"A STUDY COMPARING THREE DIFFERENT DOSES OF NEOSTIGMINE (50µgm/kg, 25µgm/kg, 12.5µgm/kg) AS REVERSAL AGENT FOR FACILITATION OF RECOVERY FROM RESIDUAL NEUROMUSCULAR BLOCKADE WITH ATRACURIUM"

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CERTIFICATE

This is to certify that the dissertation titled **"A STUDY COMPARING THREE DIFFERENT DOSES OF NEOSTIGMINE (50 µgm/kg, 25 µgm/kg, 12.5 µgm/kg) AS A REVERSAL AGENT FOR FACILITATION OF RECOVERY FROM RESIDUAL NEUROMUSCULAR BLOCKADE WITH ATRACURIUM"** presented herein **Dr. T .GIRIDHARAN** is an original work done in the Department of Anaesthesiology , Govt. Stanley Medical College and Hospital , Chennai for the award of the degree of M.D. (Branch X) Anaesthesiology under my guidance and supervision during the academic period of 2003 – 2006 .

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DECLARATION

I, **Dr. T. GIRIDHARAN** solemnly declare that the dissertation titled **" A STUDY COMPARING THREE DIFFERENT DOSES OF NEOSTIGMINE (50µgm/kg , 25µgm/kg , 12.5µgm/kg) AS A REVERSAL AGENT FOR FACILITATION OF RECOVERY FROM RESIDUAL NEUROMUSCULAR BLOCKADE WITH ATRACURIUM"** is a bonafide work done by me in the department of Anaesthesiology , Stanley Medical College and Hospital, Chennai under the able guidance of Prof . Dr.J.Ranganathan, M.D., D.A., Professor and H.O.D, Department of Anaesthesiology, Govt. Stanley Medical College and Hospital, Chennai -1

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CONTENTS

1 INTRODUCTION

Anti-cholinestrase drugs like neostigmine are given at the end of surgical procedures to accelerate recovery from residual neuromuscular blockade produced by non-depolarising neuromuscular blocking drugs.

When atracurium is used as muscle relaxant which has a novel mechanism of excretion which does not depend either on renal or hepatic function. The atracurium induced muscle relaxation can recover spontaneously but slowly. Anti- cholinesterase is needed just to speed up recovery from residual blockade .

Since the reversal agent like neostigmine has its own drawbacks of muscarinic side effects of bradycardia , hypotension , increased glandular secretions . The dose of neostigmine reduction might help in reducing these side-effects without affecting its purpose of reversing the residual neuromuscular blockade .

In addition use of neuromuscular monitor , helps us to objectively judge The recovery of the neuromuscular junction , from residual non – depolarizing blockade when used in addition to the clinical signs of recovery of muscle power .

2 AIM OF THE STUDY

To study and compare three different doses of neostigmine as reversal agent to residual neuromuscular blockade of atracurium .

1. On recovery of residual neuromuscular blockade produced by atracurium (intubating dose of 0.5 mg / kg ,top-up dose of 0.15 mg / kg)

2. On the haemo- dynamic changes.

3. On the adverse side effects.

3 PHYSIOLOGY OF NEUROMUSCULAR JUNCTION

Neuromuscular junction (NMJ) is a synapse at which an electrical impulse traveling down a nerve is converted into muscle action potential and contraction by chemical transmitters . A motor neuron along with all the muscle fibers supplied by it forms a motor unit , which follows all or none law of contraction.

PARTS OF NEUROMUSCULAR JUNCTION

To understand the physiological events occurring during neuromuscular transmission, it is essential to understand the anatomy of NMJ , which can be divided into

1. Presynaptic nerve terminal

2. Synaptic cleft

3. Post synaptic membrane acetylcholine receptors

4. Contractile apparatus

PRESYNAPTIC NERVE TERMINAL

Presynaptic nerve terminal contains all the apparatus necessary for the synthesis of acetylcholine , which exist in two forms : 20% in the soluble form in the axoplasm and 80% in vesicles , which can be further divided into a readily available pool and a reservoir pool . The vesicles are 40 – 50 nm in diameter each containing 1000 – 10000 molecules of Ach . The walls of the vesicles contains synapsins that help in anchoring the vesicles to the cytoskelatal framework of the axoplasm .

At the membrane facing the synaptic cleft , there is an electron dense patch, the active zone , around which the readily available pool of Ach vesicles arranged Electron microscopy shows small pores between the vesicles at the active zone. These are the calcium channels. The terminal also contains sodium and potassium channels.

The nerve endings on fast muscles are longer and more complicated than those on slow muscles . The reason for this is unclear. These differences in the nerve endings on the muscle surfaces may play a role in the differences in the response to muscle relaxants of fast and slow muscles .

SYNAPTIC CLEFT:

It is 20 nm wide space between the nerve terminal and the muscle end plate . The nerve and the muscles are held in tight alignment by protein filaments ,which span the cleft between nerve and end plate . The muscle surface is heavily corrugated with deep invaginations of the junctional cleft , the primary clefts and the secondary clefts , between the folds in muscle membrane . The shoulders of the folds are densely populated with acetylcholine receptors about 5 million of them in each junction. These receptors are spare in the depths between the folds. Instead these deep areas contain sodium channels. These sodium channels have two component gates , voltage and time dependant gates .

POST SYNAPTIC MEMBRANE – Ach RECEPTORS:

The Ach receptors at the NMJ are nicotinic and can be divided into presynaptic and postsynaptic . The latter are further divided into junctional and extrajunctional. The Ach receptor is a pentameric transmembrane spanning protein. The 5 protein subunits are arranged in the form of a rosette with a central ion channel. The molecular weight of the receptor is 250 000 - 270 000. The junctional receptor contains 2α , β , δ and ε . The extrajunctional receptor contains 2α , β , δ and γ which proliferate in abnormal conditions . These extra cellular surface of the alpha subunits contains high affinity Ach binding sites.

CONTRACTILE APPARATUS:

The contractile apparatus of the muscle is formed by the myofilament comprising 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 actin. The myofilaments combine to form myofibrils. The muscle plasma membrane , the sarcolemma invaginates to form T-tubules which lies in close association with sarcoplasmic reticulam which is a collection of sacs and tubules acting as a reservoir for calcium .

MECHANISM OF NEUROMUSCULAR TRANSMISSION

MECHANISM OF Ach RELEASE:

An action potential traveling down the nerve causes the sodium channels in the presynaptic nerve terminal to open , leading to sodium influx .The change in voltage produced by such an influx activates the calcium channels , which open up leading to calcium entry . Calcium mediated activation of calcium calmodulin dependent protein kinases leads to phosphorylation of synapsins in the vesicle wall, causing the vesicles to break away from the cytoskeletal framework . The vesicles then attaches to the active zones with release of Ach molecules . Each nerve impulse causes the release of around 100 - 400 quanta of Ach . Activation of around 20 – 25 % receptors is essential for impulse transmission .

BINDING OF Ach TO RECEPTOR:

The Ach molecule released into the synaptic cleft binds to the alpha subunit. binding of Ach to both the alpha subunits activates the receptor , leading to configurational changes in the receptor structure and opening up of ion channels .

This leads to depolarization of the muscle end plate which when of a sufficient magnitude causes a wave of depolarization to spread across the muscle sarcolemma by means of activation of the voltage dependent gates of the sodium channels in the perijunctional zones . This depolarization wave moving down the T – tubule causes release of calcium from sarcoplasmic reticulam. Calcium so released binds to troponin C causing tropomyosin to move and expose the myosin binding sites of action leading to the formation of cross linkage of actin and myosin heads .They slide over each other leading to shortening of the myofilaments and muscle contraction .

DISSOCIATION OF Ach FROM RECEPTOR:

The Ach molecule remain attached to its receptor for a very short period of less than 1 millisecond, after which it dissociates from the receptor and is hydrolysed by the enzyme acetylcholinestrase. It hydrolyses Ach into

acetate and choline , the choline being taken up by the presynaptic nerve terminal and used for further Ach synthesis .

