onset of action of Rocuronium when pretreated with either Esmolol, ephedrine and Placebo.

ASA Physical status I & II patients aged 18-60 yrs. posted for General surgery and ENT procedures were assigned randomly into three groups.

One group received 70 mg/kg of Ephedrine (Group n=20), second group received Esmolol 0.5 mg/kg (Group ES : n=20) and third group received saline placebo (Group n=20) is administered with fentanyl 3 mg/kg 1.v and study drug followed 30S later by thiopentone 4mg/kg followed by rocuronium at 0.6 mg/kg. Neuromuscular function was assessed by stimulation of ulnar nerve at wrist with monitoring Train of four.

Onset time of vecuronium was defined as the time from the end of its injection to disappearance of all found twitches of the train of four. They found that the onset time of Rocuronium was 43 $\pm$ 6 seconds in group receiving placebo 64 $\pm$ 6 seconds in groups receiving Esmolol and 118 $\pm$ 11 seconds in group receiving Ephedrine no significant changes were noted among the group with regard to heart rate and blood pressure.

3. M.D. Gopalakrishnan,[27] H.M. Krishna in 2007 U.K. Shenoy compared the effect of Pre-treatment with Ephedrine 75, 100, 150 mg/kg and saline on intubating conditions and hemodynamics during rapid tracheal intubation using propofol and rocuronium.

In this study one hundred adult patients were randomized into one of the four groups PE 75, PE 100, PE 150 and saline (control). Groups were pretreated with fentanyl 2mg/kg and I.V. Ephedrine 75, 100, 150 mg/kg (or) saline respectively.

1 min before rapid tracheal intubation using propofol 2.5 mg/kg and rocuronium 0.6 mg/kg. Intubating conditions were assessed. Heart rate and Mean arterial pressure were recorded before induction post induction and every minute for 5 min. Onset of action of Rocuroniun was assessed by time for disappearance of all four twitches of TOF.

In the studies they found that Ephedrine in the dosage of either 75 or 100 mg/kg given before rapid tracheal intubation with propofol 2.5 and Rocuronium 0.6 mg/kg improved intubating conditions and these was no clinically significant difference in Heart rate and mean arterial Pressure among groups.

4. Leykin Y., Pellis, et al.,[28] (2005) compared the effects of Ephedrine on intubating conditions following priming with rocuronium.

In this study four groups of randomly allocated Patients (n=31) ASA I-II were induced with propofol 2.5 mg/kg. Groups I & II were primed with 0.04 mg/kg of Rocuronium followed by 3 min priming interval. Intubation was performed at 30S.

In groups III and IV same sequence was repeated without priming with Rocuronium.

In groups I and II Ephedrine (210 mg / kg) was injected before propofol. In group III, IV equal volume of normal saline was injected. Jaw relaxation, vocal cord position and diaphragmatic response were used to assess intubating condition.

They found that Ephedrine in Combination with propofol significantly improved clinical intubating conditions at 30S following priming with rocuronium compared with priming with Ephedrine without priming with rocuronium.

5. KYO S. Klim,[29] MIA Cheong et al (2002) compared the effect of Ephedrine on Vecuronium. In this study three groups of randomly allocated Patients (n=120) ASA II were divided to receive either Ephedrine (30,70, (or) 110 mg/kg (or) saline.

Induced with prpofol and neuromuscular black was monitored by Train of four. They found that Both Ephedrine 70 and 110 mg/kg improved intubating conditions at 2 min after Vecuronium. However, 110 mg/kg was associated with adverse hemodynamic effects. They concluded that Ephedrine 70 mg/kg given before the induction of anaesthesia improved tracheal intubating conditions at 2 min after Vecuronium by increasing cardiac output without significant adverse hemodynamic effects.

6. C.H. Tan, M.K. Onisong et al.[30], compared the influence of induction technique on intubating conditions 1 min. after rocuronium administration with poropofol ephedrine combination and propofol. In this study 100 ASA I (or) 2 patients aged 18-65 were randomly allocated to receive either propofol 2.5 mg/kg and Ephedrine 15g in combination (or) propofol 2.5 mg/kg alone followed by rocuronium 0.6 mg/kg. Intubating conditions were assessed with criteria of cooper et al.

The study found that intubating conditions were clinically acceptable in all patients, but the proportion of Excellent intubating conditions was significantly higher in propofol - Ephedrine group.

7. D.W. Han, D.H.Chun, T.D.Kweon S.Shin[31] studied the significance of "injection timing of Ephedrine to reduce the onset time of rocuronium Anaesthesia 2008;63:856 – 860.

In this study 75 adult male patients were used . They were randomly separated into three groups ,denoted to the time in which ephedrine was given. The early group ephedrine 70microgram/kg given 4min before rocuronium.Next group saline given at 4 min.In the last group ephedrine given at 30 seconds.

The study found that the onset of action of rocuronium was significantly shorter in Early group.

8. Smith and RSD Saad,[32] in 1998, compared the onset of action and the intubating conditions after rocuronium O.6mg/kg and vecuronium 0.1mg/kg. The time of intubation was determined by clinical judgment. alone like the ease of ventilation, jaw relaxation and upper airway tone. They concluded that time to laryngoscopy and completion of intubation were markedly shorter in the rocuronim group.

Rocuronium group also resulted in significantly better intubation conditions. There were no significant differences between the groups in hemodynamic response to laryngoscopy or in oxygen saturation before or after tracheal intubation.

9. Benoit Plaud, Bertrant Debaene et a1[33]., in 2001, measured the evoked response to train-of-four stimulation in twelve patients at the thumb,eyelid and superciliary arch after 0. 5 mg/kg rocuronium during propofol - fentanyl - nitrous oxide anaesthesia. In 12 other patients laryngeal adductor neuromuscular blockade was assessed via the cuff of tracheal tube and compared with the adductor pollicis and the corrugators supercilii after 0. 6 mg/kg rocuronium. They found that with the dose of 0.6 mg/kg of rocuronium, maximum blockade was similar at the corrugators supercilii and the laryngeal adductors. They concluded that muscles around the eye vary in their response to rocuronium. The response of the corrugators supercilii reflects blockade of laryngeal adductor muscles. However the eyelid (orbicularis oculi) and thumb (adductor pollicis) have similar sensitivity

10. Mistelman, C. Plaud B et[34] al., in 1994, compared the neuromuscular blocking effect of 0.5 mg/kg rocuronium at the adductor pollicis and laryngeal adductor muscles. They demonstrated that

rocuronium produces more rapid but less intense vocal cord neuromuscular block than at the adductor pollicis. The onset time at the vocal cords was markedly shorter for rocuronium when compared to vecuronium, atracurium and succinylcholine. They recorded the onset time of 1. 4±0. 1 min at larynx with maximum block of 77±5% and 2. 5±lminutes at adductor pollicis with maximum block of 98±1 %.

11. Prein TH, Zahn P et al.,[35] in 1994, studied the ED 95 dose of rocuronium bromide, the tracheal intubating conditions and the time course of action. They concluded that the ED 95 dose of rocuronium bromide was 0.3mg/kg and the duration of action was 20 minutes.

12. Cooper R. Mirakhur et al.,[36] in 1992, compared the intubating conditions with rocuronium bromide 0.6 mg/kg and succinylcholine 1 mg/kg at 60 seconds. They used a scale to assess the intubating condition which took into consideration the ease of laryngoscopy, position of the vocal cords during scopy and the response to tracheal intubation. 14/20 patients in rocuronium group had excellent intubating conditions. 4/20 and 2/20 had good to fair and poor intubating conditions respectively. Whereas 19/20 patients in succinylcholine group had excellent intubating conditions and 1 patient had good conditions.

13. K. F. Cheong and W. H. Wong[15] in 2000, assessed the incidence of pain on injection to rocuronium and evaluated if pretreatment with lignocaine IV reduced it in 90 patients. 37% of patients in ligocaine 10mg group, 7% in lignocaine 30mg group and 77% in control group who received saline pretreatment had pain. They concluded that lignocaine pretreatment decreased the incidence and severity of pain on injection of rocuronium.

14. M. Rose and M. Fischer[16] in 2001, identified 24 patients who met the clinical and laboratory criteria for anaphylaxis to rocuronium. They suggested that rocuronium is intermediate in its potency to cause allergy in known relaxant reactors compared with low risk agents like pancuronium, vecuronium and high risk agents like alcuronium and succinylcholine.