MECHANISM OF NON – DEPOLARISING BLOCKADE:

Non – depolarizing muscle relaxant are drugs having an affinity for the alpha subunits of the acetylcholine receptors mainly at the postjunctional nicotinic receptors and also at the prejunctional sites of nerve endings . Binding of these relaxants to the alpha subunits of a Ach receptor cannot open the ion channel and it also prevent further binding of Ach molecule . So an action potential is not developed and there is no contraction of muscle fibre .This competitive blockade of Ach receptor is termed as non – depolarizing blockade.

MARGIN OF SAFETY:

Atleast 75 % of receptors must be occupied before neuromuscular transmission is impaired and if more 90 % of the receptors are occupied , transmission fails.

CHARACTERISTIC FEATURES:

1. Slow onset to maximal effect and slow recovery compared to succinylcholine

2. The central muscles like the diaphragm , larynx , masseter , orbicularis oculi tend to be affected earlier and recover sooner than those of the peripheral [adductorpollicis] probably as a result of preferential perfusion.

3. Presence of fade and post- tetanic potentiation.

4. Despite flaccid paralysis , the muscles are still able to respond to direct stimulation.

5. The muscle block is reversed pharmacologically by anticholinestrase drugs.

MECHANISM OF DEPOLARISING N M J BLOCKADE :

Depolarising agents like suxamethonium cause initial depolarization of endplate due to acetylcholine like actions , which is transduced into muscle contraction , but repeated action on the receptor leads to a persistent depolarizing voltage . This influences the sodium channels in the vicinity of

the endplate , the perijunctional area , where the transmembrane voltage causes the voltage gates to remain open and the time gates to remain closed , thereby preventing further ion entry through the channel . Further spread of the depolarization is arrested , and it remains confined to the endplate only . With the progress of depolarization arrested , the channels in the remainder of the muscle are freed of the depolarizing influence and return to their resting state . Thus 3 discrete zones can be delineated namely

1. Endplate – persistently depolarized.
2. Perijunctional area – sodium channels still under the depolarizing influence are frozen in closed state .
3. Rest of the muscle – relaxed , as sodium channels return to resting state .

4 PHARMACOLOGY

NEOSTIGMINE:

MECHANISM OF ACTION:

It produces reversible inhibition of acetylcholinestrase by formation of a carbamyl ester complex at the esteratic site of the enzyme . Carbamylated acetylcholinestrase has a half – time of about 15 to 30 minutes. This carbamylated acetylcholinestrase cannot hydrolyse acetylcholine until the carbamate – enzyme bond dissociates.

STRUCTURE ACTIVITY RELATIONSHIP:

Acetylcholinestrase consist of an anionic and an esteratic site that are so arranged that they are complimentary to the natural substrate acetylcholine . The anionic site of the enzyme binds the quaternary nitrogen of acetylcholine . This binding serves to orient the ester linkage of acetylcholine to the esteratic site of acetylcholinestrase .

Neostigmine is a quaternary ammonium derivative of physostigmine , having a greater stability and equal or greater potency .

PHARMACOKINETICS:

Elimination half time: 7 7 minutes.

Volume of distribution: 0 .7 L / Kg.

Clearance: 9.2 ml / kg / min.

Renal contribution to total clearance [%] : 54 % .

Speed of onset: Intermediate.

Duration: 54 minutes.

Principle site of action: postsynaptic.

Anticholinergic dose: 20 microgram / kg

Lipid solubility: Poorly lipid soluble.

Onset of action: 7 to 11 min.

Metabolism: hepatic metabolism - 50 %. Principle metabolite - 3 – hydroxyl – phenyl - trimethylammonium , which has 1 / 10 th the antagonist activity of the parent compound .

Influence of patient age : dose required to produce equivalent effect is less in infants and children than in adults . Duration of maximum response produced by neostigmine is prolonged in elderly compared with younger patients reflecting a smaller extra – cellular fluid volume and slowed rate of plasma clearance in elderly patients.

PHARMACOLOGICAL EFFECTS:

Reflects the accumulation of acetylcholine at muscarinic and nicotinic cholinergic receptor sites .

Cardio – vascular system:

Bradycardia and / or bradydysrythmias such as nodal and ventricular escape beats and asytole . It reflects slowing of the conduction of cardiac impulse through the atrio – ventricular node . Decrease of systemic blood pressure probably reflects decrease in systemic vascular resistance , although the coronary and pulmonary circulations may manifest an opposite response .

Gastro-intestinal tract:

Enhance gastric fluid secretion by parietal cells and increase the motility of the entire G.I.T., particularly large intestine reflecting the effects of accumulated Ach on the ganglion cells of Auerbach's plexus and on smooth muscle fibers . Increase the incidence of post – operative nausea and vomiting. Combination of atropine with neostigmine has been found to decrease gastric cardiac sphincter pressure .Lower portion of the oesophagus is stimulated by neostigmine resulting in increase in tone and

peristalsis .

Genito – urinary tract:

Stimulation of urethral peristalsis and contraction of the detrusor muscle of the urinary bladder .The external sphincter and trigone are relaxed .

Respiratory tract:

Cholinergic stimulation of bronchi produces bronchoconstriction and have potential to increase airway resistance .

Glands:

Augments production of secretions of glands innervated by postganglionic cholinergic fibers [bronchial , lacrimal , sweat , salivary , gastric , intestinal , and pancreatic acinar glands].

Eyes:

Causes constriction of iris – miosis and cilliary muscle – inability to focus for near vision . Intraocular pressure declines because the outflow of aqeous humor is facilitated .

CLINICAL USES:

1. Antagonist-assisted reversal of neuromuscular blockade:

Reflects increased availability of acetylcholine at the NMJ due to inhibition of acetylcholinestrase . Improves the chance of two acetylcholine molecules to the alpha subunit of the nicotinic cholinergic receptors. They are typically administered during the time when spontaneous recovery from neuromuscular blockade is occurring such that the effect of pharmacologic antagonist adds to the rate of spontaneous recovery from the neuromuscular blocking drug .

Neostigmine appears preferable to either edrophonium or pyridostigmine when > 90 % twitch depression is to antagonizedDose of neostigmine required for recovery of first twitch height [injected when twitch height is 10 % of control] atracurium induced neuromuscular blockade .

ED 50 - 10 micro gm / kg

ED 80 - 22 micro gm / kg

Recommended doses of neostigmine according to response to train – of - four stimulation .

None - none

<2 - 0.07 mg / kg

3- 4 - 0.04 mg / kg

The dose of atropine to be added is one –half that of neostigmine . The dose of glycopyrollate is one – fourth of that of neostigmine .

Events that influence reversal of neuromuscular blockade:

1. Intensity of neuromuscular blockade at the time of pharmacologic reversal.
2. Nondepolarising neuromuscular – blocking drug being reversed.
3. Certain antibiotics.
4. Hypothermia.
5. Respiratory acidosis associated with a PaCO2 of > 50 mmhg.
6. Hypokalemia.
7. Metabolic acidosis.

Treatment of Myasthenia gravis:

Increases the response of skeletal muscles to repetitive impulses presumably by increasing the availability of endogenous acetylcholine . Oral dose of neostigmine is 30 times than the I.V. Dose. The interval between the oral doses is usually 2 – 4 hrs.

Post - operative analgesia:

Intrathecal injection of 10 – 30 µg produce analgesia without ventilatory Depression , although nausea is common .

ATRACURIUM

Atracurium is a bisquaternary benzylisoquinolinium nondepolarising neuromuscular blocking drug [mixture of ten geometric isomers]

ED 95 - 0.2mg / kg

Onset of action.

3 to 5 minutes.

Duration of action.

20 to 35 minutes.

Site of action

Acts on both presynaptic and postsynaptic cholinergic receptors. Atracurium may also produce neuromuscular blockade by directly interfering with passage of ions through channels of nicotinic cholinergic receptors.

Protein binding

82 % of atracurium is bound to plasma proteins , presumably albumin

pH

Adjusting the pH of commercial solution to 3.25 to 3.65 minimizes spontaneousin vitro degradation . Atracurium probably should not be mixed with alkaline drugs or exposed to solutions with more alkaline Ph , as are present in delivery tubing used for infusion of I.V . Fluids.

Solubility

The iodide salt besylate provides water solubility.

Temperature of storage.

Atracurium should be stored at 4 to 8 degree Celsius. Potency of atracurium Stored at room temperature decreases approximately 5 % every 30 days .

Clearance.

Hoffmann elimination; spontaneous non – enzymatic degradation at normal body temperature and pH by a base catalyzed reaction A second and simultaneously occurring route of metabolism is hydrolysis by non – specific plasma esterases . These two routes of metabolism are independent of hepatic and renal function as well as plasma cholinesterase activity .Overall

ester hydrolysis accounts for estimated 2 / 3 rd of atracurium degradation, whereas Hoffmann elimination provides a safety net especially in patients with impaired hepatic and renal function .

Laudanosine is the major metabolite of both the pathways of metabolism of atracurium with Hoffmann elimination resulting in 2 molecules and ester hydrolysis resulting in 1 molecule of laudanosine for every molecule of atracurium that is metabolized .Electrophilic acrylates are also formed by Hoffmann elimination .

Cumulative effects:

Absence of significant cumulative drug effect is due to rapid clearance of Atracurium from plasma that is independent of renal or hepatic function . Lack of a significant drug cumulative effect minimizes the likelihood of Persistent neuromuscular blockade when prolonged surgical procedures require repeated doses or a sustained continuous infusion of atracurium.

Cardio - vascular effects:

The rapid I.V. administration of 3 times ED 95 of atracurium increases heart rate by 8.3 % and decrease mean arterial pressure by 21.5 % . These

circulatory changes are transient , occurring 60 to 90 seconds after administration of atracurium and disappearing within 5 minutes . Facial and truncal flushing in some patients such as release of histamine . If the same dose of atracurium administered over 30 to 75 seconds or rapidly but in patients pretreated with H1 and H2 receptor antagonist does not evoke circulatory changes despite similar increase in plasma concentration of histamine as present in those receiving the same dose rapidly without pretreatment it is estimated that the plasma histamine concentration must double .

Histamine realease evoked by atracurium does not occur repeatedly because tissue istamine stores are not replenished for several days . Therefore a decrease in systemic blood pressure due to drug induced histamine release is less likely to occur to the same magnidude on repeat dosing .CVS effects previously attributed to histamine release may reflect prostacycline releaseand its vasodilating effects on peripheral vasculature mediated by H1 and H2 receptors .

Pediatric patients:

Effective doses of atracurium are similar in adults and children [2 to 16 – Years old] when differences in extra cellular fluid volume or minimized Calculating the dose mg / sq.m rather than a mg / kg basis Infants 1 to 6 months old require approximately ½ the dose of atracurium given to older

children to achieve the same degree of neuromuscular blockade . These data imply that infants are more sensitive than children or adults . Recovery from atracurium – induced neuromuscular blockade , however , is more rapid in infants [23 min] than children and adolescents [29 min] .

Elderly patients:

The rate of recovery and the duration of neuromuscular blockade is similar in young and the elderly . This lack of influence of aging on dosing of atracurium most likely reflects the independence of clearance mechanism from age - related effects on renal and hepatic function . Changes in volume of distribution of atracurium that occur with aging will not influence the clearance of atracurium from the plasma . Failure of aging to alter responsiveness of the the NMJ is documented by similar plasma concentrations of atracurium necessary to depress single twitch response 50 % in elderly and young adults .

5 NEUROMUSCULAR MONITORING

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

Types of stimulation;

1. Electrical
2. magnetic

Principles of peripheral nerve stimulation

The reaction of single muscle fibre to a stimulus follows an all or none pattern. The response of the whole muscle depends on the no . of muscle fibres activated After administration of neuromuscular blocking drugs response of the muscle decreases in parallel with the no of fibres blocked .The electrical stimulus applied is usually at least 20 % - 25 % above that necessary for a maximal response

Patterns of nerve stimulation:

1. Single twitch stimulation:

Single supramaximal stimuli is applied. Frequency of stimulation is from 1.0 HZ – 0.1 HZ. 1HZ stimulation shortens the time necessary to determine supramaximal stimulatio

2. Train of four stimulation:

Introduced by Ali & associates in 1970s. Four supramaximal stimulation are given every 0.5 seconds at a frequency of 2HZ When used continuously stimulation is repeated every 10 th or 20 th second .Dividing the amplitude of fourth response by the first response gives the train of four ratio . Degree of neuromuscular block can be read from T-O-F response . Fade in the T-O-F after succinylcholine signifies development of phase Π block Less painful , unlike tetanic stimulation , does not affect the degree neuromuscular block.

3. Double-burst stimulation:

Two short burst of 50 HZ tetanic stimulation separated by 750 msecs. Duration of each square wave impulse is 0.2 msec Most commonly used is DBS with 3 impulse in each of two tetanic stimuli. In non-paralysed muscle two short muscle contractions of equal strengths will be elicited .In partly paralysed muscle the 2nd response will be weaker .T O F ratio closely correlate with D B S ratio DBS was developed with specific aim of allowing manual (

tactile) detection of small amount of residual blockade during recovery and immediately after administration of anticholinesterase. Absence of fade in manual evaluation of response to DBS does not exclude residual neuromuscular block.

4. Tetanic stimulation

Tetanic stimulation consists of very rapid delivery of electrical stimuli. Most commonly used pattern in clinical practice is 50 HZ stimulation given for 5 sec. During normal neuromuscular transmission and a pure depolarizing block muscle response to tetanic stimulation is sustained but during a non-depolarizing block and a phase - 2 block , the response will not be sustained. Fade in response to tetanic stimulation is normal considered a presynaptic event. Fade depends primarily on the degree of neuromuscular blockade and also depends on the frequency , the length of stimulation and on how often tetanic stimuli are applied during the partial non- depolarizing blockade , the tetanic stimulation is followed by a post- tetanic increase in twitch tension (post-tetanic facilitation of transmission) . The degree and duration of PTF depends on the degree of neuromuscular block with PTF disappearing within 60 seconds of tetanic stimulation very painful, not acceptable in unanaesthetised patient .In the late phase of neuromuscular recovery , tetanic stimuli may produce a lasting antagonism of neuromuscular. Tetanic stimulation has very little place in clinical anaesthesia.

5. Post – tetanic count stimulation:

It is used to quantify intense neuromuscular blockade (i.e. TOF= 0) of peripheral muscles by applying tetanic stimulation (50HZ for 5 secs) and observing the post – tetanic response to single twitch stimulation given at 1 HZ starting 3 seconds after the end of tetanic stimulation. The time until return of the first response to TOF stimulation is related to the no of post – tetanic twitch responses present at a given time . The main application of PTC is evaluation of degree of neuromuscular blockade when there is no reaction to single twitch or TOF stimulation .PTC is also used whenever sudden movement should be eliminated and to ensure elimination of any bucking or coughing in response to tracheo-bronchial stimulation such that the neuromuscular block should be so intense that no response to post-tetanic twitch stimulation can be elicited (PTC = 0) . The response to PTC stimulation depends primarily on the degree of neuromuscular blockade. It also depends on the frequency and duration of tetanic stimulation and the first post – tetanic stimulus , the frequency of the single – twitch stimulation , and the length of single twitch stimulation before tetanic stimulation .

Because of possible antagonism of neuromuscular blockade tetanic stimulation should not be given more often than every 6 minutes .

The Nerve Stimulator:

The wave form should be monophasic and rectangular.

The length of the pulse should not exceed 0.2 – 0.3 msec.

Stimulation should be at constant current.

Battery operated.

Battery check is desirable.

Should be able to generate 60-70 ma and not >80 ma

Built –in warming system & current level display is Desirable.

Polarity of electrodes should be indicated.

Modes desirable

TOF –single and repeatitive mode.

Single twitch – 0.1 and 1.0 HZ

Tetanic stimulation -50 HZ.

Built in time constant system to facilitate PTC.

Atleast one DBS – preferably DBS 3,3 .

Stimulating electrodes:

Made of disposable pregelled silver or silver chloride surface electrodes of

conducting area 7-8 mm in diameter. When the needle electrodes are used.They should be placed subcutaneously but never in a nerve.