MATERIALS AND METHODS

It was a prospective, Randomized, Double blinded(subject), Case control study conducted in the Institute of Anaesthesiology and Critical Care, Madras medical college and Government General Hospital, Chennai

INCLUSION CRITERIA:

- MALES AND FEMALES
- ASA PHYSICAL STATUS 1,2,3
- AGE 15 YEARS AND OLDER
- ELECTIVE PATIENTS GIVEN GENERAL ANESTHESIA
- PATIENT WHO HAD GIVEN INFORMED CONSENT

EXCLUSION CRITERIA:

- NOT SATISFYING INCLUSION CRITERIA
- EMERGENCY SURGERIES UNDER GA
- PATIENTS WITH NEUROMUSCULAR DISORDERS,CARDIOVASCULAR DISEASE.

- HEPATIC OR RENAL DISEASE
- PATIENTS WITH DIFFICULT AIRWAY
- INTAKE OF DRUGS KNOWN TO INTERACT WITH MEUROMUSCULAR JUNCTION OR EPHEDRINE
- INCREASED RISK OF PULMONARY ASPIRATION

MATERIALS :

- INJECTION EPHEDRINE 70 MICROGRAM /KG
- DRUGS – FENTANYL,GLYCOPYRROLATE,THIOPENTONE,XYLOCARD,ROCURONIUM BROMIDE,NORMAL SALINE,EMERGENCY DRUGS.
- MACINTOSH LARYNGOSCOPE WITH 3,4 BLADES
- ENDOTRACHEAL TUBES OF VARIOUS SIZES
- MONITORS- ECG,NIBP,SPO2,NEUROMUSCULAR MONITOR

PRIMARY OUTCOME MEASURES:

- ONSET TIME OF ROCURONIUM AFTER TEST DRUG AND PLACEBO

SECONDARY OUTCOME MEASURES:

- INTUBATING CONDITIONS AFTER TEST DRUG AND PLACEBO

- HEMODYNAMIC VARIABLES

METHODOLOGY

PREMEDICATION: INJ.MIDAZOLAM 2 MG IV,

INJ.GLYCOPYROLLATE 0.2 MG

10 MIN BEFORE TEST DRUG
↓
TEST DRUG IS GIVEN 1 MIN BEFORE INDUCTION
↓
JUST BEFORE INDUCTION INJ.XYLOCARD
1.5 MG/KG IV GIVEN
↓
INDUCTION: INJ.FENTANYL 2 μG/KG IV ,
INJ.THIOPENTONE 5 MG/KG IV
↓
1 MIN AFTER INDUCTION INJ.ROCURONIUM 0.6 MG /
KG IV GIVEN
↓
ONSET TIME OF ROCURONIUM IS TAKEN FROM THE TIME OF INJECTION OF DRUG TO THE DISAPPEARANCE OF T1 IN TOF AND DISAPPEARANCE OF SINGLE TWITCH STIMULATION
PATIENT IS THEN INTUBATED AND CORMACK AND EHANE GRADE AND POGO SCORE ASSESSED

EPHEDRINE DOSE – 70 μg/kg

PLACEBO- SALINE 5ml

MEASUREMENTS

- Ulnar nerve was monitored using nerve stimulator.
  Supramaximal stimulus kept during induction.

- Disappearance of single twitch stimulation and disappearance of T1 of TOF is the goal.

- Stop clock was started from drug injection until disappearance of single twitch stimulation and disappearance of T1 of TOF.

Blood pressure and heart rate was measured

- Baseline
- After pre-medication,
- After test drug administration,
- Induction
- During intubation
- 1,3 min after intubation.
- CORMACK LEHANNE GRADING AND POGO SCORE

CORMACK AND LEHANE GRADING SYSTEM[38-40]:

Entire vocal cord visualized	-	Grade I
Posterior part of vocal cords seen	-	Grade IIa
Arytenoids only seen	-	Grade IIb
Epiglottis only seen (liftable)	-	Grade IIIa
Tip of epiglottis only seen (adherent)	-	Grade IIIb
No glottis structure seen	-	Grade IV

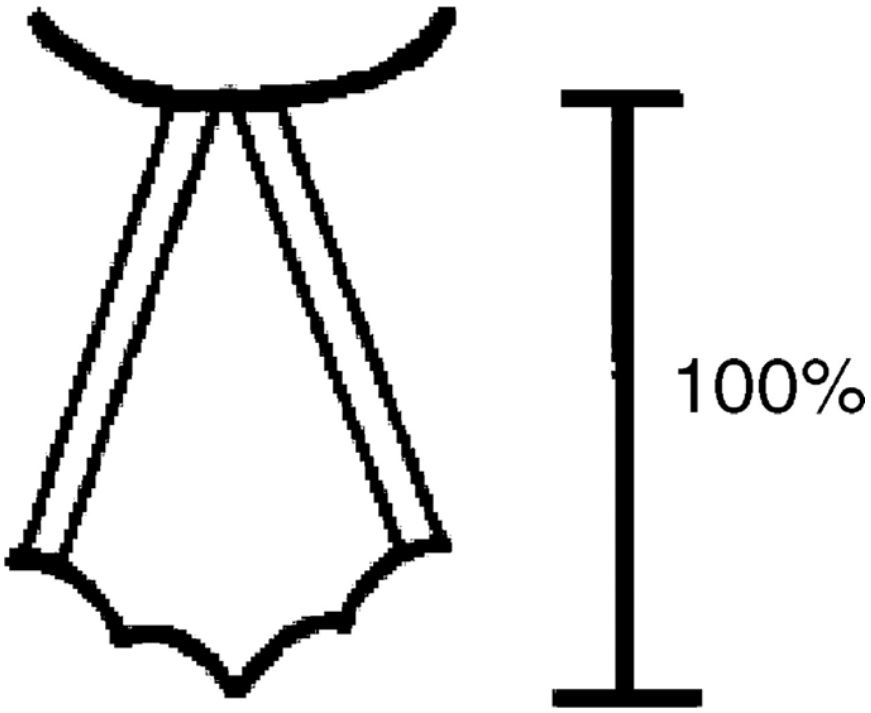
POGO SCORE[40-42]:

It represents the percentage of glottis opening seen, defined by the linear space from the anterior commisure to the interarytenoid notch.

A score of 100% is a full view of the glottis from the anterior commisure to the interarytenoid notch . A pogo score of 0% means that even the interarytenoid notch is not seen .

Thus, if only the lower third of the vocal cords and the arytenoids are visible a score of 33%is given.

This may be a better classification of the glottis view than the cormack and lehane's class I and II , as it offers nothing in between these two grades of glottic view.



OBSERVATION AND RESULTS

This prospective, randomized, single blind (subject), case controlled study compared the Effects of intravenous Ephedrine on the onset time of rocuronium bromide and intubating conditions measured by haemodynamic alterations and pogo score.

PRIMARY OUTCOME MEASURES:

- ONSET TIME OF ROCURONIUM AFTER TEST DRUG AND PLACEBO

SECONDARY OUTCOME MEASURES:

INTUBATING CONDITIONS USING

- HEMODYNAMIC VARIABLES
- POGO SCORE AND CORMACK AND LEHANE GRADING

All data were collected and tabulated.

DEMOGRAPHIC VARIABLES:

60 patients were randomly selected and included in this study. Thirty patients were randomly assigned to receive PLACEBO of 5ml

saline (group A) and thirty patients received the test drug of 70microgram/kg EPHEDRINE (group B). Mean age, sex distribution and weight of the patients in both the group were compared and there was no significant difference between the groups.

Comparison between the onset time of rocuronium in patients who received placebo and test drug ephedrine is tabulated as follows

T-Test

	GROUP				
	PLACEBO n=30		EPHEDRINE n=30		
	Mean	SD	Mean	SD	P value
ONSET TIME	60.23	17.154	50.70	15.454	0.027
POGO SCORE	74.40	26.94	90.40	15.67	0.013

CORMACK LEHANE GRADING

Chi square test:

	CL grade I	CL grade II
PLACEBO	14	16
EPHEDRINE	25	5

Onset time of rocuronium bromide after placebo of 5ml saline was studied in thirty patients and the mean time of onset was found to be 60.23 seconds. Standard deviation was calculated and found to be 17.154

Onset time of rocuronium after test drug of 70 microgram/kg of Ephedrine was studied in thirty patients and the mean time for onset of action was found to be 50.70 seconds with standard deviation of 15.454

Both the results were statistically analysed with T-Test and P value was found to be 0.027

Intubating conditions were assessed with POGO SCORE AND CARMAK LEHANE grading

Using POGO score intubating conditions were graded and mean percentage calculated for placebo as 74.40 with standard deviation 26.94 when given Ephedrine the mean percentage was found to be 90.40 with Standard deviation of 15.67.