Site of nerve stimulation:

The Ulnar nerve is the most popular site .Electrode should be applied on the volar aspect of the wrist .Distal electrode is applied 1 cm proximal to the point at which the proximal flexion crease of wrist crosses radial side of the tendon to the flexor carpi ulnaris muscle .The proximal electrode should be placed 2-5 cm proximal to the distal electrode .The stimulation elicits finger flexion and thumb adduction. The placement of negative electrode distally elicits greatest neuromuscular response .

Sensitivity of muscles to neuromuscular blocking drugs:

Diaphragm is the most resistant of all the muscles to depolarizing and non-depolarizing drugs. It requires 1.4 to 2.0 times the drug than adductor pollicis. The onset of action time is shorter for diaphragm and recovery is shorter than peripheral muscles .Muscles of the larynx,and corrugator supercilli are less resistant than the diaphragm . Most sensitive are the abdominal muscles, orbicularis occuli, peripheral muscles of the limbs, geniohyoid ,massetter, upper limb muscles.

Possible causes: a) Ach receptor density. b) Ach release c) CholinestraseActivity. d) Muscle fibre composition e) Innervation ratio (no of NMJ) f) Blood flow. g) Muscle temperature.

Other evoked muscle action potentials:

Mechano –myography.

Electro-myography.

Accelero-myography

Phono-myography.

Peizo-electric myography.

Use of nerve stimulator without recording equipment:

Tactile and visual evoked response is still the most common form of clinical neuromuscular monitoring. When possible ,the response to nerve stimulation should be evaluated by feel and not by eye and the thumb response rather than that of the fifth finger should be evaluated .Both central and peripheral cooling should be avoided otherwise it may reduce the twitch tension and the TOF ratio , may affect nerve conduction , decrease the rate of release of Ach ,and muscle contractility ,increase skin impedance ,and reduce the blood flow to the muscles.

During induction of anaesthesia:

Should be attached to the patient before induction of anaesthesia but should not be turned on until after the patient becomes unconscious. Single twitch stimulus at 1HZ used to seek supramaximal stimulation. Change the mode to TOF. Neuromuscular blocking agent is injected. Trachea is intubated when response to TOF is zero.

During intra-operative period:

The muscle response to TOF nerve stimulation reappears within 4-8 min the time until return of response to TOF stimulation may be evaluated by using the post-tetanic count.

Twitch depression of 90% will be sufficient .one or two the response to TOF stimulation can be felt. The patient may breath, hiccup, even cough at the depth of block. To ensure paralysis of diaphragm the blockade should be so intense that PTC-stimulation is zero at the thumb.

During reversal of neuromuscular blockade:

Antagonism of non-depolarising block should not be initiated before atleast two response to TOF stimulation can be felt or before obvious clinical signs of returning neuromuscular function are present. To achieve rapid reversal (within

10 min) to a TOF ratio of 0.7 in more than 90% of patients , three and preferably four responses should be present at the time of neostigmine injection. Critical episodes of post-operative residual block should be an infrequent occurrence. For tactile evaluation greater sensitivity is achieved with DBS 3, 3. Even absence of manual fade in the DBS response does not exclude clinically significant blockade. Therefore, manual evaluation of response to nerve stimulation should always be considered in relation to reliable clinical signs and symptoms of residual neuromuscular blockade

Clinical Test Of Post-operative Neuromuscular Recovery:

Unreliable:

Sustained eye opening.

Protrusion of tongue.

Arm lift to opposite shoulder.

Normal tidal volume.

Normal or near normal vital capacity.

Maximum inspiratory pressure <40-50 cm H2O

Reliable:

Sustained head-lift for 5 seconds

Sustained leg-lift for 5 seconds

Sustained hand-grip for 5 seconds.

Sustained tongue depressor test.

Maximum inspiratory pressure of > or = to 40-50 cm H_2O.

6 REVIEW OF LITERATURE

Atracurium besylate is an non-depolarising neuromuscular blocking drug of intermediate duration of action . It has unique metabolism of non-specific esterase hydrolysis and Hoffmann's elimination . Spontaneous recovery of residual blockade has been recorded but was slow, needs anticholinestrase neostigmine to facilitate recovery of residual blockade .

Literature was reviewed to compare the recovery of residual neuromuscular blockade when reversed with three doses in descending order (50 ,25 ,12.5 µgms / kg) of neostigmine .

1. **Gencarelli PJ et al[39],** (1982) studied the antagonism of ORG NC 45 pancuronium and atracurium neuromuscular blockade by neostigmine and found that ED 80 for pancuronium, vecuronium, and atracurium were 45, 24,and 22 µgms respectively .

2. **Cronnelly R et al[38],** (1982) studied edrophonium : duration of action and atropine requirement in humans during halothane anaesthesia , and found that ED 80 for pancuronium , vecuronium , and atracurium were 680 , 460 , and 440 µgms / kg respectively .

3. **Jones JE et al**[7], (1988) studied using neostigmine 1.25 mg or 0.625 mg to antagonize neuromuscular blockade produced by either atracurium 0.5 mg / kg or vecuronium 0.1 mg / kg in four group of patients (n = 45) when the first EMG response of the train of four (A'0 had recovered to 10 % of control (A) . The time for A / A' and train of four ratio (D' /A') to reach 70 % was recorded . It was found that , after both atracurium and vecuronium , neostigmine 1.25 mg considerably accelerated the recovery and when compared with previous results , differed little from neostigmine 5.0 mg or 2.5 mg .

Neostigmine 0.625 mg also significantly accelerated recovery of after atracurium and was comparable to neostigmine 1.25 mg. However, with neostigmine 0.625 mg after vecuronium , recovery of D' / A' (but not A' / A) was little faster than spontaneous . Neostigmine 1.25 mg appears to be almost as effective as neostigmine 5 mg or 2.5 mg in antagonizing considerable block (90 % of depression of twitch height) produced by either atracurium or vecuronium , but neostigmine 0.625 mg is not sufficient , especially after vecuronium .

4. **Erkola O et al**[1] , (1989) studied the spontaneous recovery of atracurium and vecuronium , monitored electromyographically during 0.5 % isoflurane anaesthesia in 60 patients undergoing plastic surgery . The recovery time from T 1 75 % to TOF ratio 75 % , indicating the recovery

rate of residual neuromuscular blockade,with atracurium was about 15 min after both the initial and the second recoveries With vecuronium , the respective recovery times were significantly (P less than) longer (25.6 min and 38.5 min , respectively) . It is concluded that with vecuronium there is slower spontaneous recovery of residual neuromuscular blockade than with atracurium .

5. **Kirkegaard – Nielsen et al[2],** (1995) studied to determine the time to peak effect of neostigmine (time to peak antagonism) during vecuronium or atracurium induced neuromuscular block and to determine the effect on time to peak effect of neostigmine during atracurium induced neuromuscular block , when the dose of neostigmine is increased from 35 µ gm / kg to 70 µgm / kg and concluded that the time to peak effect of neostigmine 35 µgm / kg is about 6 to 10 min when antagonizing a constant degree of atracurium or vecuronium induced neuromuscular block at a twitch height at a point between 4% to 11% . Even though the time to peak effect was longer with atracurium than with vecuronium clinically significant differences between the antagonizing effect of atracurium versus vecuronium block was not demonstrated . The time to peak effect during atracurium induced block decreased when the dose of neostigmine was increased from 35 to 70 µ gm / kg .

6. **Harper NJ et al[3],** (1994) studied in 57 patients undergoing gynecological surgeries to establish a dose response relationship when neostigmine was given to antagonize atracurium induced block . 3 groups received neostigmine 20 ,40 ,80 μ gm / kg at 5- 10 % recovery of compound muscle action potential at the adductor pollicis (profound block) in which antagonism was prolonged by reducing the dose of neostigmine from 40 μgm to 20 μgm / kg , but not shortened by increasing the dose to 80 μgm / kg . Another 3 groups received one of these doses at 40 – 50 % neuromuscular recovery (light block) at this block there was no significant difference between the 3groups in the time taken to reach a TOF ratio of 0.7 . It was suggested that smaller doses of neostigmine than are given commonly produce adequate antagonism of atracurium induced neuromuscular block .

7. **Neilsen HK et al[4],** (1994) studied in 52 healthy women anaesthetized with thiopentone , fentanyl , droperidol , and nitrous oxide in whom spontaneous and neostigmine facilitated recovery of atracurium induced neuromuscular block monitored with PTC of TOF stimulation of the ulnar nerve and mechanomyography . The results suggest that pre-reversal time is the strongest predictor of reversal time when neostigmine is administered during intense atracurium blockade . To achieve the optimal time saving effect , neostigmine must be given 18 min (the time saved by giving neostigmine) plus 7 to 11 min (needed for neostigmine to reach its peak effect) giving a total of 25 to 29 min before TOF ratio 0.7 .

As TH 1 is between 1% and 10% 25 to 29 min before TOF ratio 0.70 is reached during spontaneous recovery , the optimal level of neuromuscular blockade for neostigmine administration in atracurium blockade is when TH1 is between 1% and 10% . And concluded that the reversal time can be predicted as 27.3 min- (0.89 x prereversal time) and the optimal time of neostigmine administration in atracurium blockade appears to be when TH1 is 1% - 10% .

8. **Fox MA et al[5],** (1987) studied antagonism of atracurium induced neuromuscular blockade with neostigmine (one or two doses of 2.5 mg) was compared , using electromyography , with spontaneous recovery . Spontaneous recovery to the TOF ratio of 70% was slow , in the order of 1 hr after a initial dose of 0.5 mg / kg and 45 min after incremental dose of 0.2 mg / kg .It is concluded that antagonism of atracurium with one dose of neostigmine is usually desirable , that two doses are unnecessary , and that the spontaneous recovery is slower than is generally realized .

9. **Goldhill DR et al[6],** (1991) studied in 36 patients in whom anaesthesia was maintained with nitrous oxide and 0.5% isoflurane an atracurium – induced neuromuscular block was either allowed to recover spontaneously or antagonized with one of 4 doses of neostigmine (15 ,35 ,55 , 75 µ gm / kg) .There appears no benefit in giving a larger dose than 35 µgm / kg of neostigmine as a single bolus.

10. **Stirt JA et al[11],** (1983) studied effects of halothane and of prior administration of suxamethonium on atracurium neuromuscular blockade . Halothane potentiated the intensity of block produced by atracurium 0.1 or 0.15 mg / kg. Duration of block was prolonged (27 %) by halothane with a small dose of atracurium (0.15 mg /kg) and was also prolonged (29 %) with larger doses of atracurium (0.4 mg /kg) . Prior suxamethonium 1 mg / kg increased intensity of block after atracurium 0.15 mg / kg from 52 % (control) to 84 % , but caused minimal change in duration of atracurium blockade .

11. **Chapple DJ et al[15],** (1983) studied the effects of various drugs used during anaesthesia on the neuromuscular blocking effect of atracurium . Clinically effective doses of diazepam, morphine, pentazocine, pethidine, ketamine ,althesin, methohexitone, septrin, lignocaine , propranolol, calcium chloride or azathioprine did not significantly alter the action of atracurium . Recovery of from atracurium was not prolonged during an infusion of hexamethonium or sodium nitroprusside , indicating that , despite the severe hypotension , the inactivation of atracurium was unimpaired . The action of atracurium was enhanced by tubocurarine, halothane, gentamycin , neomycin , and polymixin and was antagonized by adrenaline and transiently by suxamethonium . However, pretreatment with suxamethonium did not affect the subsequent block by atracurium.

12. **Parker C J et al[22],** (1993) studied in 38 patients the plasma concentration profile of atracurium and its effect on the electromyographic first response of the TOF . One of 3 techniques was used to supplement anaesthesia with 66 % nitrous oxide in oxygen , 0.9 % isoflurane ,0.5 % halothane ,or midazolam 3- 10 mg . A four parameter threshold pharmacodynamic model was fitted to the data in each patients .Compared with a group of patients anesthetized with an i.v. technique , the steady state plasma concentration producing 50% block was reduced by halothane and to a greater extent by isoflurane .The rate constant for exit from the effect compartment correlated negatively with age and was greater in female patients , but unaffected by anaesthetic technique .The values of gamma , the slope of the concentration response curve , and of the threshold were not affected significantly by age, sex ,or anaesthetic technique .

13. **Astley BA et al[25],** (1986) studied the recovery of respiration following neuromuscular blockade with atracurium 0.3 mg / kg in one group and 0.2 mg / kg of alcuronium in another group , judged by serial measurement of tidal volume , blood gas values , and peripheral neuromuscular function judged by the response of the adductor pollicis muscle were studied . adequate recovery of respiratory muscle function was present in atracurium group within 15 min of the onset of spontaneous respiration , whereas in alcuronium group took 30 min . At this time there was marked peripheral neuromuscular blockade with peak tetanic height values less than 25% of control in both groups. It was concluded that recovery of the respiratory

muscles from neuromuscular block by atracurium and alcuronium occurred more rapidly than the recovery of small muscles of the hand , but that adequate tidal volume , in the absence of other clinical signs , should not be regarded as a reliable indication of complete return of neuromuscular function.

14. **Jones RM et al[26],** (1984) studied the evoked reversal characteristics of atracurium in 21 patients using edrophonium or neostigmine and a TOF pattern of stimulation. Reversal with edrophonium was more rapid than with neostigmine. A T4 ratio of 0.5 was confirmed to be compatible with the reliable and safe reversal of atracurium induced neuromuscular blockade.

15. **Kirkegaard – Neilsen et al[36],** (1995) studied in 44 women scheduled for gynecological surgeries to evaluate the use of tactile responses of adductor pollicis to DBS and TOF for monitoring moderate and profound levels of neuromuscular blockade . The tactile responses are compared with mechanomyographical measurements in the contralateral arm during recovery from neuromuscular blockade . Time from injection of the initial dose of atracurium until tactile reappearance of the first twitch in DBS was 24.6 min median . This was more rapid than the time until reappearance of the first twitch in TOF 32.8 min ($P < 0.05$) . It is concluded that tactile evaluation of responses of DBS stimulation can estimate deeper levels of blockade than evaluation of responses to TOF.

7 MATERIALS AND METHODS

This study was conducted at Government Stanley Hospital , Chennai in the patients undergoing adeno-tonsillectomy ,and tonsillectomy.

After institutional approval and informed consent , 90 patients were enrolled in the study .

INCLUSION CRITERIA:

All ASA physical status(1 & 2) patients aged between 5 – 15 years scheduled for tonsillectomies and adeno - tonsillectomies under general anaesthesia .

EXCLUSION CRITERIA:

1. Neuromuscular disease.
2. Patients receiving any medication known to interact with neuromuscular blocking agents
3. Known allergy to any medication.
4. Anticipated difficult intubation.
5. Morbidly obese
6. ASA physical status 3, 4, & and 5.
7. Age below 5 years and more than 15 years .

PREOPERATIVE EVALUATION:

In all the patients age , body weight , preoperative blood pressure , and pulse rate were recorded .History regarding previous anaesthesia and surgeries , any significant medical illness , medications and allergy were recorded .

Complete physical examination and airway assessment was done.

Following laboratory investigations were done.

1. Haemoglobin %, packed cell volume.
2. Urine – albumin, sugar.
3. Bleeding time, and clotting time.
4. Blood - sugar, urea, creatinine.
5. Chest x-ray.
6. Electrocardiogram

PREMEDICATION:

All patients received injection atropine 20 µgm / kg intramuscularly at least 1hour prior to surgery .

INDUCTION OF ANESTHESIA:

On arrival in the operating room intravenous access was secured with 22G ,20G, 18G cannula in a vein in the dorsum of hand . Isolyte – P infusion was started.

Following monitors are connected to the patient:

1. Non invasive blood pressure
2. Precordial sthethoscope
3. Electrocardiogram
4. Pulse oximeter.
5. Neuromuscular monitor.

Basal recordings were noted.