Here the intubating conditions were better in the Ephedrine group with a P value of 0.013

P value is 0.01 which is statistically significant and the ephedrine group is associated with better intubating conditions

The other secondary outcome studied is the hemodynamic changes ,which includes Heart rate and Blood pressure

Heart rate and Blood pressure is noted with baseline value , after giving premedication ,after giving test drug , after induction, intubation ,one minute and three minute after intubation.

In the study it was found that Heart rate and Blood pressure was not altered significantly.

HEART RATE	GROUP				
	PLACEBO		EPHEDRINE		P VALUE
	MEAN	SD	MEAN	SD	
Baseline	89.07	18.398	88.53	16.598	0.907
Premedication	92.33	18.421	92.97	14.041	0.881
Test drug	93.13	18.822	97.43	16.569	0.352
Induction	98.07	18.097	103.67	12.928	0.173
Intubation	99.53	15.462	116.30	11.490	0.059
1 min after intubation	105.77	19.098	112.20	15.298	0.155
3 min after intubation	100.60	17.399	106.50	13.495	0.148

BLOOD PRESSURE	GROUP				
	PLACEBO		EPHEDRINE		PVALUE
	MEAN	SD	MEAN	SD	
Baseline systolic	131.37	15.270	126.63	12.931	0.210
Baseline diastolic	86.97	7.613	86.23	9.971	0.750
Premedication systolic	127.90	14.928	123.37	13.087	0.216
Premedication diastolic	84.77	8.59	80.93	7.629	0.073
Test drug systolic	123.23	15.710	126.73	14.137	0.368
Test drug diastolic	83.37	8.096	85.80	11.613	0.350
Induction systolic	103.93	17.382	113.47	11.221	0.148
Induction diastolic	75.73	13.465	81.33	12.732	0.103
Intubation systolic	115.97	18.299	121.70	10.107	0.138
Intubation diastolic	81.10	14.719	87.43	16.827	0.126
1 min after intubation systolic	136.57	28.803	127.83	19.298	0.173
1 min after intubation diastolic	92.60	19.344	86.57	13.056	0.162
3 min after intubation systolic	129.33	18.318	123.07	12.649	0.129
3 min after intubation diastolic	85.23	11.422	82.03	11.33	0.281

DISCUSSION

The cardinal requirements of general anaesthesia are

1. Loss of all sensation

2. Sleep(unconsciousness)

3. Muscle relaxation and

4. Abolition of reflexes

In the modern practice of balanced anaesthesia , these modalities are achieved by combination of drugs,each drug for a specific purpose.

In high risk patients who are prone to aspiration, rapid sequence induction is the preferred technique of induction. Succinylcholine continues to be the relaxant of choice where there is a need for rapid tracheal intubation as it consistently provides muscle relaxation within 60 – 90 seconds. When Succinylcholine is contraindicated in some patients the onset of action of non-depolarizing drugs can be accelerated by various methods.

The fast and reliable onset time of suxamethonium is the gold standard against which all other muscle relaxants are compared but some side effects preclude its use in all patients.[43]

This has led to a long standing interest in decreasing the onset time of non-depolarizing Neuromuscular blocking drugs,resulting in the development of faster drugs.[44]

Silveverman SM, Culling RD demonstrated that the timing principle for rapid sequence induction is a reliable alternative in cases where suxamethonium is contraindicated [45]

Mohamed Naguid has demonstrated that priming a rocuronium block with rocuronium resulted in a neuromuscular block comparable to that of suxamethonium in both the onset of action and intubating conditions. [46]

These alternative Timing and Priming principles reduce the onset time of these drugs but can also lead to adverse effect such as development of muscle weakness, difficulty in breathing , loss of the protective reflexes of the airway and pulmonary aspiration[15,16] before the induction of anaesthesia (9-11) or increased duration of neuromuscular blockade[47]

PRETREATMENT WITH EPHEDRINE

The use of ephedrine during the induction of general anaesthesia has been described to accelerate the onset of action of rocuronium and improve intubating condition.[24-31]

Studies using induction agents that maintain cardiac output and arterial blood pressure like ketamine,etomidate have suggested that the use of these drugs was associated with faster onset of action and better intubating conditions .[26,27]

Ephedrine by increasing the cardiac output and tissue perfusion and resulting in faster delivery of rocuronium to the laryngeal and diaphragmatic muscles might have shorten the onset of action of rocuronium and intubating conditions[27]

In our study thiopentone was used as induction agent. In various studies propofol was also used as induction agent.[37]

Various doses of Ephedrine were used for this purpose

Gopalakrishnan M.D , U.K. Shenoy in their study used ephedrine in the dose of 75, 100, 150 microgram /kg[27]

Hernan R.munoz in their study used 70, 210, 260 microgram/kg of ephedrine[24]

In our study we used 70microgram/kg of ephedrine and compared it with Saline. We decided to use the smallest dose (70microgram/kg) to minimize the possibility of adverse effects.

Audibert G, Donati F[48] onset of Neuro Muscular block after tourniquet inflation.Comparison of suxamethonium and vecuronium British journal of anaesthesia 1996;75:436 – 440 in their study showed that

the effects of cardiac output and circulation time may be considerably greater for fast acting muscle relaxants such as suxamethonium and rocuronium than intermediate acting muscle relaxants including mivacurium and vecuronium.[49]

In our study rocuronium was chosen since it is the non- depolarizing Neuromuscular blocking drug in clinical use with the fastest onset time.[36]

In our study we used 70microgram/kg of ephedrine one minute before induction with inj thiopentone 5mg/kg and one minute after induction inj rocuronium 0.6mg/kg I.V was given.In few studies propofol is used in combination with ephedrine as induction agent.[37]

TIME OF ONSET OF ACTION

M.D. Gopalakrishna, U.K.Shenoy etal,[27] British journal of anaesthesia 2007;99:191-194

In their study used ephedrine at doses of 75,100,150microgram/kg and saline, used Train of four(TOF) ratio monitoring in response to ulnar nerve stimulation . The lack of agreement between the blockade characteristics at the laryngeal muscles and the adductor pollicis is well demonstrated in the literature[50-53]

However as the site of monitoring was the same in all four groups , the results can still be compared for the difference in onset of Nero muscular block.

In our study we used ezteemII Neuromuscular monitor was used. Onset time of Rocuronium is taken from the time of injection of drug to the disappearance of

1. T1 in Train of four

2. Dissapeaarance of single twitch stimulation

We found that the mean time for onset of action of rocuronium in placebo group to be 60.23 seconds and ephedrine pretreated group onset of action was found to be 50.70 seconds with P value of 0.02

Complete abolition of single twitch was observed in 27 patients in each group. In the remaining six patients 95% twitch depression was achieved.

SIGNIFICANCE OF TIMING OF INJECTION OF EPHEDRINE: D.W. Han, D.H.Chun, T.D.Kweon S.Shin[31] studied the significance of "injection timing of Ephedrine to reduce the onset time of rocuronium Anaesthesia 2008;63:856 – 860.

In this study 75 adult male patients were used . They were randomly separated into three groups ,denoted to the time in which ephedrine was given. The early group ephedrine 70microgram/kg given 4min before rocuronium.Next group saline given at 4 min.In the last group ephedrine given at 30 seconds.

The study found that the onset of action of rocuronium was significantly shorter in Early group.

In our study Ephedrine was given one minute before induction and rocuronium was given one minute after induction which give around three to four minutes for ephedrine to get its peak circulatory effects .

INTUBATING CONDITIONS

Intubating conditions depend on many factors the most important of which are the degree of relaxation of the muscle involved,the depth of anaesthesia,the anatomy of the upper airway and the skill of the anaesthetist.The superior intubating conditions associated with suxamethonium not because of its rapid onset but may because it has a greater potency at the laryngeal muscles than non-depolarizing blocking drugs[43] .However Gopalakrishna M.D, U.K.Shenoy etal[27], British journal of anaesthesia 2007;99:191-194 assessed the intubating conditions as per the intubation scoring system of the consensus conference on good clinical research practice in pharmacodynamic studies of Neuromuscular block of Copenhagen consensus.[52] and found that pretreatment with 75 and 100 microgram/kg ephedrine group had significantly better intubating conditions .