The neuromuscular monitor was connected to the patients forearm in which the ulnar nerve is stimulated and contraction of the adductor pollicis is to be monitored the patients were systematically randomized into three groups of thirty each. Each patient was given injection pentazocine 0.5 mg / kg intravenously. After preoxygenation for 3 minutes , anaesthesia was induced with injection thiopentone 5 mg / kg over 20 seconds, after the patient

becomes unconscious single twitch stimulation was used in 1HZ to determine the supramaximal stimulation current strength required. An intubating dose of injection atracurium 0.5 mg / kg given intravenously and mask ventllation with oxygen 6 lpm done for 3-4 minutes and then endotracheal intubation done .Anaesthesia was maintained with nitrous – oxide (66 %) and oxygen (33 %) and halothane was used in 0.5 % concentration. Muscular relaxation maintained with top-up doses of atracurium 0.15 mg / kg.

AFTER THE SURGICAL PROCEDURE:

At the end of surgical procedure , the time when spontaneous respiration attempts are reappearing, the number of responses to train of four stimulation at that time was recorded. The patients were systematically randomized into three groups of thirty each. When the train of four response recorded was 3 or 4 , Reversal of neuromuscular blockade was given as follows,

Group A - Neostigmine 50 µgm / kg + Atropine 20 µgm / kg .

Group B - Neostigmine 25 µgm / kg + Atropine 20 µgm / kg .

Group C -Neostigmine 12.5 µgm / kg + Atropine 20 µgm / kg .

The following observations were recorded:

1. AT THE TIME OF NEOSTIGMINE ADMINISTRATION.

The heart rate , blood pressure , oxygen saturation , time duration from last dose of Atracurium to administration of reversal , and number of responses to TOF stimulation at the time of administration of reversal were recorded .

2. AFTER ADMINISTRATION OF NEOSTIGMINE

a) Neuromuscular recovery:

1. Time required for responses to TOF stimulation without fade from administration of neostigmine.

2. Time required for responses to DBS stimulation without fade from administration of neostigmine .

3. Time required for clinical signs (sustained head & leg lift & eye opening & hand grip) to become positive from administration of neostigmine .

b) Haemodynamic changes:

Heart rate , blood pressure , monitored every 5 minutes for 1hour after neostigmine administration and minimum and maximum parameters are recorded .

c) Adverse side effects:

Patients were monitored for nausea, vomiting, bradycardia, and hypotension were recorded.

STATISTICAL ANALYSIS:

The data was computed and all values expressed as mean +/- S.D. The data was analyzed using student independent t test , anova F test and Chi-square test as appropriate .

8 OBSERVATIONS

The study was conducted on 90 patients randomly allotted into three groups as given below. 95% Confidence level assumed for statistical tests.

DRUG DOSAGE AND SCHEDULE

Group	Dose of Neostigmine	Sample size	Abbreviation
A	50 microgram/kg	30	N1
B	25 microgram/kg	30	N2
C	12.5 microgram/kg	30	N3

DEMOGRAPHIC PROFILE

Age, Sex, Weight and Physical status are compared between three groups.

AGE DISTRIBUTION

Age	Group A	Group B	Group C
5 – 10	17	14	16
11 – 15	13	16	14

Mean Age +/- SD 9.73 +- 3.352 10.17 +- 3.239 10.0 +- 3.14

P Value – 0.87 – Not Significant (Using ANOVA F Test)

SEX DISTRIBUTION

Sex	Group A	Group B	Group C
Male	14	16	16
Female	16	14	14

P Value – 0.84 – Not Significant (Using Chi-square Test)

WEIGHT DISTRIBUTION

Weight	Group A	Group B	Group C
1 – 10	0	1	0
11 – 20	11	9	8
21 – 30	11	10	13
31 – 40	8	10	9

Mean Weight +/- SD 26.33 +- 7.608 25.77 +- 7.592 26.77 +- 7.749

P Value – 0.88 – Not Significant (Using ANOVA F Test)

PHYSICAL STATUS DISTRIBUTION

Physical status	Group A	Group B	Group B
PS – 1	22	20	21
PS – 2	8	10	9

P Value – 0.857 – Not Significant (Using Chi-square Test)

OBSERVATIONS BEFORE NEOSTIGMINE ADMINISTRATION

TIME DURATION FROM LAST DOSE OF ATRACURIUM (MIN)

Group	N	Mean	Std.Dev	ANOVA F-Test	P – Value
Group A	30	21.6	4.166	0.82	0.45
Group B	30	20.37	3.891		
Group C	30	20.6	3.856		
Total	90	20.86	3.965		

P Value – 0.82 – Not Significant (Using ANOVA F Test)

NO OF TOF RESPONSE AT REVERSAL

Group	N	Mean	Std.Dev	ANOVA F-Test	P – Value
Group A	30	3.53	0.507	0.18	0.84
Group B	30	3.6	0.498		
Group C	30	3.6	0.498		
Total	90	3.58	0.497		

P Value – 0.84 – Not Significant (Using ANOVA F Test)

HEART RATE (BPM) BEFORE NEOSTIGMINE ADMINISTRATION

Group	N	Mean	Std.Dev	ANOVA F-Test	P – Value
Group A	30	109.77	10.9	1.5	0.22
Group B	30	104.80	9.496		
Group C	30	108.33	13.231		
Total	90	107.63	11.381		

P Value – 0.22 – Not Significant (Using ANOVA F Test)

SYSTOLIC BLOOD PRESSURE BEFORE NEOSTIGMINE ADMINISTRATION

Group	N	Mean	Std.Dev	ANOVA F-Test	P – Value
Group A	30	107.33	12.299	0.22	0.80
Group B	30	109.33	11.121		
Group C	30	108.33	11.472		
Total	90	108.33	11.539		

P Value – 0.80 – Not Significant (Using ANOVA F Test)

DIASTOLIC BLOOD PRESSURE BEFORE NEOSTIGMINE ADMINISTRATION

Group	N	Mean	Std.Dev	ANOVA F-Test	P – Value
Group A	30	70.67	10.807	2.74	0.07
Group B	30	73.67	6.687		
Group C	30	68.67	6.814		
Total	90	71.00	8.487		

P Value – 0.07 – Not Significant (Using ANOVA F Test)

OBSERVATIONS AFTER ADMINISTRATION OF NEOSTIGMINE:

TIME REQUIRED FOR TOF RESPONSE WITHOUT FADE (MIN)

Group	N	Mean	Std.Dev	ANOVA F-Test	P – Value
Group A	30	4.27	1.76	3.88	0.02
Group B	30	5.17	2.001		
Group C	30	5.73	2.363		
Total	90	5.06	2.122		

P Value – 0.02 –Significant (Using ANOVA F Test)

P – Value shows significant difference. The time duration is very small and hence the difference in mean values can be neglected.

TIME REQUIRED FOR DBS RESPONSE WITHOUT FADE (MIN)

Group	N	Mean	Std.Dev	ANOVA F-Test	P – Value
Group A	30	4.83	1.821	2.85	0.07
Group B	30	5.63	1.866		
Group C	30	6.03	2.236		
Total	90	6.37	2.106		

P Value – 0.07 – Not Significant (Using ANOVA F Test)

TIME REQUIRED FOR CLINICAL SIGNS TO BE POSITIVE (MIN)

Group	N	Mean	Std.Dev	ANOVA F-Test	P – Value
Group A	30	5.967	1.7515	1.74932	0.179
Group B	30	6.2	1.9546		
Group C	30	6.93	2.4904		
Total	90				

P Value – 0.179 – Not Significant (Using ANOVA F Test)

TIME REQUIRED FOR EXTUBATION FROM NEOSTIGMINE ADMINISTRATION (MIN)

Group	N	Mean	Std.Dev	ANOVA F-Test	P – Value
Group A	30	7.93	1.837	1.58	0.21
Group B	30	8.27	2.196		
Group C	30	8.93	2.572		
Total	90	8.38	2.236		

P Value – 0.21 – Not Significant (Using ANOVA F Test)

COMPARISON OF HAEMODYNAMIC PARAMETERS BEFORE AND AFTER NEOSTIGMINE ADMINISTRATION

Systolic Blood Pressure

Group	SBP	Mean	N	Std.Dev	t-Test	P – Value
Group – A	SBP(Basal)	107.33	30	12.299	0.727	0.472
	SBP(Mean)	105.5	30	7.233		

P Value – 0.472 –Not Significant (Using Paired sample t-Test)

Group	SBP	Mean	N	Std.Dev	t-Test	P – Value
Group – B	SBP(Basal)	109.33	30	11.121	0	1.0
	SBP(Mean)	109.33	30	6.91		

P Value – 1.0–Not Significant (Using Paired sample t -Test)

Group	SBP	Mean	N	Std.Dev	t-Test	P – Value
Group – C	SBP(Basal)	108.33	30	11.472	-2.65	0.012
	SBP(Mean)	111.66	30	8.937		

P Value – 0.012– Significant (Using Paired sample t -Test)

Diastolic Blood Pressure

Group	DBP	Mean	N	Std.Dev	t-Test	P – Value
Group – A	DBP(Basal)	70.67	30	10.807	0.468	0.643
	DBP(Mean)	69.66	30	6.149		

P Value – 0.643– Not Significant (Using Paired sample t -Test)

Group	DBP	Mean	N	Std.Dev	t-Test	P – Value
Group – B	DBP(Basal)	73.67	30	6.687	1.88	0.069
	DBP(Mean)	71.66	30	4.97		

P Value – 0.069–Not Significant (Using Paired sample t -Test)

Group	DBP	Mean	N	Std.Dev	t-Test	P – Value
Group – C	DBP(Basal)	68.67	30	6.814	-2.212	0.0349
	DBP(Mean)	70.83	30	6.02		

P Value – 0.0349–Significant (Using Paired sample t -Test)

Heart Rate

Group	Heart Rate	Mean	N	Std.Dev	t-Test	P – Value
Group – A	Heart Rate(Basal)	109.77	30	10.9	8.37	0.001
	Heart Rate(Mean)	90.63	30	14.98		

P Value – 0.001–Significant (Using Paired sample t -Test)

Group	Heart Rate	Mean	N	Std.Dev	t-Test	P – Value
Group – B	Heart Rate (Basal)	104.8	30	9.496	-0.935	0.35
	Heart Rate (Mean)	106.33	30	8.22		

P Value – 0.35–Not Significant (Using Paired sample t -Test)

Group	Heart Rate	Mean	N	Std.Dev	t-Test	P – Value
Group – C	Heart Rate (Basal)	108.33	30	13.231	-6.657	0.001
	Heart Rate (Mean)	115.01	30	11.92		

P Value – 0.001–Significant (Using Paired sample t -Test)

OXYGEN SATURATION

Group	Spo2	Mean	N	Std.Dev	t-Test	P – Value
Group – A	SPO2 (Basal)	98.86	30		3.618	0.001
	SPO2 (Mean)	98.35	30	0.374		

P- Value 0.001 - Significant (Using Paired sample t- test)

Group	Spo2	Mean	N	Std.Dev	t-Test	P – Value
Group – B	SPO2 (Basal)	98.46	30		0.166	0.86
	SPO2 (Mean)	98.45	30	0.15		

P- value 0.86 -Not significant (Using paired sample t-test)

Group	Spo2	Mean	N	Std.Dev	t-Test	P – Value
Group – C	SPO2 (Basal)	98.8	30		0.0	1.0
	SPO2 (Mean)	98.	30	0.3619		

P value 1.0 -Not significant (Using paired sample t- test)

9 RESULTS

1. Statistical analysis by Anova – F test and Chi- square test showed there is no significant differences in distribution of age , sex , weight , and physical status between the three study groups .

2. Statistical analysis by Anova – F test showed that the

   a) The time required for the TOF response to recover without fade showed a mean as group A (4.27 +/- 1.76 min), group B (5.17 +/- 2.001), group C 5.73 +/- 2.122) Anova-F test -3.88, P value 0.02 shows a negligible statistical significance in speed of recovery of response to TOF stimulation.

   b) The time required for the DBS response to recover without fade showed a
   mean as group A (4.83+/- 1.821), group B (5.63+/- 1.866), group C (6.03+/- 2.236) Anova-F test 2.85 , P value 0.07 shows there is no statistical significance among three groups in speed of recovery of response to DBS stimulation.

   c) The time required for recovery of clinical signs of adequate muscle

power showed a mean for group A (5.967+/-1.7515) , group B (6.2+/-1.9546) , group C (6.93+/-2.4904) Anova –F test 1.749 ,P- value 0.179 shows there is no statistical significance in recovery of muscle power after neostigmine among three groups .

c) The time required for extubation after administration of neostigmine showed a mean for group A (7.93+/- 1.837) , group B (8.27+/- 2.196), group C (8.93+/- 2.572) Anova –F test 1.53 , P value 0.21 shows there is no statistical significance among the three groups in time required for extubation .

3) Effective extubation conditions are observed in all patients in all the three groups even though the dose of neostigmine was reduced in groups B & C .

4) Statistical analysis by paired sample t- test showed that the mean heart rate , systolic blood pressure , diastolic blood pressure , are higher in Group – C than the other groups

Group C (115.01+/-11.97, 111.6+/- 8.937, 70.83+/-6.02)

Group B (106.33+/- 8.22, 109.33+/- 6.91, 71.66+/- 4.97)

Group A (90.63+/-14.98, 105.5+/-7.233, 69.66 +/- 6.149).

10 DISCUSSION

In patients undergoing general anaesthesia requiring muscle relaxation with non - depolarising neuromuscular blocking drugs at the end of the surgical procedure the residual neuromuscular blockade needs to be reversed with anticholinestrase drugs like neostigmine which facilitates recovery from NMJ blocking agents so that patient recovers adequate muscle power to protect the airway , maintain breathing without external assistance .

Though spontaneous recovery from NMJ blocking drugs can occur through their metabolism and excretion .The process is very slow and time consuming and without documented evidence of TOF ratio of 0.9 and sufficient signs of clinical muscle power recovery, spontaneous recovery from NMJ blocking drugs could not be allowed without reversal agents.

Atracurium an NMJ blocking agent of intermediate duration of action has a novel metabolism which does not depend on hepatic or renal function. It has a potential to recover spontaneously even in patients with hepatic / renal failure.

According to “Stoelting – textbook of pharmacology & physiology[40] “, atracurium residual blockade requires lower dose of neostigmine (ED – 80 – 22µg/Kg)

In our study 3 doses of Neostigmine, in descending order from 50 µg/Kg, 25 µg/Kg, and 12.5 µg/Kg were compared in their ability to reverse atracurium in these residual NM Blockade in patients undergoing short surgical procedure –

Adenotonscillectomy and Tonscillectomics in the age groups of 5 years to 15 years with each group of 30 Nos.

The groups are compared based on the time duration of recovery of 4 responses to train of four stimulation of ulnar N, at wrist (Adductor policies), without fade recovery of 2 responses to double burst stimulation of Adductor policies without fade and time required for extubation of patient in each groups and recovery of reliable clinical signs of NM recovery.

The Adductor policies responds to train of four and double burst stimulation are assessed visually and manually (tactile) and not by graphical record.

The associated side effects and haemodynamic changes, respiratory rate and oxygen saturation are observed for 60min, after the administration of neostigmine in each group.

EXTUBATING CONDITIONS

Jones J.E. etal[7] (1988) showed that NM blockade produced by atracurium 0.5mg/Kg can be reversed with 1.25mg and 0.625mg neostigmine and both the groups had significant acceleration of recovery and differed little from neostigmine 5mg or 2.5mg but when vecuronium was reversed with 1.25mg and 0.625mg of neostigmine, the 0.625mg of neostigmine is not sufficient after vecuronium.

Erkola O et al[1] (1989) showed in 60 patients undergoing plastic surgery were given atracurium and vecuronium monitored electromyographically during 0.5% of Isofurane anaesthesia. The spontaneous recovery to POF ratio 75% was about 15 min. compared to 25.6 to 38.5 min with vecuronium.

Kirkegaard – Nielson et al[2] (1995) showed time to peak effect during atracurium induced block, decreased when the dose of neostigmine was increases from 35 – 70 µg/Kg and concluded that the time to peak effect of neostigmine 35µg/Kg is about 6 – 10min when antagonizing constant degree of atracurium induced NM Blockade at a twitch height at a point between 4% - 11%

Nielsen HK et al[4] (1994) showed the optimal level of NM Blockade for neostigmine administration when atracurium blockade is TH1 is between 1% and 10% and optimal time to give neostigmine from the last dose of atracurium must be 18min and concluded that reversal time can be predicted as 27.3min (0.89 x Pre reversal time)

FOX M A et al[5] (1987) showed spontaneous recovery of TOF ratio to 70% is 1 hr after initial dose of 0.5mg/Kg and 45min after incremental dose of 0.25mg/Kg and that the spontaneous recovery is slower than generally recognized and it is concluded that antagonism of atracurium with 1 dose of neostigmine is usually desirable.