In our study we used POGO score and cormack Lehane classification to assess the intubating conditions.

We found that the mean POGO score for Placebo group was found to be 74.40 and for Ephedrine group to be 90.40 proving better intubating condition in ephedrine group.

HEMODYNAMIC CHANGES

1. Smith and R.S.D Saad [32]demonstrated that rocuronium resulted in significantly better intubating conditions compared with vecuronium but with no significant reduction in the hemodynamic response to intubation

2. Hernan R.Munoz, Alenjandro etal[24], in international anaesthesia society Anaesthesia anal 1997;85:437 – 440 in their study found that pretreatment with 70microgram/kg ephedrine found that there was no significant hemodynamic changes in group treated with placebo and ephedrine

In our study we considered a 20% change in hemodynamic variables from baseline was regarded as clinically significant. We found that the Baseline Heart rate and Blood pressure were comparable between groups.

There was a significant increase in the heart rate and systolic and diastolic blood pressure when compared to Placebo group at most of the time intervals of the study period. But it is not raised at statistically significant levels

INCIDENCE OF ADVERSE EFECTS

There are reports of various adverse effects of rocuronium bromide like pain on injection,hypotention ,wheel response,flushing , bronchospasm and anaphylaxis are possible after the administration of rocuronium(). In our study we used injection Xylocard[15] before rocuronium administration and there was no significant adverse effect to rocuronium.

Also in our study we did not find any adverse effect of greater than 20% raise in Heart rate and Bloodpressure and arrhythmias in any of our patients.

SUMMARY

In our study, the effect of intravenous “Ephedrine” on the onset time and intubating conditions of rocuronium bromide was compared with “Placebo”.

All the patients in Ephedrine group were pretreated with ephedrine 70microgram/kg prior to induction and rocuronium 0.6mg/kg was given . All the patients in “Placebo” group were given 5ml Saline prior to induction .

Onset of action is determined by abolition T1 in TOF and absence of single twitch stimulation in Neuro muscular monitor .

The onset of action of Rocuronium was significantly shorter in “Ephedrine”group when compared to “Placebo” group.

Ephedrine group provided better intubating conditions when compared with Placebo group

There was no clinically significant difference between the two groups with respect to heart rate and blood pressure changes.There was no significant incidence of adverse effects in both groups

CONCLUSION

It may be concluded from this study that “Ephedrine given at the dose of 70microgram/kg significantly shortens the onset time of Rocuronium bromide and provides better intubating conditions with minimal haemodynamic changes.”

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PROFORMA

NAME: **AGE:** **SEX:** **I.P. NO.**

DIAGNOSIS: **WT:** **MMS CLASS:**

SURGERY PERFORMED: **TEST DRUG:**

1. HEMODYNAMICS:

	HR	***BP***
BASELINE		
AFTER PREMEDICATION		
AFTER TEST DRUG		
AFTER INDUCTION		
AFTER INTUBATION		
1 MIN		
3 MIN		

2. TIME:

TEST DRUG	**SEC**
TIME FOR DISAPPEARANCE OF TI IN TOF OR STS	**SEC**

3. INTUBATING CONDITIONS:

- **CORMACK LEHANNE GRADE –**
- **POGO SCORE –**

INFORMATION ON THE STUDY

EFFECT OF I.V EPHEDRINE ON THE ONSET TIME AND INTUBATING CONDITIONS OF ROCURON1UIVI BROMIDE.

Rocuronium is used to administer General Anaesthesia. Ephedrine fastens the onset of action of rocuronium. This also helps us to reduce the dose of Rocuronium and hence prolonged musule relaxant action after minor surgical procedures. The time Interval between the patient becoming unconscious and Intubation is decreased as rocuronium 'onset of action is fasterned. This helps in prevention of Aspiration. Since onset of action is comparable with Suxamethonium. It can be used as an alternative where Suxamethonium is Contra indicated. The use of Ephedrine can cause untoward increase in Heart rate and blood pressure. In case of such occurance it will be continuously monitored and treated by the doctor appropriately. No major complications causing morbidity / mortality are so far reported. Knowing this information, I consent to whole heartedly participate in the above study.

Name: Patient's Signature

Thumb Impression:

PATIENT CONSENT FORM

STUDY TITLE : Prospective randomized controlled study of iv ephedrine on the onset time and intubating conditions of rocuronium bromide.

STUDY CENTRE : Department of Anaesthasiology, Madras Medical College.

PARTICIPANT NAME : AGE : SEX:

I.P.NO :

I confirm that 1 have understood the purpose of procedure for the above study. I have the opportunity to ask the question and all my questions and doubts have been answered to my satisfaction.

I have been explained about the possible complications that may occur during this study like increase in heart rate and blood pressure and in case of such occurrence it will be continuously monitored and treated accordingly .1 have been informed that no other major complication has been reported so far with the use of ephedrine .

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving any reason,

I understand that investigator, regulatory authorities and the ethics committee will not need my permission to look at my health records both in respect to the current study and any further research that may be conducted in relation to it, even if I withdraw from the study". I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from the study of iv ephedrine on the onset time and intubating conditions of rocuronium bromide

1 hereby consent to participate in this

Dale: Signature /Thumb impression of patient

Place Patient name :

Signature of the investigator: Name of the investigator:

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No: 04425305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Jaganathan. S
PG in MD Anaesthesiology
Madras Medical College, Chennai -3

Dear Dr. Jaganathan .S

The Institutional Ethical Committee of Madras Medical College reviewed and discussed your application for approval of the project / proposal / clinical trail entitled " Prospective randomized controlled study of iv ephedrine on the onset time and intubation conditions of rocuronium bromide "No 87082010.

The following members of Ethical committee were present in the meeting held on 24.08.2010 conducted at Madras Medical College, Chennai -3.

1. Prof. S.K. Rajan, MD	-- Chairperson
2. Prof. J. Mohanasundaram, MD,Ph.D,DNB Dean, Madras Medical College, Chennai -3	-- Deputy Chairman
3. Prof. A. Sundaram, MD Vice Principal , MMC, Chennai -3	-- Member Secretary
4. Prof R. Nandhini, MD Director, Institute of Pharmacology, MMC, Ch-3	-- Member
5. Prof. C. Rajendiran , MD	-- Member
Director, Institute of Internal Medicine, MMC, Ch-3	-- Member
6. Prof. Md. Ali, MD, DM	-- Member
Professor & Head ,,Dept. of MGE, MMC, Ch-3	-- Member
7 Prof. Shantha Ravishankar, MD Professor of Neuro Pathology, MMC, Ch-3	-- Member
8. Tmt. Arnold Soulina	-- Social Scientist

We approve the trail to be conducted in its presented form.

Sd /. Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information / informed consent and asks to be provided a copy of the final report

Member Secretary, Ethics Committee

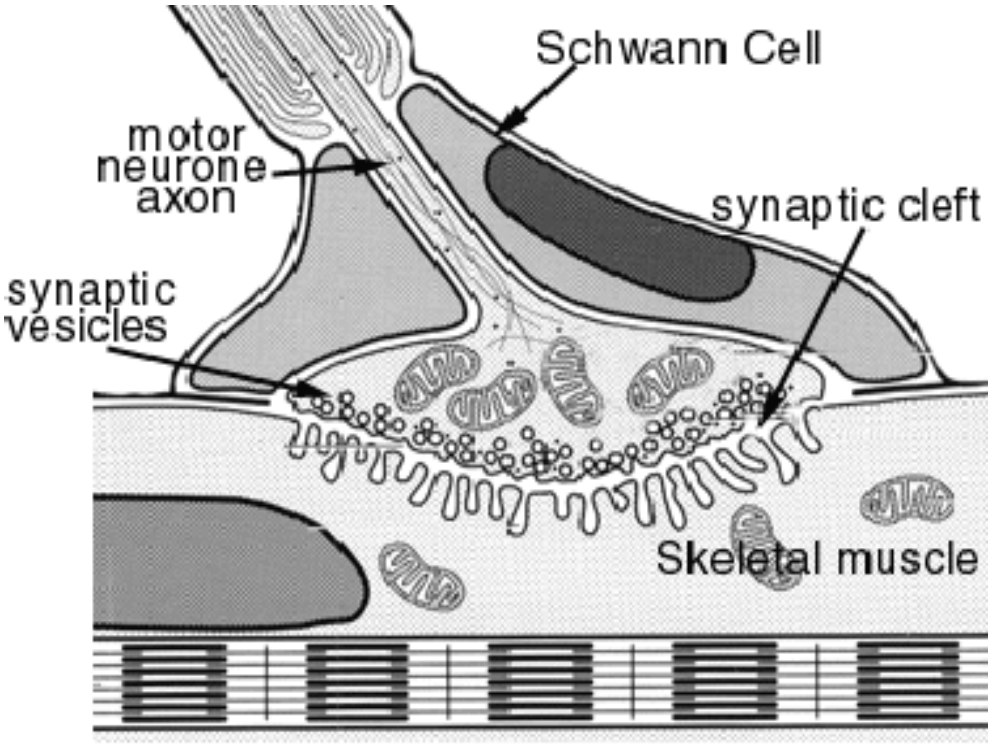
ஆய்வு குறித்தான விவரம்

மயக்கமடையச் செய்ய பயன்படுத்தபடும் ராக்குரோனியம் மருந்து வேலை செய்ய ஆரம்பிக்கும் நேரம் மற்றும் மருந்து கொடுக்கும்போது ஏற்படும் இருதயம் மற்றும் இரத்த அழுத்த மாற்றங்களின்மேல் எ.ஃபிடிரின் எனும் மருந்தின் தாக்கம்.

மயக்கம் செலுத்துவதற்கு ராக்குரோனியம் எனும் மருந்து பயன்படுத்தப்படுகிறது. எபிடிரின் எனும் மருந்தை அதற்குமுன் செலுத்துவதால் ராக்குரோனியம் மருந்து வேலை செய்ய ஆரம்பிக்கும் நேரம் குறைகிறது. இதனால் ராக்குரோனியம் மருந்தின் அளவும் குறைகிறது. எனவே அறுவை சிகிச்சை முடித்த பிறகும் நோயாளி மயக்கத்தில் இருக்கும் நிலை குறைகிறது. நோயாளி மயங்கியதற்கும் சுவாசகுளாயில் என்டோடிரகியல் டியூப் செலுத்துவதற்கும் இடையே இருக்கும் நேரம் குறைகிறது. இதனால் நுரையீரல் பாதிப்பு குறைகிறது. மேலும் ராக்குரோனியம் மருந்து வேலை செய்ய ஆரம்பிக்கும் நேரம் சக்சாமெத்தோனியம் மருந்தை போல் உள்ளதால் அது உபயோகிக்க முடியாத சமையங்களில் ராக்குரோனியத்தை உபயோகிக்கலாம்.எபிடிரின் மருந்து பயன்படுத்துவதால் இரத்த அழுத்தம் மற்றும் இருதயத்துடிப்பு சற்று அதிகமாக வாய்ப்பு உள்ளது. அப்படி நேர்ந்தாலும் அது உடனே மருத்துவரால் கண்டறியப்பட்டு மருந்துகளால் சரி செய்யப்படும். இந்த மருந்தினால் உடல் நலக்குறைவோ, மரணமோ ஏற்பட வாய்ப்புகள் இல்லை. இந்த விவரங்கள் அறிந்த நான் மேற்கூரிய ஆய்வில் முழுமனதுடன் பங்கேற்கிறேன்.

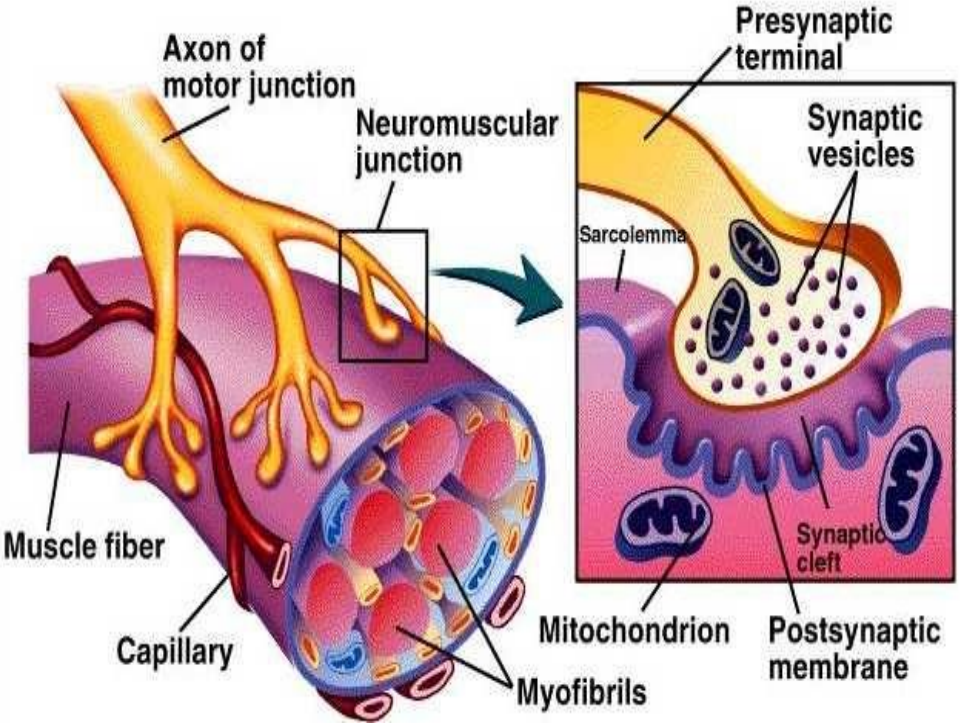
பெயர்: பங்கு பெறுபவரின் கையொப்பம்

இடது கை கட்டைவிரல் ரேகை



Neuromuscular junction

Neuromuscular Junction



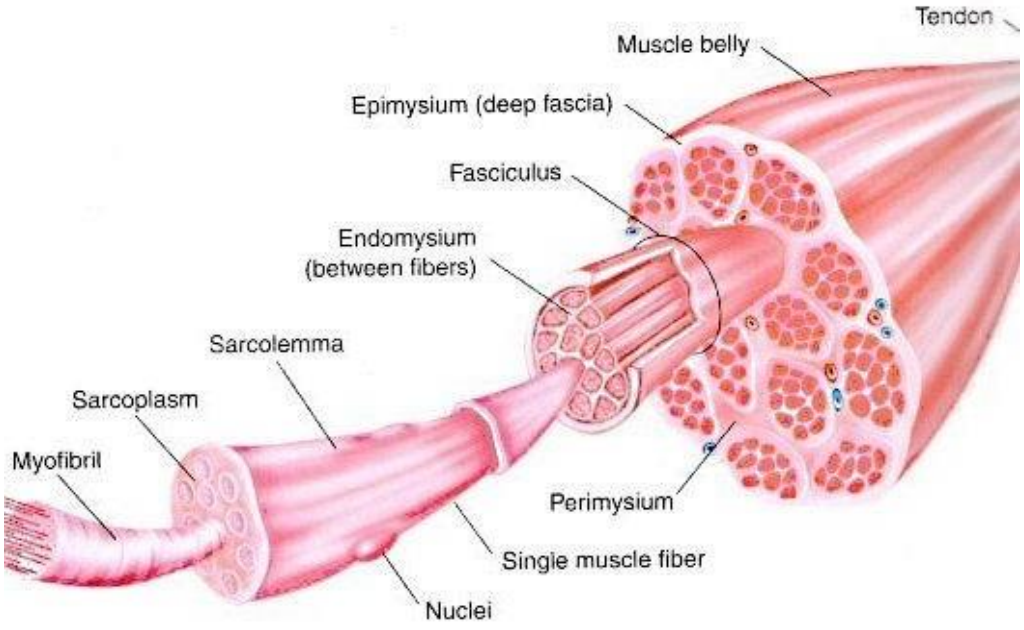
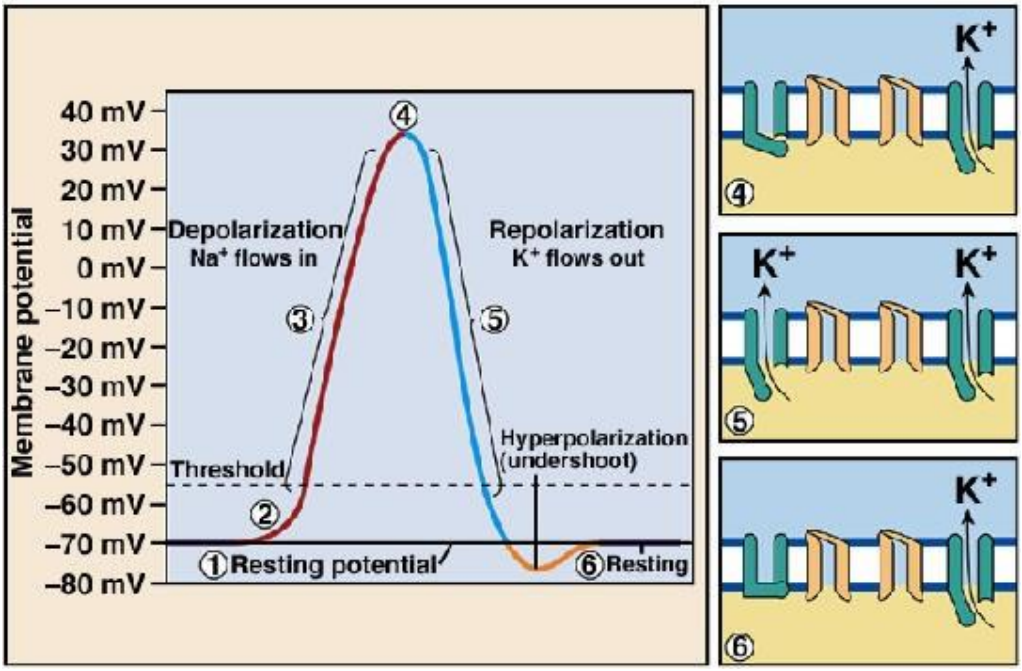


Figure 1: Muscle belly split into various component parts (from Essentials of Strength Training & Conditioning, National Strength & Conditioning Association)

Action Potential (2)



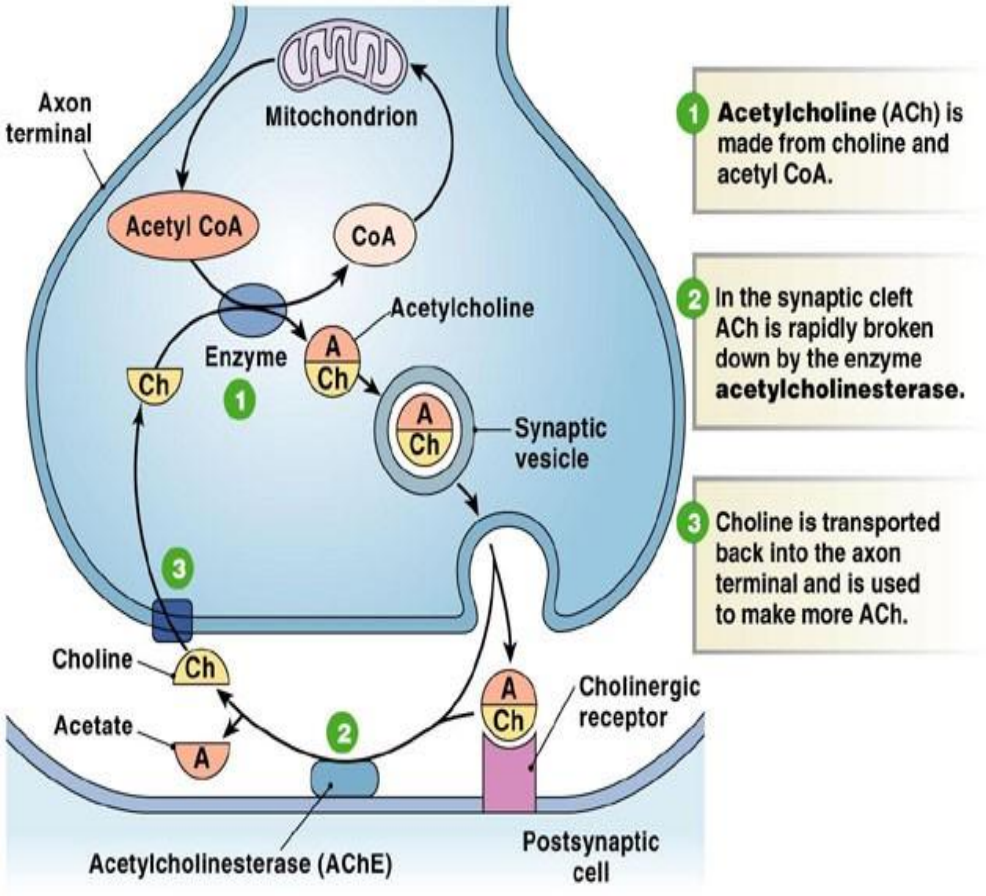
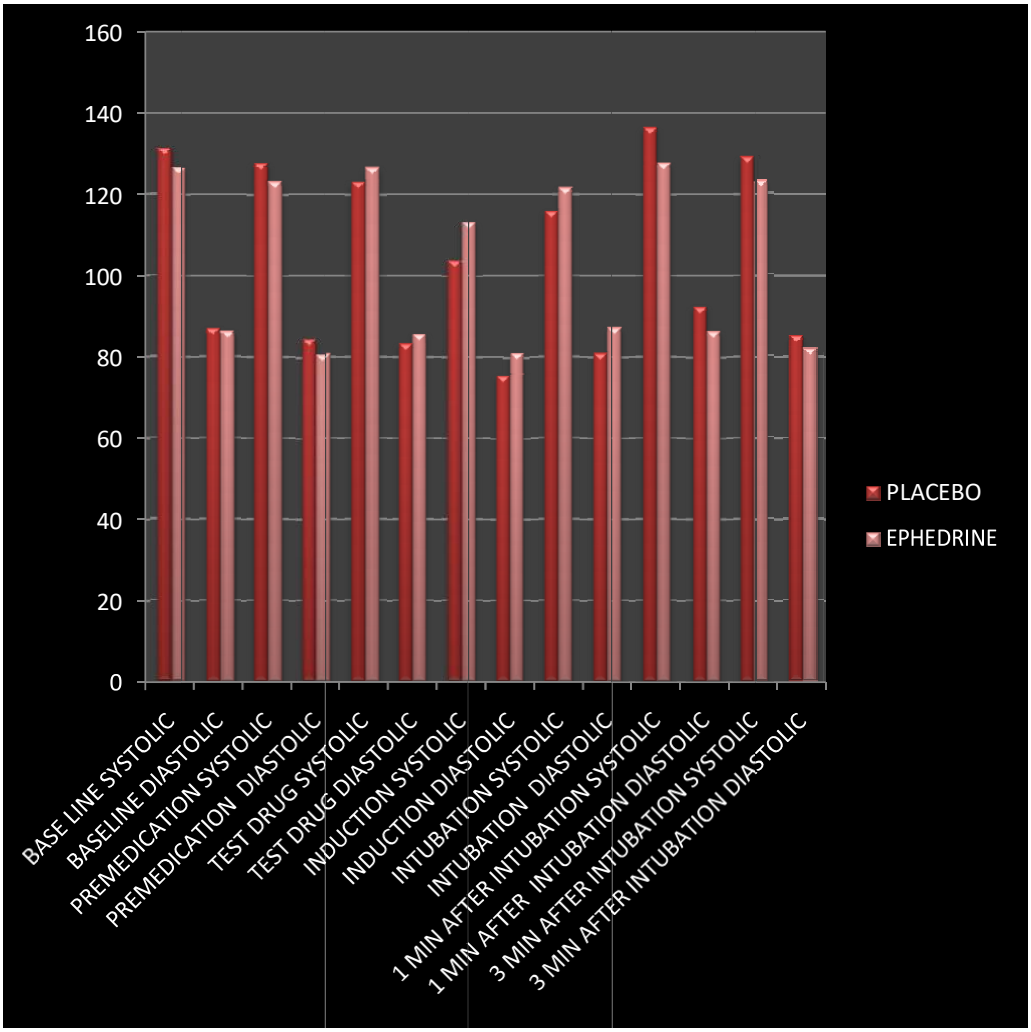


Fig. 8-22


160
140
120
100
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60
40
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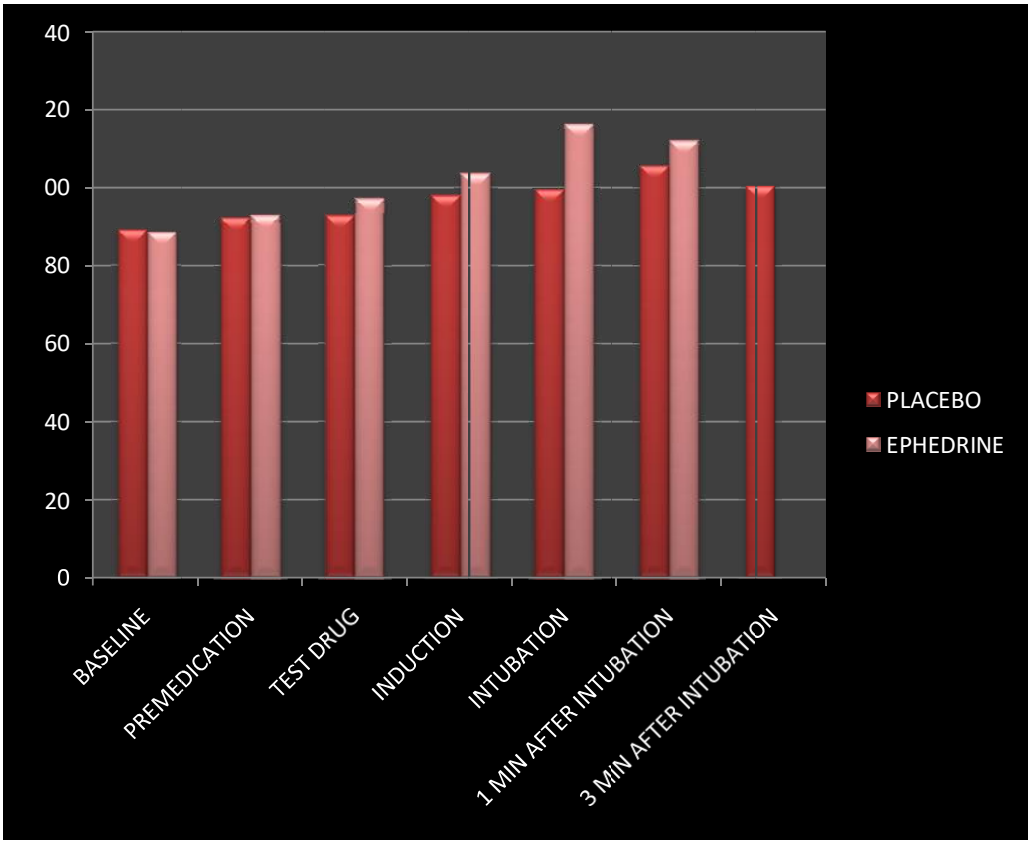
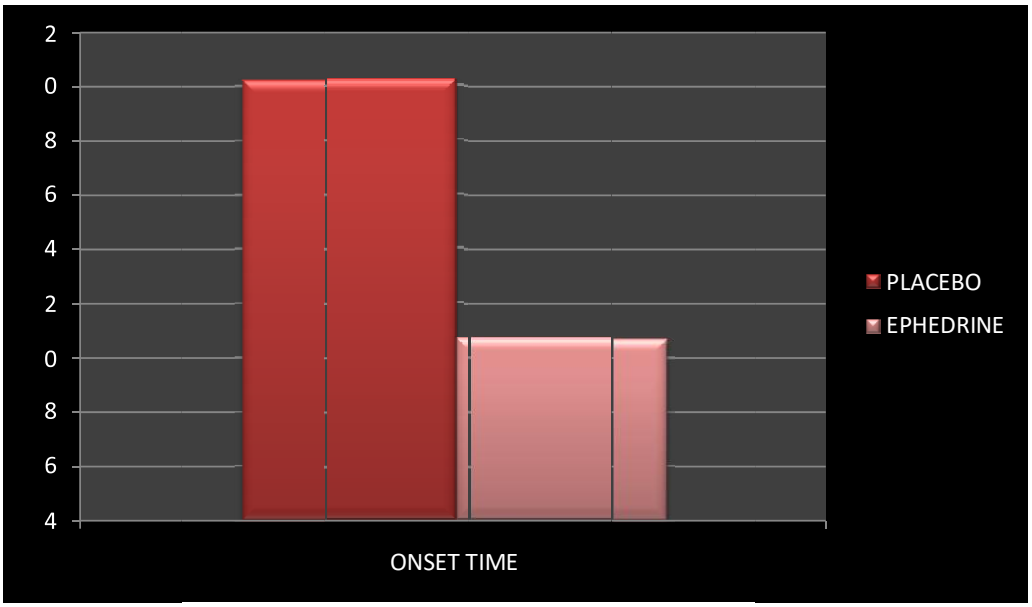
0
PLACEBO
EPHEDRINE
BASE LINE SYSTOLIC
BASELINE DIASTOLIC
PREMEDICATION SYSTOLIC
PREMEDICATION DIASTOLIC
TEST DRUG SYSTOLIC
TEST DRUG DIASTOLIC
INDUCTION SYSTOLIC
INDUCTION DIASTOLIC
INTUBATION SYSTOLIC
INTUBATION DIASTOLIC
1 MIN AFTER INTUBATION SYSTOLIC
1 MIN AFTER INTUBATION DIASTOLIC
3 MIN AFTER INTUBATION SYSTOLIC
3 MIN AFTER INTUBATION DIASTOLIC


40
20
00
80
60
40
20
0
BASELINE
PREMEDICATION
TEST DRUG
INDUCTION
INTUBATION
1 MIN AFTER INTUBATION
3 MIN AFTER INTUBATION
PLACEBO
EPHEDRINE


2
0
8
6
4
2
0
8
6
4
ONSET TIME
PLACEBO
EPHEDRINE

Sl. No.	name	age	sex	weight	mms	drug	hr_base	hr_pre	hr_test	hr_ind	hr_int	hr_1min	hr_3min	bps_base	bpd_base	bps_pre	bpd_pre	bps_test	bpd_test	bps_ind	bpd_ind
1	SUBRAMANI	36	M	60	I	1	74	65	66	91	95	95	94	148	89	134	92	130	90	128	92
2	SUSEELA	17	F	50	I	1	122	127	122	116	120	126	109	110	87	110	80	110	80	118	74
3	ANANDHAN	32	M	50	I	1	86	79	82	94	108	113	110	144	95	140	90	130	88	100	70
4	BHAVANI	19	F	50	I	1	125	121	120	124	110	108	112	120	80	120	83	110	80	113	81
5	KANCHANA	28	F	50	I	1	110	133	130	121	122	138	126	140	80	130	80	130	74	100	80
6	MANICKAMMAL	38	F	45	I	1	80	86	86	90	90	97	102	123	91	116	93	116	93	114	90
7	MALLIGA	51	F	60	II	1	90	80	82	93	98	102	92	130	80	120	70	110	84	90	72
8	USHARANI	50	F	60	I	1	66	82	80	74	70	75	62	172	100	168	98	160	90	99	69
9	FATHIMA	23	F	70	I	1	86	106	122	116	110	124	110	130	80	120	80	110	86	90	60
10	ANANDHI	42	F	55	I	1	81	86	84	81	83	80	96	124	86	124	87	120	84	110	80
11	KASTHURI	55	F	50	II	1	102	98	95	94	90	96	90	132	87	149	96	149	96	90	61
12	SRINIVASAN	30	M	50	I	1	88	98	102	116	106	130	114	124	93	133	87	133	80	100	73
13	HABITHA BEEVI	45	F	50	I	1	101	96	97	110	114	115	113	128	89	128	90	120	80	90	60
14	RESHMA	39	F	56	I	1	52	68	67	62	72	67	62	130	80	126	80	100	74	90	60
15	KANNAN	30	M	65	II	1	86	79	82	94	106	112	110	144	95	142	90	130	88	100	70
16	KANNIYARAM	50	M	55	II	1	72	62	64	76	80	113	71	119	72	117	70	117	71	100	66
17	KULANTHAI	44	M	66	II	1	86	100	120	116	110	124	110	130	80	120	80	110	90	87	58
18	MADHAN	42	M	60	II	1	88	96	95	94	82	80	94	122	84	120	80	110	86	90	60
19	KOLANJI	35	F	60	II	1	110	96	99	113	110	108	106	138	94	128	95	128	95	98	62
20	VIJAYALAKSHMI	36	F	50	I	1	120	125	120	114	113	119	108	106	85	104	80	110	70	109	85
21	DEVI	26	F	50	I	1	98	103	104	109	110	124	122	114	83	110	71	124	86	110	73
22	LAKSHMI	37	F	45	I	1	75	93	96	102	108	108	111	131	98	130	97	130	90	146	111
23	CHINNARAJI	37	F	70	I	1	106	105	108	103	100	117	113	153	97	156	91	156	91	144	88
24	SARASWATHI	50	F	70	II	1	52	68	67	62	72	67	62	130	80	127	80	100	74	90	60
25	RATHI	41	F	60	II	1	93	84	86	67	72	82	86	153	92	151	90	150	90	140	96
26	GAYATRI	22	F	40	I	1	104	101	86	130	115	130	118	113	76	113	76	106	73	101	72
27	KALAIVANI	30	F	56	I	1	74	66	66	91	94	94	92	144	88	132	90	128	88	126	90
28	RAMESH	25	M	55	I	1	75	92	95	100	106	106	104	106	85	104	80	110	70	108	86
29	RAVI KUMAR	25	M	50	II	1	90	92	88	93	110	117	114	150	103	135	97	130	90	127	93
30	GANESH	54	M	80	II	1	80	83	83	96	110	106	105	130	80	130	70	130	70	130	80
31	GEETHA	38	F	50	II	2	86	93	100	101	126	140	108	149	90	160	95	160	90	140	99
32	SARASWATHY	23	F	40	I	2	106	116	108	120	135	126	118	120	80	130	84	140	92	100	70
33	KUMUDHA	45	F	55	II	2	64	76	57	72	84	82	80	130	80	120	74	110	80	100	66
34	PADMA	40	F	55	I	2	96	103	115	110	140	118	116	110	80	109	81	107	68	90	64
35	MANJULA	30	F	50	I	2	84	76	94	98	130	102	110	130	80	120	70	130	80	100	76
36	DHARANI	18	F	45	I	2	110	113	122	124	138	144	112	120	70	110	80	120	66	110	80
37	RANI	23	F	55	I	2	67	78	89	90	112	123	90	110	90	119	90	130	80	109	89
38	SUSEELA	47	F	60	II	2	90	95	102	110	120	108	110	140	80	134	94	140	98	140	110
39	ARJUNAN	16	M	40	II	2	84	81	116	120	118	108	92	140	70	130	80	140	90	130	80
40	PARVATHY	30	F	50	I	2	114	110	120	114	122	118	120	120	80	130	70	100	80	120	70
41	RANI	20	F	45	I	2	64	76	84	98	98	97	95	112	71	130	80	120	76	140	100
42	DEEPA	28	F	50	II	2	103	102	97	107	119	118	113	120	70	110	80	107	64	110	80
43	NANDINI	24	F	55	I	2	101	96	113	120	122	129	111	127	90	131	90	140	88	120	92
44	DHANALAKSHMI	26	F	52	I	2	110	107	112	109	114	96	124	135	91	133	90	132	89	130	94
45	NALINA	31	F	50	I	2	121	119	128	130	130	104	103	152	97	130	81	130	80	140	90
46	BHAVANI	16	F	50	I	2	87	96	113	114	111	120	133	152	90	149	91	148	103	148	102
47	RAMANA	18	M	68	II	2	90	75	82	95	100	126	124	120	80	110	74	140	90	106	70
48	CHINNATHAMBI	40	M	50	II	2	71	86	82	85	90	92	109	132	86	132	86	131	87	118	80
49	LAKSHMI	38	F	65	II	2	80	84	86	97	96	92	75	130	84	110	82	120	76	100	66
50	SUMATHY	20	F	40	I	2	101	106	92	94	101	115	114	126	84	120	80	114	76	127	82
51	MANISHA	18	F	55	I	2	106	94	99	102	108	124	119	117	74	101	65	102	65	110	62
52	MANJULA	23	F	45	II	2	84	114	102	109	120	130	120	100	80	100	76	110	80	90	70
53	ARUN KUMAR	16	M	50	I	2	81	94	64	90	120	107	106	130	80	120	70	130	74	110	70
54	NAGALINGAM	39	M	50	I	2	99	104	96	98	89	109	108	129	85	128	86	130	89	102	73
55	VIJI	23	F	60	I	2	78	91	90	105	96	123	100	130	85	129	81	121	76	119	83
56	KARTHICK	29	M	56	II	2	83	74	92	97	128	100	108	128	78	118	70	130	78	98	74
57	LAKSHMANAN	35	M	60	I	2	66	78	88	92	110	122	88	108	88	118	88	128	80	108	90
58	DURAI	40	M	66	I	2	100	94	112	118	116	106	94	140	70	130	80	120	76	140	100
59	MEENATCHI	35	F	70	I	2	64	76	84	98	98	97	95	112	71	130	80	140	90	130	80
60	RAJAN	33	m	66	I	2	66	82	84	93	96	90	100	130	82	110	80	132	90	126	78

bps_int	bpd_int	bps_1	bpd_1	bps_3	bpd_3	onset	cl_grade	pogo	ip_no
130	100	143	107	130	90	50	I	90	72410
118	70	149	116	118	81	40	II	60	70969
140	100	180	110	153	100	80	II	30	70970
92	63	90	60	114	72	100	I	100	70073
120	70	140	110	130	90	50	II	90	71678
114	89	136	108	99	79	50	I	100	29286
100	74	150	90	140	86	95	II	60	70536
119	83	120	74	157	97	65	I	90	63510
110	80	90	64	100	70	45	II	100	78533
119	85	117	89	118	89	55	I	80	67540
90	61	150	100	111	80	45	II	50	69739
107	76	173	110	163	105	75	I	100	30410
96	70	69	55	130	96	55	I	100	65828
90	64	134	70	136	74	70	I	80	68114
140	100	172	108	150	100	80	II	80	71145
110	66	155	93	144	89	65	I	100	67800
108	76	166	110	162	105	75	II	80	70899
110	80	90	64	100	70	45	I	100	64431
99	60	120	66	110	64	80	I	100	46245
127	100	120	94	120	74	40	I	100	71222
110	66	124	91	110	83	50	II	30	57888
93	78	100	76	110	70	54	II	40	66374
140	90	176	124	125	92	40	II	50	68145
90	55	140	70	145	75	78	I	90	67871
126	85	159	99	140	90	40	I	100	68132
147	102	159	100	135	82	45	II	70	70515
128	100	140	106	130	90	80	II	80	77567
126	100	118	94	120	74	50	II	80	66742
120	90	167	110	140	100	60	II	60	70220
160	100	150	110	140	90	50	II	50	61557
190	110	180	100	140	107	35	II	80	76895
100	80	120	70	90	60	31	I	100	77088
120	74	110	80	120	70	58	I	100	70820
140	100	113	81	113	80	40	I	90	68572
150	110	126	92	120	84	39	I	100	74022
140	110	120	80	110	70	70	I	100	72903
150	99	114	80	120	70	40	I	100	66788
130	80	120	74	110	80	32	II	50	73285
120	70	110	80	120	74	100	I	100	70554
110	80	140	90	108	70	45	I	100	72477
114	75	114	77	113	76	34	I	100	73406
125	80	125	87	93	67	35	I	100	74094
131	86	145	94	143	99	55	I	90	73494
140	109	129	94	145	109	25	I	100	72829
140	96	169	113	117	82	60	I	60	72899
151	105	153	106	164	101	45	I	100	71333
110	70	120	80	108	70	47	I	100	73661
138	80	120	70	121	65	43	II	50	71554
120	70	140	90	110	70	32	I	90	72410
120	80	134	87	117	76	43	I	100	72564
110	70	127	92	106	68	37	I	90	27617
96	56	100	70	104	76	42	I	80	72418
130	92	120	74	110	80	37	I	80	72099
117	84	172	128	124	88	60	II	100	68416
160	127	127	92	131	82	35	I	100	68449
146	108	124	90	118	82	38	I	100	68504
148	98	112	78	118	72	42	II	100	68900
114	74	114	76	112	76	34	I	100	72830
120	70	110	80	120	74	100	I	100	73449
120	80	127	92	118	76	55	I	80	78955