GOLDHILL D R et al[6] (1991) showed that in 36 patients maintained with nitrous

oxide and 0.5% of Isoflurane and atracurium induced NM Block reversed with 1 of 4 doses of neostigmine (15, 35, 55, 75μg/Kg) concluded that no benefit in giving a larger dose than 35μg of neostigmine as a single bolus.

ASTLEY B A et al[25] (1986) showed the recovery of respiration following NM blockade with atracurium was within 15min of last dose of atracurium before adequate recovery of peripheral NM function judged by response of adductor policies muscle and showed that adequate tidal volume in the absence of other clinical signs and should not be regarded as reliable indication of complete return of NM function.

In the present study neostigmine was administered after recovery of spontaneous breathing efforts and number of TOF response was (mean group A – 3.53, group B – 3.6, group C – 3.6, P – value – 0.84) between 3 and 4 and among the 3 groups, no. of TOF response at reversal is not significant.

After administration of neostigmine time required for TOF response recovery without fade in min had a mean of 4.27 min in group – A, 5.17 in group – B, 5.73 in group – C. This minor difference in speed of recovery was shown to be significant by statistical test. The P – value 0.02 even though clinically not significant.

Time required for DBS response without fade (min) showed a mean of 4.83 in group – A, 5.63 in group – B, 6.03 in group – C. P – Value of 0.07. There is no

significant statistical difference among the 3 groups.

When comparing time required for extubation from neostigmine administration(min) showed mean of 7.93 in group – A, 8.27 in group – B, 8.93 in group – C and there is no statistically significant difference.

Clinically acceptable extubating conditions are obtained in all the 3 groups under study and all the patients had reliable signs of clinical muscle power recovery for extubation. The mean time for recovery of adequate muscle power were group A – 5.97 , group B – 6.2 , group C – 6.93 min , P- value is 0.179 shows there is no statistical significance among the three groups . This shows atracurium induced neuromuscular blockade could be reversed with clinically insignificant difference in speed of recovery even with lower dose of neostigmine (25µg, 12.5µg).

HAEMODYNAMIC CHANGES

The neostigmine is an anticholinestrase. In addition to nicotinic receptor effects, it also acts on the muscarinic receptors and can produce parasympathomimetic action on the heart and slows down the heart rate. To avoid the muscarinic effects of neostigmine an anticholinergic drug like atropine is given along with neostigmine.

In our study the group A (50µgm/kg) had significant reduction in mean heart rate after administration of neostigmine (90.3+/-14.98) compared with the mean of

heart rate before neostigmine administration (109.76+/-10.9) P value 0.001. The group C had significantly higher heart rate (115.01+/-11.97) compared with mean of basal heart rate (108.33+/-13.231), this may be due to the unopposed action of atropine because of the lower dose of neostigmine in group C (12.5 µgm/kg) .

In the group A 2 patients had bradycardia (58, 59 respectively) treated with atropine 20µgm/kg. This may be because of neostigmine administration in higher dose (50µgm/kg)

The group A and B had no significant difference in systolic and diastolic blood pressures when compared with systolic and diastolic blood pressure before neostigmine administration.

The group C had statistically higher systolic blood pressure (111.6+/-8.937) than the basal value (108.33+/-11.472) and statistically significant increase in diastolic blood pressure (70.83+/-6.02) compared with basal values (68.66+/-6.814).But these changes in the diastolic blood pressure are clinically insignificant .

ADVERSE EFFECTS

The adverse effects looked upon were nausa, vomiting, bradycardia, hypotension because of the muscarinic effect of neostigmine.

In our study only two patients of group A had bradycardia and no patient in any of the three groups had nausea or vomiting or hypotension. The bradycardia was treated with atropine 20µgm/kg intravenously.

11 SUMMARY

1. The lower doses of neostigmine (25 µgm/kg, 12.5 µgm/kg) provided equally effective reversal of atracurium induced neuromuscular blockade as the higher dose (50µgm/kg)

2. The mean time required for recovery of adequate muscle power after neostigmine in all three groups were approximately equal and difference among them were statistically insignificant (5.97+/-1.7515, 6.2+/-1.95. 6.93+/-2.49) .

3. The mean time required for extubation in all the three groups approximately equal (7.93+/-1.837, 8.27+/-2.196, 8.93+/-2.572 respectively)

4. The mean time for the recovery of the two responses to DBS without any fade in response was also approximately equal in all the three groups (4.83+/-1.821, 5.63+/-1.866, 6.03+/-2.236)

5. The heart rate showed a significantly lower mean value in group A (neostigmine 50µgm/kg) 90.63+/-8.37 compared with basal value 109.76+/-10.9.

6. The group A had 2 patients with significant bradycardia who received the higher dose (50μgm/kg) of neostigmine
7. No patient in any of the three groups had side effects like nausea, vomiting, or hypotension.

12 CONCLUSION

1. Satisfactory facilitation of recovery from residual neuromuscular blockade produced by atracurium (given in intubating dose 0.5mg/kg and incremental dose of 0.15 mg/kg) are achieved with reduced doses of neostigmine (25μgm/kg and 12.5 μgm/kg).

2. Lower doses of neostigmine avoid the significant decrease in heart rate.

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Chapter 9, Page no:232

PROFORMA

A STUDY COMPARING THREE DIFFERENT DOSES OF NEOSTIGMINE (50µgm/kg, 25µgm/kg,12.5µgm/kg) AS REVERSAL AGENT FOR FACILITATION OF RECOVERY FROM RESIDUAL NEUROMUSCULAR BLOCKADE WITH ATRACURIUM .

Name : Group :

Age : Sex :

Ip. No :

Weight :

Unit :

PREOPERATIVE ASSESSMENT:

Airway	:	Hb	:	
General condition	:	Urine	:	Albumin.
Pulse rate	:			Sugar.
Blood pressure	:	Blood	:	sugar.
C.V.S.				Urea.
R.S.		Serum	:	creatinine.

E.C.G. electrolytes.

Chest-X- ray Bleeding time.

A.S.A: Clotting time.

Platelet count:

PREMEDICATION :

Injection Atropine 20µgm/kg IM 60 minutes before surgery.

INDUCTION OF ANAESTHESIA:

Injection Pentazocine 0.5mg/kg I.V.

Pre-oxygenation

Induction agent Thiopentone – 5mg/kg I.V.

Identification of supramaximal stimulus in mA.

Relaxant for intubation Atracurium 0.5mg/kg.

Intubation.

Relaxant for surgery Atracurium 0.15mg/kg.

Ventilation: Intermittent positive pressure ventilation.

Halothane 0.5% used until the conclusion of surgery.

Nitrous oxide / oxygen in ratio of 66 % / 33% used for maintenance of anaesthesia .

OBSERVATIONS BEFORE ADMINISTRATION OF NEOSTIGMINE.

Time of administration of loading dose of atracurium 0.5mg/kg:

Time of administration of top-up dose of atracurium:

1st	2nd	3rd	4rth	5th	6th	7th	8th

OBSERVATIONS MADE AT THE TIME OF ADMINISTRATION OF NEOSTIGMINE & ATROPINE.

Time of last dose Of atracurium given.	TOF response at the time of administration of reversal agent .	Heart rate.	Blood pressure. Sbp/dbp.	SpO2.

OBSERVATIONS MADE AFTER ADMINISTRATION OF NEOSTIGMINE:

Time req. for TOF response without fade	Time req. for DBS without fade	Time req. for clinical Signs to be present.	Time of extubation.

HAEMODYNAMIC AND RESPIRATORY PARAMETERS AFTER EXTUBATION .

PARAMETERS	5	10	15	20	25	30	35	40	45	50	55	60min
Heart rate												
Blood pressure												
SpO2												
Resp.rate.												

ADVERSE EFFECTS: