POST-OPERATIVE RESIDUAL PARALYSIS AFTER USE OF ATRACURIUM OR CISATRACURIUM IN MAIN OPERATING THEATRES POST ANAESTHESIA CARE UNIT OF THE KENYATTA NATIONAL HOSPITAL

A DISSERTATION PRESENTED IN PART FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF A MASTER OF MEDICINE DEGREE IN ANAESTHESIA, UNIVERSITY OF NAIROBI

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POST- OPERATIVE RESIDUAL PARALYSIS AFTER USE OF ATRACURIUM OR CISATRACURIUM IN THE MAIN OPERATING THEATRES POST ANAESTHESIA CARE UNIT OF THE KENYATTA NATIONAL

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DECLARATION

I declare that this dissertation is my original work and has not been submitted for a degree award in any university.

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This dissertation has been submitted for the degree of Masters of Medicine in Anaesthesiology with my approval as a university supervisor.

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DEDICATION

Special dedication to the Almighty God for the strength and courage to have reached this far.

To my entire family for their tremendous support and guidance. Special thanks to my wife and daughter, my mother and late father, my brother Mwalimo Charles and Sr. Dorothy for their continued support and encouragement throughout my training.

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List of abbreviations

1. ASA ..... American Society of Anaesthesiologists
2. AChE..... Acetylcholinesterase
3. Ach..... Acetylcholine
4. ARDS..... Acute Respiratory Distress Syndrome
5. ICP..... Intracranial pressure
6. ICU..... Intensive Care Unit
7. KNH..... Kenyatta National Hospital
8. NMBD..... Neuromuscular blocking drugs
9. NMJ..... Neuromuscular junction
10. PACU..... Post-anaesthesia Care Unit
11. SPSS..... Statistical Package for the Social Sciences.
12. TOF..... Train Of Four
13. TOFR..... Train Of Four Ratio
14. UON..... University of Nairobi

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1.0: ABSTRACT

1.1: Background: Neuromuscular blocking drugs are routinely used in major operations especially those that require muscle relaxation. Adequate muscle relaxation creates optimal conditions for easy access of the site of operation.

After the operation the effects of most of these drugs if not all have to be reversed by the appropriate antagonist. Occasionally the effects are not adequately reversed and the patients may have some degree of residual paralysis.

Complete reversal can be assessed clinically or objectively using a nerve stimulator after the administration of the reversal agent. Adequate reversal eliminates the possibility of residual paralysis and therefore prevention of the associate complications.

1.2: Methodology: The study was an observational descriptive study. It was carried out in the main theatres post anaesthesia care unit of the Kenyatta National Hospital. Data was captured electronically using SPSS and analysis done using SPSS version 17 and presented graphically. Residual paralysis was assessed clinically using head lift for five seconds and holding tongue depressor between the incisors and objectively by measuring TOFR using TOF watch on the ulnar nerve.

1.3: Results: A total of 263 patients aged between 18 and 65 years who had undergone elective surgery were assessed. Post operative residual paralysis was found to be about 14% and 50% using clinical and objective assessment respectively on arrival to post anaesthesia care unit. A TOFR ratio of less than 0.9 was used to indicate residual paralysis.

1.4: Conclusion: There is significant Post operative residual paralysis in the main operating theatres post anaesthesia care unit of the Kenyatta National hospital. This was found to be higher using clinical assessment as compared to objective assessment using the TOFR.

2.0: INTRODUCTION AND LITERATURE REVIEW

Muscle relaxants were first used nearly a century ago after the use of inhalational anaesthetics. Curare, originally used in hunting and tribal warfare by the South Americans is the first known neuromuscular blocking agent (1, 2). Neuromuscular blocking drugs have become an established part of anaesthetic practice since Griffin and Johnson in Montreal first described the use of curare to facilitate muscle relaxation in a healthy man undergoing an appendicectomy in 1942(8). They suggested that *d*-tubocurarine is a safe drug to use during surgery to provide skeletal muscle relaxation.

In 1943 Cullen described its use in 131 patients who had received general anesthesia for their surgery. In 1954, Beecher and Todd suggested that there was an increase in mortality in patients receiving d-tubocurarine (3, 4). The increased mortality was probably due to a general lack of understanding of the pharmacology of neuromuscular blockers and their antagonism. The effect of residual neuromuscular blockade postoperatively was not appreciated, guidelines for monitoring muscle strength had not been established, and the importance of pharmacologically antagonizing any residual blockade was not understood.

Since the discovery of curare and its use in anaesthesia many other neuromuscular blocking agents have been discovered. The mode and site of action has been well established. These discoveries have revolutionized muscle relaxation in anaesthesia (5). They basically have their effect at the neuromuscular junction on the nicotinic muscle type receptors (6).

The neuromuscular junction is made up of a motor neuron and a motor endplate with a synaptic cleft dividing them (7).

Neuromuscular blocking agents can be classified according to the mode of action at the NMJ, duration of action and structural formula.

1) Mode of action at the NMJ

a) Depolarizing drugs e.g. succinylcholine the only drug in clinical use and decamethonium
b) Non- depolarizing drugs e.g. pancuronium, cisatracurium, atracurium

2) Duration of action

a) Ultra-short acting e.g. succinylcholine
b) Short acting e.g. mivacurium, rapacuronium
c) Intermediate acting e.g. atracurium, cisatracurium, rocuronium, vecuronium
d) Long acting e.g. pancuronium, d-tubocurarine

3) Structural classification of the non-depolarizing drugs

a) Aminosteroids e.g. pancuronium, vecuronium
b) benzylisoquinolines
   Naturally occurring e.g. curare
   Synthetic e.g. atracurium, mivacurium

Depolarizing neuromuscular blocking drugs are agonist of acetylcholine at motor end plate nicotinic receptors. They depolarize postsynaptic and extrajunctional receptors. Succinylcholine is the only drug available in clinical practice. It is hydrolyzed by plasma cholinesterase. Upon injection of succinylcholine and before paralysis is manifest, some disorganized muscular activity is frequently observed. This phenomenon is called fasciculation. The main indication is to facilitate tracheal intubation. It is especially indicated for "rapid sequence induction," when a patient presents with a full stomach and the possibility of aspiration of gastric contents is high. In this situation manual ventilation of the lungs is avoided, to reduce the probability of aspiration because of excessive intra-gastric pressure caused by gas forced via face mask.

Non-depolarizing NMBDs antagonize the action of ACh in a competitive manner at the postsynaptic nicotinic receptor. By binding to one or both alpha-subunits they prevent access of ACh to depolarize the receptor. Binding of antagonist to nicotinic receptors is dynamic, with repeated association and dissociation. 92% of the post-junctional nicotinic receptors must be occupied to produce a complete block (8).

The ideal NMBD is non-depolarizing with a rapid onset of action. The duration of action should be predictable and if necessary readily reversed by anticholinesterases. It should not cause any haemodynamic disturbance and should not release histamine. It should not cause

anaphylaxis, malignant hyperthermia or prolonged block. It should be ready mixed for use, stable at room temperature, painless on injection and cheap to use. Its elimination should be independent of organ function and have no active or toxic metabolites (9, 10, and 11).

The effects of non-depolarizing NMBDs can be reversed by anticholinesterasases once recovery from the blockade has commenced e.g. neostigmine, or edrophonium that inhibits the action of acetylcholinesterase at the NMJ. This allows acetylcholine to accumulate therefore competing with the diminishing concentration of the neuromuscular blocking drug at the post-synaptic membrane and potentiating recovery from residual neuromuscular blockade. Anticholinesterase drugs especially neostigmine also inhibits the action of plasma cholinesterase and may therefore potentiate and lengthen the blockade produced by succinylcholine. Edrophonium is shorter acting than neostigmine and only suitable for reversing a light to moderate block. Neostigmine is the most reliable. It is necessary to give an anti-muscarinic agent at the same time with neostigmine to counteract parasympathomimetic side-effects of these drugs. In contrast, the novel cyclodextrin sugammadex can be used to reverse any degree of neuromuscular block produced by rocuronium or vecuronium (12, 13).

NMBD's have several clinical uses. They are used in combination with other anaesthetic drugs to create optimal operating condition especially where muscle relaxation is required e.g. abdominal surgery and to facilitate tracheal intubation. They are also used in intensive care in some patients on mechanical ventilation to suppress spontaneous respiration and improve patient ventilator synchrony and enhance gaseous exchange e.g. patients with ARDS or tetanus. They can also be used to reduce the risk of barotrauma, muscle oxygen consumption and movement in patients with increased ICP. They do not have analgesic or sedative properties therefore adequate sedation and analgesia is essential prior to their use (14).

Atracurium and cisatracurium which are intermediate synthetic benzylisoquinolines were used in this study. The duration of action of these drugs is between 20-50 minutes.

2.1: Atracurium

It's a Bisquaternary ammonium benzylisoquinolines compound of intermediate duration of action. It is degraded via Hofmann degradation which is a non-enzymatic process directly related to temperature and pH and through non-specific ester hydrolysis involving a group of tissue esterases not related to plasma or acetylcholinesterases.

The byproducts are laudanosine which has CNS stimulating effects and acrylate fragments. The duration of action is not affected by age, renal or hepatic function therefore no dose adjustment is required.

It releases histamine in dose related manner which is associated with hypotension, tachycardia and skin flushing.

2.2: Cisatracurium

This is an isomer of atracurium. Its metabolism is similar to that of atracurium.

Duration of action is not related to dose and age. Though anaphylactic reactions have been reported it's devoid of histamine release therefore no cardiovascular side effects as compared to atracurium.

2.3: complications of residual paralysis

Postoperative residual paralysis after use of neuromuscular blocking drugs remains a common occurrence despite the use of pharmacological agents to reverse their effects (15, 16, 17).

A study by Mojtaba Rahimi Varposhti et al in postoperative residual block in post-anaesthesia care unit more than two hours after the administration of a single intubating dose of atracurium showed that 22.2% of the patients had a TOFR of <0.9 , however after 2 hours every patient had a TOFR of greater than 0.9 (18). This study gave the impression that two hours after administration of an intermediate acting NMB and arrival to PACU can probably guarantee absence of residual paralysis.

In a study done by Glen S Murphy et al on association of atracurium with postoperative recurarization showed that at the time of tracheal extubation 58% and 88% of the patients had

a TOFR of <0.7 and <0.9 respectively. In the same study TOFR done on arrival in PACU showed 8% and 32% of the patients had TOFR of <0.7 and <0.9 respectively (19).

C. McCaul et al in a study of the association of residual post-curarization with atracurium showed that at antagonism 70% of patients had a TOFR of <0.7 and 65% had a TOFR of <0.7 at extubation. In this study the sole variable was found to be the duration of surgery (20).

Post-operative residual paralysis is associated with several complications most of which involve the upper airway and upper gastrointestinal system muscle groups resulting in significant morbidity including severe permanent brain damage or death due to severe hypoxic brain injury. (21.22).

Even minimal degrees of neuromuscular blockade (TOFR <0.9) will cause functional impairment of the muscles of the pharynx and oesophagus causing significant incoordination of these muscles resulting to frequent aspiration (23, 24, 25).

Residual paralysis also delays discharge from the PACU (26, 27).

It also impairs hypoxic ventilatory response probably due to effects of muscle relaxants on the carotid body (28).

Minor degree of residual paralysis can cause diplopia, decreased grip strength, inability to maintain incisor teeth apposition, inability to sit up without assistance, severe facial weakness, including inability to maintain an airtight seal around a drinking straw with the lips, and overall generalized muscle weakness (29, 30).

2.4: Assessment of residual paralysis

Several studies have documented persistence of neuromuscular block in PACU even after adequate use of acetylcholinesterase inhibitors. The incidence has been shown to range between 4%-50% depending on the type of NDMB drug used and the diagnostic criteria used. Considering the complications associated with residual paralysis it's therefore prudent to monitor the level of neuromuscular blockade both intra- and postoperatively. This can only be achieved by developing simple guidelines to prevent, diagnose and treat residual paralysis whenever NMBDs are used (31).

More often than not, the degree of neuromuscular blockade during and after anesthesia is evaluated using clinical criteria alone but this has been associated with significant residual neuromuscular paralysis postoperatively (32). Objective monitoring of the degree of neuromuscular block during and after anesthesia should therefore reduce the complications associated with residual neuromuscular blockade (33, 34).

During and recovery from anesthesia it is impossible to evaluate muscle power by testing muscle strength but instead anaesthesiologists use clinical tests to assess muscle power directly and to estimate neuromuscular function indirectly. All these tests, however, are influenced by factors other than the degree of neuromuscular blockade e.g. the duration of action of the NMBD used, duration of the operation, level of analgesia and whether a reversal agent was given making them very subjective. Therefore, nerve stimulation remains the most reliable and objective method of assessing the level of neuromuscular blockade.

The only agents that have been widely used to reverse neuromuscular blockade are acetylcholinesterase inhibitors.

A new selective binding agent, sugammadex has become available in some parts of the world (35). This agent belongs to a group of cyclodextrins (cycloamyloses), which make up a family of cyclic oligosaccharides (36).

Sugammadex acts by forming a 1:1 inclusion complex with some steroidal non-depolarizing NMBAs thereby terminating their action. After intravenous administration, sugammadex binds to free rocuronium molecules in the plasma, decreasing their free concentration. This creates a concentration gradient, promoting the movement of rocuronium away from the NMJ back into the plasma where it is further encapsulated by sugammadex molecules terminating their action rapidly (37, 38). Sugammadex is ineffective against succinylcholine and benzylisoquinolines e.g. atracurium because it cannot form a complex with these agents (39).

Absence of residual paralysis means that neuromuscular transmission has recovered fully and the patient can breathe normally, cough and clear secretion, and can protect the upper airway from aspiration of gastric contents. Prior to the introduction of TOF stimulation in the 1970's anaesthesiologist used to rely on clinical assessment. TOFR has now become the gold standard for assessment of the absence of residual paralysis. In a study conducted by Ali *et*

al. on six healthy awake volunteers, vital capacity, inspiratory force, and expiratory force were found to be normal when TOFR was more than or equal to 0.70 therefore this was considered to indicate adequate neuromuscular recovery (40).

However in the 1990s, several studies conducted indicated that clinically, significant neuromuscular block still persists at TOFR of 0.7. In human volunteers, hypoxic ventilatory drive was shown to be decreased by vecuronium up to a TOFR more than or equal to 0.9 (41). In another study, the ability to swallow was also found to be impaired when the TOFR was less than 0.9 (42). Masseter muscle function, assessed by the ability to hold a tongue depressor between one's teeth against resistance, did not return to normal up to a TOFR of between 0.8–0.9 (43). Therefore, a revisited TOFR threshold more than or equal to 0.90, obtained by force measurement or mechanomyography, was proposed in the late 1990s.

2.5: Clinical evaluation

This is based on some tasks that can be performed by the patient or evoked stimulation of motor nerve assessed by tactile or visual evaluation (44).These are subjective methods which depends on the clinician and the results cannot be reproduced.

Clinical evaluation can only be done to a patient who can cooperate and follow instructions. These tests basically asses the muscle power.

Sustained head or leg lift for more than 5 seconds is commonly used but this has been shown to correspond to a TOFR of 0.45 to 0.75 which is below the recommended TOFR of 0.9 and above (45).

Ability to hold a tongue depressor between the teeth as someone tries to pull it out is the most reliably clinical test corresponding to TOFR of >0.8-0.9 (46).

The above two clinical tests are the most reliable however a TOFR of 0.9 is still above the equivalent of these tests. Though hand grip and eye opening are also used but are not as sensitive as the above two tests.

Others are respiratory test which include recovery of spontaneous breathing using adequate tidal volume, ability to take deep breaths and return to normal of end tidal carbon dioxide.

2.6: Patterns of Nerve Stimulation

Neuromuscular function can be assessed by applying a supramaximal stimulus to a peripheral nerve then measuring the associated muscular response. The reaction of a single muscle fiber follows one or none law but the response of the whole muscle depends on the number of fibers activated.

A motor unit consists of a motor neuron and a muscle separated by a neuromuscular junction. If a nerve is stimulated with sufficient intensity, all fibers supplied by the nerve will react, and the maximum response will be triggered. The nerve that is used should have a motor element, must be close to the skin and the contraction in the muscle which the nerve supplies must be visible (47).

After administration of a neuromuscular blocking drug, the response of the muscle decreases in parallel with the number of fibers blocked. The reduction in response during constant stimulation reflects the degree of neuromuscular blockade. For this to be effective a supramaximal stimulus is required therefore the electrical stimulus applied is usually at least 20% to 25% above that necessary for a maximal response. This is achieved by increasing the voltage until a point where there is no response then increased by an additional 20-25 %. However a supramaximal electrical stimulation hurts, which is not a concern during anesthesia, but during recovery the patient may be awake enough to experience the discomfort of nerve stimulation. Though submaximal current during recovery has been advocated, the accuracy is unacceptable (48, 49, 50).

In clinical practice five patterns of nerve stimulation are commonly used.

1. Train-of-four stimulation.
2. Single twitch stimulation
3. Tetanic stimulation.
4. Post-tetanic count stimulation.
5. Double burst stimulation

2.7: Train-of-four stimulation

This is the most commonly used mode of nerve stimulation in clinical practice. It was developed in 1970 by Ali and colleagues in an attempt to provide a clinical tool to assess neuromuscular block in anaesthetized patients (51) and quantitatively estimates the degree of neuromuscular blockade without the need for a controlled response.

This method constitutes application of four supramaximal stimuli at 2Hz over 2 seconds on a peripheral nerve (commonly the ulnar nerve) and repeated at least after every 10 seconds either intermittently or continuously. Lee in 1975 correlated the movements of the fifth finger with recorded thumb abduction in response to TOF stimulation of the ulnar nerve (52).Other nerves that may be used include the facial nerve and peroneal nerve or posterior tibial nerve of the lower extremity. The amplitude of the four evoked supramaximal stimuli is then measured and the degree of blockade quantified.

TOFR is obtained by dividing the amplitude of the fourth response to the amplitude of the first response.

On administration of a NMBD the fourth response to TOF stimuli is decreased relative to the first stimuli and forms the basis of fade in this class of drugs. This progressive decrease in twitch height is known as fade. Therefore in the absence of a NMBD the TOFR is 1.0.

The absence of the 4^{th} response represents 75-80% receptor blockade. When 85%, 85-90% and 90-98% of Ach receptors are blocked, T3, T2, T1 responses are abolished respectively (53). The fade in response to TOF stimulation provides the basis for evaluation.

The advantage of this method is that it is simple and does not require a control value before NMBD is administered. It is more sensitive in detecting subtle degree of NMB than single twitch stimulation. It can be used in patients who are awake because it is less painful than tetanic stimulation. Exaggerated response because of post tetanic Potentiation does not occur even if it's repeated within 2 minutes (54).

2.8: Single Twitch Stimulation

Single supramaximal stimuli are applied to a peripheral frequency of between 0.1- 1.0 Hz however 0.1Hz is generally used. The twitch height remains normal until 75% of Ach receptors are blocked but completely disappear when 90% to 95% of

Ach receptors are occupied. (55).This pattern of stimulus the twitch height must be obtained before muscle relaxant is administered and specialized recording equipment is required to compare subsequent responses. The response of stimulation is frequency dependent because frequency is increased to 1.0 Hz, fade will be observed and a faster onset of NMB can develop in the stimulated muscle. (56)

2.9: Tetanic Stimulation

This uses a high frequency of 50-200Hz with a supramaximal stimulus for a set time normally 5 seconds. A sustained muscle contraction is observed in the absence of NMBD. On administration of NMBD the muscle, depending on the degree of blockade will show signs of fade that is; it will be unable to sustain a muscular contraction. This pattern of nerve stimulation is very sensitive even in minor degrees of neuromuscular block but it is limited by the fact that tetanic stimulation is extremely painful in patients who are awake (57, 58).

2.10: Post-tetanic count stimulation

This is used to evaluate intense neuromuscular block when there is no response to single twitch or TOF stimulation. It involves application of 50Hz tetanic stimulation for 5 seconds followed, 3 seconds later by1 Hz single supramaximal stimulus (59, 60).

2.11: Double burst stimulation

This enables the clinician to manually (tactile) detect subtle degree of NMB without the use of recording devices.

2.12: Measuring Evoked Muscle Responce

It is difficult to assess muscle responses by visual or tactile means. The evoked response can be quantified using the following methods;

1) Mechanomyography (MMG) – Measures evoked muscle tension
2) Electromyography (EMG) – measurement of evoked electrical response of a muscle
3) Acceleromyography (AMG) – measurement of acceleration of a muscle. This method was used in this study.
4) piezoelectric neuromuscular monitor (P_ZEMG) - measurement of the evoked electrical response in a piezoelectric film sensor attached to the muscle
5) Phonomyography (PMG). - Contraction of skeletal muscles generates intrinsic low-frequency sounds, which can be recorded with special microphones.

3.0: JUSTIFICATION

There is increasing evidence that residual neuromuscular block is common in most PACU (61, 62). In KNH operating theaters' though not well documented but on interviewing the nursing staff in PACU, they concur that there has been occasions where reversal had to be repeated or patients had to be re-intubated. This is an indication that some patients are transferred to PACU while inadequately reversed from neuromuscular blocking drugs. These patients are evaluated clinically for adequate reversal from neuromuscular blockade as opposed to objective assessment using a nerve stimulator. A study done in 2000 in KNH PACU by Jane W Gitahi showed that 21.2% patients were inadequately reversed after use of long acting neuromuscular blocking agents. In this study however a TOFR of >0.7 was used to indicate adequate reversal and in most of these patients (90.8%) pancuronium a long acting NMBD was used (63). Currently a TOFR of 0.9 and above is considered as adequate reversal as compared to 0.7 previously (64). Also the incidence of residual paralysis depends on the NMBD used being lower in intermediate acting drugs as compared to the long acting ones (65,66).

Atracurium and cisatracurium are the commonly used intermediate NMBD's in KNH operating theatres.

This study was intended to find out the incidence of residual paralysis after use of intermediate acting neuromuscular blocking agents that is atracurium and cisatracurium following adequate reversal with an anticholinesterase, neostigmine in KNH PACU.

3.1: Hypothesis

Residual paralysis does not occur in the P.A.C.U of Kenyatta National Hospital operating theatres after use of atracurium and cisatracurium, followed by adequate reversal using an anticholinesterase, neostigmine.

4.0: OBJECTIVES

4.1: Broad objective.

To determine the incidence of post-operative residual paralysis in patients who have received atracurium or cisatracurium upon arrival in the operating theatres P.A.C.U of Kenyatta National Hospital.

4.2: Specific Objectives

i. To determine the incidence of post operative residual paralysis using the clinical assessment
ii. To determine the incidence of post operative residual paralysis using TOFR
iii. To compare post operative residual paralysis assessed by clinical tests as opposed to gold standard using TOFR
iv. To make recommendations in relation to these findings

5.0: METHODOLOGY

5.1: Study Design

This was an observational descriptive study.

5.2: Study Area

The study was conducted at the Kenyatta National Hospital main operating theatres post-anaesthesia care unit after approval was obtained from Kenyatta National Hospital/ University of Nairobi ethics and research committee.

5.3: Study Population

All patients aged between 18 and 65 years undergoing elective surgery at the Kenyatta National Hospital main theatre and had fulfilled the inclusion criteria.

5.4: Inclusion and Exclusion Criteria

Inclusion Criteria

- All ASA I and II patients who were undergoing elective surgery under general anaesthesia in the main operating theatres
- All patients who consented to participate in the study
- All adult patients aged between 18 and 65 years

Exclusion Criteria

- Patients who were undergoing emergency surgery
- Those who did not consent patients
- Patients who were undergoing elective surgery and did not require atracurium or cisatracurium or other NDMB was administered
- Any patient who had history of neuromuscular disease

5.5: Sampling Procedure

Study population was chosen randomly from elective theatre lists prepared by the surgical team and those who had fulfilled the inclusion criteria.

5.6: Sample Size

Fischer's formula was used to calculate the sample size;

$n = \frac{z^2pq}{d^2}$

Where;

n= sample size

z= standard normal deviation at the required confidence level of 1.96

p= is the proportion in the targets that is the incidence of residual paralysis after use of intermediate acting NMBD in this study atracurium and cisatracurium was used and was estimated to be 22.2% (18)

q = 1- p

d = target margin of error put at 0.05

Therefore;

$n= (1.96)^2 \times 0.222 \times (1- 0.222) / (0.05)^2$

n = 264.402

The desired sample size was therefore 264.

5.7: Study Procedure and data collection

Patients in the elective surgery lists were reviewed in the ward a day before the operation. Focused passed and current medical and surgical history was taken followed by a thorough physical examination. The patients were then classified according to ASA classification. An informed consent was then obtained from those who fulfilled the inclusion criteria. Data was the collected using a pre-tested questionnaire in the post operative care unit in the main theatres.

5.8: Anaesthetic procedure

General anaesthesia was induced intravenously with either propofol or sodium thiopentone or combination of ketamine and midazolam. Atracurium or cisatracurium was used as the muscle relaxant. Anaesthesia was then maintained with halothane or isoflurane and nitrous oxide and oxygen. Monitoring of neuromuscular blockade using a nerve stimulator was not done intra-operatively. At the end of surgery the patients were reversed with neostigmine 0.04 -0.08mg/kg and assessed clinically by the anaesthetist for adequate reversal. The patient was then transferred to PACU, received by the nurse and once was consensus reached that the patient was adequately reversed the anaesthetist was allowed to leave P.A.CU.

The patient was then assessed clinically using head lift for five seconds and ability to hold the tongue depressor between the teeth. The TOFR was then measured using TOF watch (organon) by cleaning the patient's skin and placing two E.C.G electrodes over the ulnar nerve at the wrist joint. A piezoelectric ceramic wafer (transducer) was strapped to the thumb and the acceleration of the stimulated adductor pollicis was measured. This was displayed as a percentage on the screen. This was done on arrival after the patient was received by the nurse and then repeated every 5 minutes up to the 15^{th} minute.

Note was made on the following and recorded

i. Premedication agents
ii. Induction drugs
iii. Analgesic agents used
iv. Duration of surgery
v. Total dose of muscle relaxant used
vi. Time of the last dose of the relaxant before reversal
vii. The dose and time neostigmine was administered

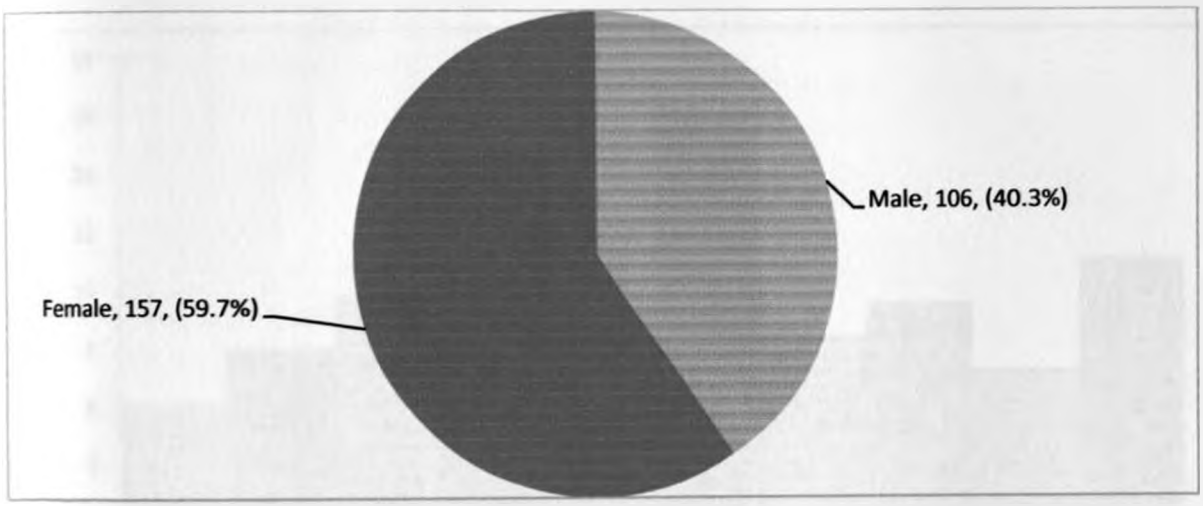
5.9: Data management and analysis

The data collected was coded, entered and managed in Microsoft access database then analysed using SPSS.

6.0: RESULTS

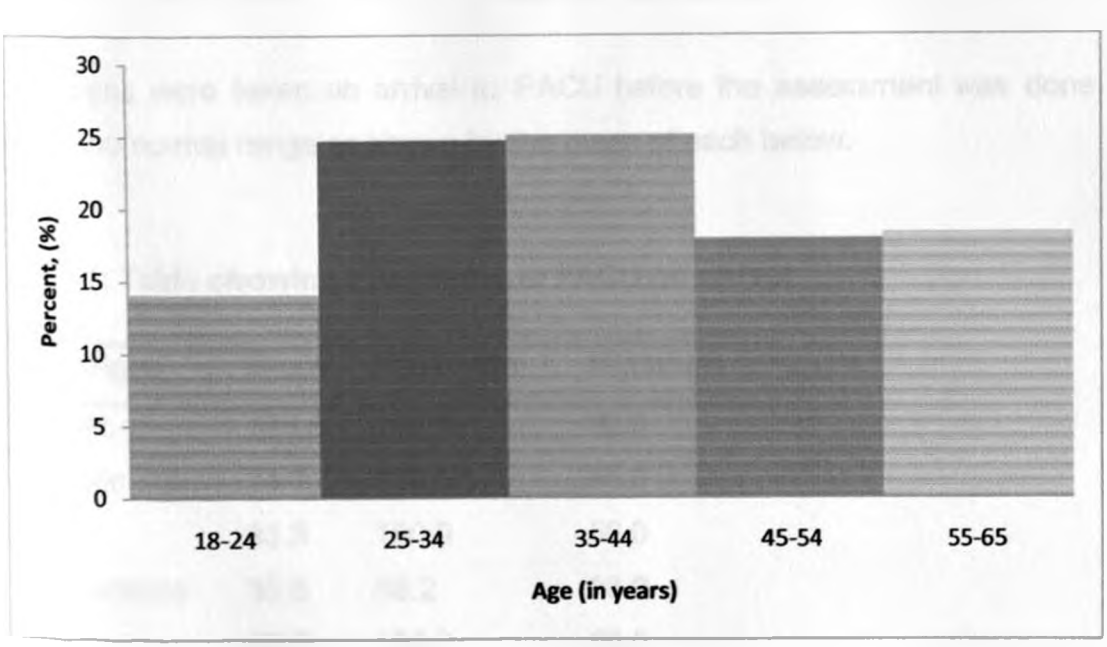
A total of 263 patients were assessed 106 males and 157 females representing 40.3% and 59.7% respectively as shown below.

Fig 1: Pie chart showing female and male distribution



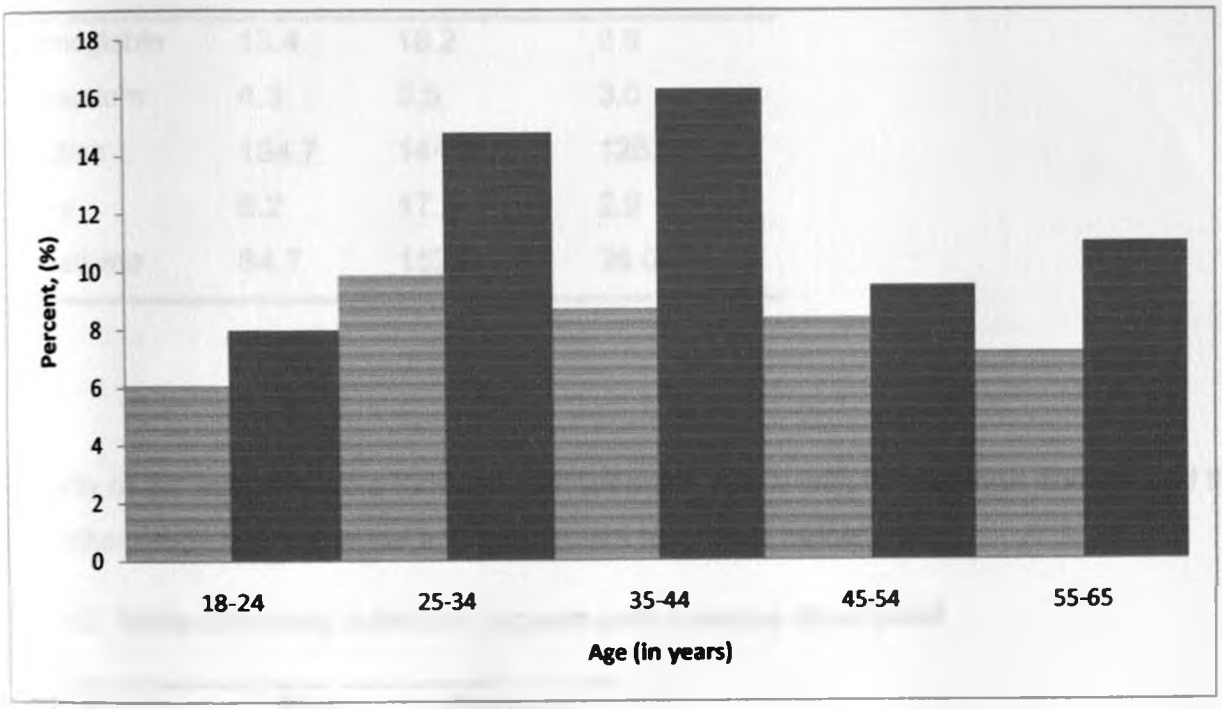
Most of the patients assessed were aged between 25 and 44 years. This reflects the age distribution in the Kenyan population. This is shown below.

FIG 2; Bar graph showing the age distribution



The male patients had small variation in age distribution but majority of females were aged between 24 and 44 years. A significant number of females aged between 55 and 65 years most likely associated with gynaecological surgeries done at this age. Bar graph below shows this distribution

FIG 3: Bar graph: female and male age distribution



Vital signs were taken on arrival to PACU before the assessment was done. Majority were within the normal range as shown by the mean of each below.

Table 1: Table showing Vital Signs at PACU on arrival

Vital Signs	Mean	Maximum	Minimum
Systolic	123.5	189.0	82.0
Diastolic	74.1	112.0	45.0
PR	83.8	180.0	56.0
Temperature	36.6	38.2	36.0
PO_2	98.7	100.0	90.0

Preoperative routine laboratory results were noted. They were within an acceptable range. This reflects the ASA classification I and II of the patients assessed. The table below shows the vital signs.

Table 2: Laboratory results preoperatively

Test	Mean	Maximum	Minimum
Hemoglobin	13.4	18.2	8.9
Potassium	4.3	5.5	3.0
Sodium	134.7	144.0	126.0
Urea	5.2	17.5	2.9
Creatinine	84.7	152.0	28.0

Majority of the patients were induced with propofol. A few with thiopentone sodium and the rest with other drugs like ketamine and midazolam as shown below

Table3: Table showing Induction agents and average does used

Agent	Freq.	Percent
Propofol	222	84.4
Thiopentone	27	10.3
others	14	5.3

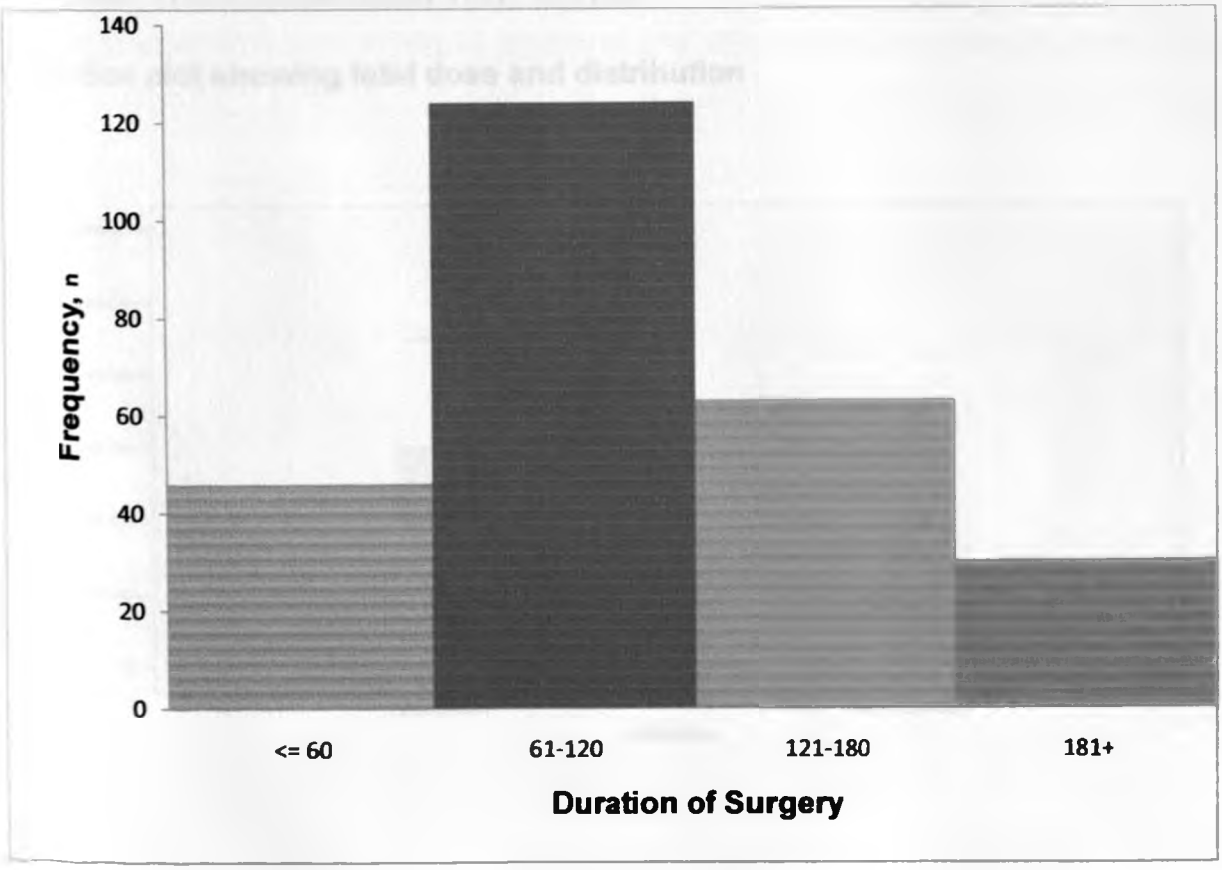
Other drugs that were used and have some effect on adequate reversal because of sedative effects are opioids analgesics. These drugs are as shown in the table below.

Table 4: Table showing Opioids used and the average doses

Agent	Freq.	Percent
Fentanyl	120	45.6
Pethidine	130	49.4
Morphine	30	11.4

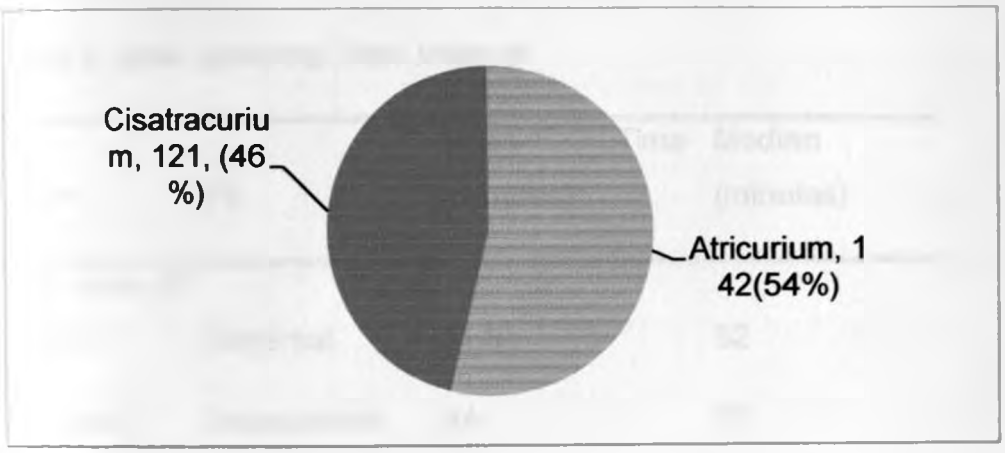
Most operations took between one and two hours with the a few lasting more than three hours as shown in bar graph below.

FIG 8: Bar graph showing the Duration of Surgery



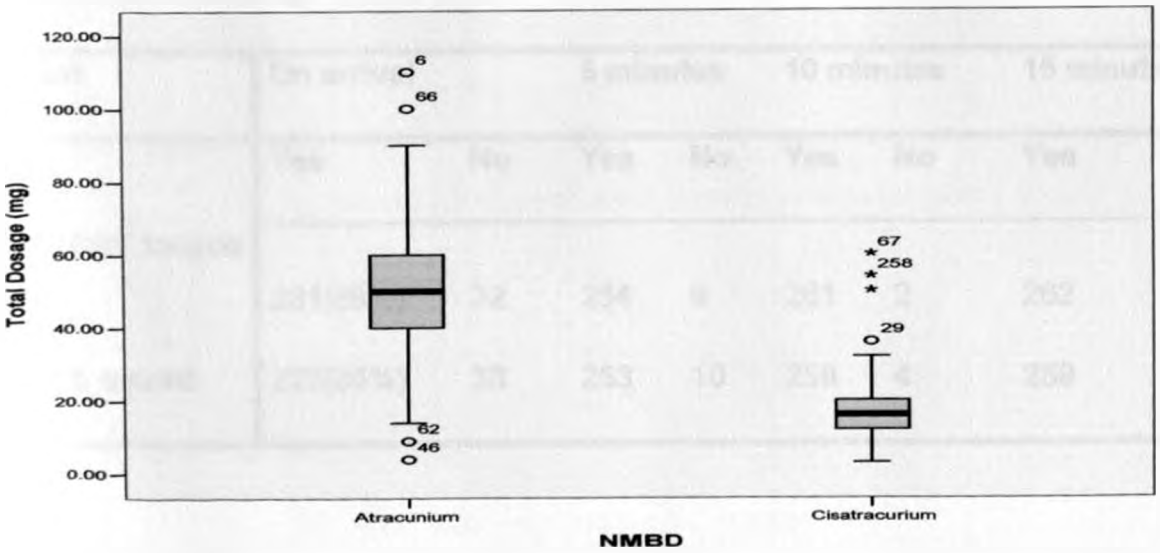
Atracurium and cisatracurium were used in this study. 54% and 46% of the patients were given atracurium and cisatracurium respectively. This is represented in the pie chart below.

FIG 5: Pie chart showing Neuromuscular blocking drugs used



The total dose of the NMBD used varied depending on the duration of surgery. Mean dose was within the normal recommended dose though they were a few patients who received very high total doses. This is shown below in the box plot

Fig 6: Box plot showing total dose and distribution



The duration of time between the last dose of NMBD and the administration of the reversal agent was noted. The time of administration of the reversal agent and the assessment was also noted. The table below shows these time intervals

Table 5: table showing Time interval

From	To	Mean Time (minutes)	Median (minutes)
Last dose of NMBD	Reversal	51.6	52
Reversal	Assessment	34	27

Clinical assessment done in PACU on arrival and after every 5 minutes up to the 15th minute was recorded. By the 15th minute most patients could perform both tests as shown below.

Table 6: Table showing Clinical Assessment in PACU

Clinical Test	On arrival		5 minutes		10 minutes		15 minutes	
	Yes	No	Yes	No	Yes	No	Yes	No
Ability to Hold tongue depressor	231(88%)	32	254	9	261	2	262	1
Head lift for 5 second	225(86%)	38	253	10	259	4	259	4

Clinical assessment done on arrival and duration of surgery was compared. This was to assess the effect of duration of surgery and residual paralysis. This is presented in the two tables below. (For the two clinical tests)

Table 7: Ability to hold tongue depressor on arrival against duration of surgery

	Ability to hold tongue depressor on arrival				
Duration of Surgery	No, (n)	%	Yes, (n)	%	p value
<= 60	5	15.6	41	17.7	
61-120	14	43.8	110	47.6	0.862
121-180	8	25.0	55	23.8	
181+	5	15.6	25	10.8	

Table 8: Head lift for 5 seconds on arrival against duration of surgery

	Head Lift for 5 Seconds on arrival				p value
Duration of Surgery	No	%	Yes	%	
<= 60	5	13.2	41	18.2	
61-120	14	36.8	110	48.9	
121-180	13	34.2	50	22.2	0.243
181+	6	15.8	24	10.7	
Total	**38**	**100.0**	**225**	**100.0**	

Clinical assessment to compare residual paralysis of the individual drugs as show in the table below.

Table 9: Neuromuscular Blocking drug against Clinical Assessment

		Neuromuscular Blocking Drug used				
		Atracurium		Cisatracurium		p value
Ability to hold tongue depressor		Freq.	%	Freq.	%	
	Arrival					
	No	17	12.0	15	12.4	0.916
	Yes	125	88.0	106	87.6	
	5 Mins					
	No	4	2.8	5	4.1	0.559
	Yes	138	97.2	116	95.9	
	10 mins					
	No	1	0.7	1	0.8	0.909
	Yes	141	99.3	120	99.2	
	15 Mins					
	No	0	0.0	1	0.8	0.278
	Yes	142	100.0	120	99.2	
Head lift for 5 seconds	**arrival**					
	No	20	14.1	18	14.9	0.856
	Yes	122	85.9	103	85.1	
	5 mins					
	No	4	2.8	6	5.0	0.365
	Yes	138	97.2	115	95.0	
	10 Mins					
	No	2	1.4	2	1.7	0.872
	Yes	140	98.6	119	98.3	
	15 Mins					
	No	2	1.4	2	1.7	0.872
	Yes	140	98.6	119	98.3	

Objective assessment was done using TOF watch and the overall TOFR recorded as shown below

Table 10: Table showing overall TOFR assessment at PACU

TOFR	Mean	Median	< 90, n (%)	≥ 90, n (%)
On Arrival	0.86	0.90	132 (50.2)	131 (49.8)
5 minutes	0.94	1.00	62 (23.6)	201 (76.4)
10 minutes	0.99	1.00	9 (3.4)	254 (96.6)
15 minutes	1.00	1.00	2 (0.8)	261 (99.2)

The TOFR of those patients who used atracurium and cisatracurium was assessed and recorded. This was to compare the residual paralysis of the two drugs as shown in the table below.

Table 11: Neuromuscular Blocking drug against TOFR

	Neuromuscular Blocking Drugs				
TOFR	**Atracurium**		**Cisatracurium**		**p value**
	Freq.	%	Freq.	%	
On arrival					
< 90	64	45.1	68	56.2	0.072
>= 90	78	54.9	53	43.8	
5 minutes					
< 90	28	19.7	34	28.1	0.111
>= 90	114	80.3	87	71.9	
10 minutes					
< 90	3	2.1	6	5.0	0.206
>= 90	139	97.9	115	95.0	
15 minutes					
< 90	0	0.0	2	1.7	0.126
>= 90	142	100.0	119	98.3	

TOFR was assessed against the duration of surgery as shown below.

Table 12: TOFR on arrival against the duration of surgery

TOFR on Arrival					
	< 90		≥ 90		p value
Duration of Surgery	**No.**	**%**	**No.**	**%**	
<= 60	19	14.4	27	20.6	
61-120	66	50.0	58	44.3	0.461
121-180	30	22.7	33	25.2	
181+	17	12.9	13	9.9	
Total	**132**	**100**	**131**	**100**	

Both clinical and objective assessment was done against the duration of surgery and the odds ratio calculated, this was to show the probability of residual paralysis in relation to the duration of surgery. This is shown in the table below.

Table 13: Table showing the shortest and longest duration of surgery and both clinical and objective assessment and the Odds (OD) ratio

		Duration of Surgery					
		181+		≤ 60			
	On Arrival	Freq.	Percent	Freq.	Percent	OR	p value
Tongue							
	No	5	50.0	5	50.0	1.6	0.465
	Yes	25	37.9	41	62.1		
Head lift							
	No	6	54.5	5	45.5	2.1	0.269
	Yes	24	36.9	41	63.1		
TOFR							
	< 90	17	47.2	19	52.8	1.9	0.190
	≥90	13	32.5	27	67.5		

7.0: DISCUSSION

A total of 263 patients were assessed 157 females and 106 males which represented 59.7% and 40.3% respectively. Majority were in the age group of between 25 to 44 years. All these patients were either ASA class 1 or 11 therefore the vital the laboratory results done preoperatively were within normal range. The observed vital signs on arrival to PACU and subsequently after every 5 minutes up to the 15th minute were generally within normal ranges.

142 patients were given atracurium and 121cisatracurium representing 54% and 46% respectively. The induction agents used were propofol 222 patients and thiopentone 18 patients. Anaesthesia was maintained with halothane or isoflurane and nitrous oxide. Opioids analgesics used were within the normal recommended dosages. Majority of the operations took between 60 and 120 minutes.

Post operative residual paralysis is still a common finding in most PACU's (19, 67). Several clinical tests have been used. The gold standard for assessment of adequate reversal is the train of four ratio (TOFR) of equal or greater than 0.9.

The most reliable clinical tests which correspond to a TOFR of about 0.45-0.86 are the head lift for 5 seconds and the tongue depressor test. A study done in awake volunteers by Kopman AF Yee PS et al showed that there is some relationship between TOFR and the clinical signs and symptoms of residual paralysis (46).

Clinical assessment done on arrival did not show any significant difference between the ability to hold the tongue depressor and head lift for 5 seconds which was about 14%. Subsequent assessment using clinical tests showed improvement and by the 15th minute majority of the patients could perform both tests. This could not be compared to the results obtained using TOFR which showed significant residual paralysis of about 50%.

The quality of clinical assessments of neuromuscular function requires that patients are awake and cooperative and without the residual effects of other anesthetic drugs on arrival in the PACU (46). These conditions are not always possible to achieve.

When these patients were assessed using the TOFR a significant post operative residual paralysis was found as defined using a TOFR > or = 0.9. This means that most of these patients could perform the clinical tests in the presence of some degree of residual paralysis.

A study done in 2000(3) where a TOFR of 0.7 was used found the incidence of 21.2% which could be attributed to the lower TOFR that was recommended then (63).

Neuromuscular blocking agents are used in surgery especially where adequate muscle relaxation is required e.g. abdominal surgery. There is no ideal NMBD currently in the market though some are associated with fewer side effects. The mode of action is the same in all these drugs but they differ in their pharmacodynamics and pharmacokineticskinetics. The duration of action and elimination and subsequent termination of their action play a role in post operative residual paralysis (10).

In this study atracurium and cisatracurium, intermediate acting NMBD which are degraded via a non-enzymatic process the Hofmann degradation were used. This process is affected by the body temperature and pH. These drugs do not necessarily require anticholinesterase for reversal as shown by Hayes *et al.* that there was no significant difference in the incidence of postoperative residual block between patients who did or did not have their block reversed (15).However previous studies have shown a high incidence of residual paralysis when reversal was not administered. Administration of reversal agents at the end of anesthesia after use of these drugs is advised to avoid the known deleterious consequences of residual paralysis especially when objective assessment is not available. However, the administration of reversal agent does not guarantee the lack of residual paralysis in all patients when they arrive in the PACU (68,69). Hayes *et al.* reported that even after administration of the reversal there was still significant post operative residual paralysis in PACU. Bertrand Debaene et al. showed that after single intubating dose of intermediate acting non-depolarizing muscle relaxant, residual paralysis occurred in the PACU more than 2 hours after administration. Whatever the thresholds used to define residual paralysis is common, even more than 2 hours after the administration of muscle relaxant (67). Where there is adequate recovery assessed objectively then administration of reversal serves no purpose.

In this study the duration of time from the last top up of NMBD to administration of anticholinesterase was 51.6 minutes. This is a factor in adequate recovery because of the non enzymatic breakdown of these drugs. The average duration between the administration of the reversal and assessment of the TOFR was 34 minutes this compares to a study done by

Kopman et al which found that 17% of patients had a TOFR of < 0.9 after administration of reversal where rocuronium was used (70).

Residual paralysis i.e. a TOF ratio of 0.7-0.9 impair pharyngeal muscle function, reduce lower esophageal sphincter tone, increase the risk of aspiration, produce upper airway obstruction and impair the hypoxic ventilatory response. This has resulted to significant morbidity and mortality postoperatively. The key solution to this problem is adequate monitoring both intra- and post-operatively using objective assessment. This will ensure that there is complete recovery of neuromuscular function before the time of tracheal extubation.

There is a great variation in individual sensitivity to neuromuscular blocking drugs. Some of these factors which may prolong reversal should be excluded like in individuals with obstructive sleep apnoea, the elderly and hypothermia. Rapidity of recovery has been shown to depend on the intensity of blockade at the time of reversal. It has been suggested that neostigmine dose should be titrated according to the degree of reversal.

It was found that reduced doses of neostigmine may be adequate to reverse low levels of residual paralysis. Therefore quantitative assessment of residual paralysis is advocated to reduce and treat residual paralysis adequately (71, 72).

Four patients who had residual paralysis on the 15th minute were given a second dose of neostigmine. They were transferred to the ward after they were assessed and found to be adequately reversed. Two of these patients were under general anaesthesia for more than 180 minutes while one was given an opioid analgesic upon arrival to PACU.

8.0: CONCLUSION AND RECOMMENDATIONS

8.1: Conclusion

1) There is minimum clinical residual paralysis after the use of intermediate NMBD in the KNH main operating theatres PACU.
2) There is significant post operative residual paralysis of about 50% as assessed objectively using TOFR of equal or greater than 0.9
3) Post operative residual paralysis was found to be greater when assessment was done objectively using TOFR as compared to clinical assessment.

8.2: Recomendations

1) Standard protocols on assessment of recovery using the most reliable clinical tests should be established.
2) Objective assessment using the TOFR especially in those patients considered to be at a higher risk of residual paralysis.
3) Intra-operative monitoring of the level of blockade so as to minimize unnecessarily higher doses of NMBDs.
4) In the absence of objective monitoring it is safe to use reversal agents in all the patients even in those who are well reversed clinically
5) A local study to compare the incidence of post-operative residual paralysis in those patients administered neostigmine and those that are not reversed.

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APPENDIX 1

INFORMED CONSENT FORM

I ..... of ..... do hereby give consent for myself/my ..... to participate in the above study whose nature, benefits and risks have been fully explained to me by the researcher. I have not been coerced or promised any financial benefit to participate. I have been assured of confidentiality and that am free to withdraw from the study at any stage.

Signature .....

I ..... Confirm that I have explained the nature of the study to the participant detailing the benefits and risks of the study and have not withheld any information. I have assured the participant of her/his confidentiality and the right to withdraw from the study at any stage.

Signature.....

FOMU YA IDHINI

Mimi.....kutoka.....ninaku bali/ninamkubaliya..... wangu kushiriki katika huu utafiti.Nimeelezwa juu ya manufaa na madhara yanayoambatana na utafiti. Ninakubali kushiriki kwa hiari yangu bila kushurutishwa au kuahidiwai manufaa ya kifedha.

Nimeahidiwa kuwa habari zote nitakazotoa zitahifadhiwa kwa siri na nina uhuru wa kujiondoa kwenye utafiti huu wakati wowote

Sahihi .....

Mimi.....naidhinisha kwamba nimemualezea mshiriki kwa kina kuhusu utafiti huu,manufaa na madhara yote bila kuficha..Pia nimemweleza kuwa habari zozote atakazozitoa zitahifadhiwa kwa siri na kwamba ana uhuru wa kujiondoa kwenye utafiti huu wakati wowote bila masharti yeyote.

Sahihi ya mtafiti.....

APPENDIX 2

CONSENT EXPLANATION

Introduction

My name is Dr Mwasaru Nestor Daniel a post graduate student in anesthesia at the University of Nairobi. I conducted a survey on post-operative residual paralysis after use of intermediate acting non-depolarizing neuromuscular blocking drugs in the P.A.C.U of the Kenyatta National Hospital main operating theatres. The study took place between March and April 2012.

Purpose of the study

The aim of this research was to determine the incidence of post-operative residual paralysis in patients who had received intermediate acting non-depolarizing neuromuscular blocker upon arrival in the P.A.C.U of Kenyatta National Hospital main operating theatres.

Interventions.

The procedure involved use of a questionnaire after clinical assessment and measurement of the train of four using a TOF watch. This was done upon arrival in the P.A.C.U and repeated after every 5 minutes up to the 15^{th} minute. There were interventions except for four patients who still had residual paralysis after 15 minutes and a repeat dose of neostigmine 2.5mg and atropine 1.0mg was given.

Voluntary participation.

The participation in this study was voluntary and the patients had the right to withdraw from the study at any stage.

Risks and benefits.

The participants were not exposed to any risks. Those that had residual paralysis after 15 minutes were treated accordingly. The results and recommendations will be made available to the ethics and research committee, University of Nairobi and KNH.

Confidentiality.

Confidentiality and research ethics was maintained throughout the research. Serial numbers instead of names were used to identify participants.

Contacts

For any further clarification or question please feel free to contact the following.

Dr Mwasaru N D – 0722764664 or mwalimon@yahoo.com

Dr Nabulindo S – 0721418587 or susanenabulindo@yahoo.com

Prof Ngumi Z - 0722218921 or zngumi@gmail.com

APPENDIX 3

QUESTIONNAIRE

Serial No.....

1. Initials ..... Sex .....
2. Diagnosis .....
3. Operation .....
4. ASA Classification.....
5. Age (yrs) a)18 – 24 ☐
   b) 25 - 34 ☐
   c) 35 - 44 ☐
   d) 45 - 54 ☐
   e) 55 - 65 ☐
6. Vital Signs (on arrival to PACU)

BP..... PR ..... Temp..... PO2.....

7. laboratory work-up

Test	Results
Haemoglobin	
Potassium	
Sodium	
Urea	

Creatinine	
Others (specify)	

8. Premedication

Agent	Dose	Time
Pethidine		
Atropine		
Aminoglycosides		
Others (specify)		

9. Induction agents

Agent	Dose	Time
Propofol		
Thiopentone		
Ketamine		
Midazolam		
Diazepam		
Others (specify)		

10. Maintenance

Agent	
Halothane	
Isoflurane	
Nitrous oxide	
Oxygen	
TIVA (specify)	
Others (specify)	

11. Analgesia

Drug	Dose	Time
Fentanyi		
Pethidine		
Morphine		
Remifentanyl		
Diclofenac		
Paracetamol		
Others (specify)		

12. Neuromuscular blocking drug

Atracurium	Time							Total
	Dose							
Cisatracurium	Time							
	Dose							

13. Duration of surgery

a) ≤60 mins ☐

b) 61-120 mins ☐

c) 121-180mins ☐

d) ≥181mins ☐

14. Reversal agent used

Drug	Total Dose	Time
Neostigmine (0.04-0.08)		
Atropine		
Others (specify)		

15. Clinical assessment

Clinical Test	On arrival	5 minutes	10 minutes	15 minutes
Ability to hold tongue depressor				
Head lift for 5 seconds				

16. TOFR assessment

On arrival	5 minutes	10 minutes	15 minutes	

APPENDIX 4

ASA Physical Status (PS) Classification System*:		
ASA PS Category	**Preoperative Health Status**	**Comments, Examples**
*ASA PS classifications from the American Society of Anesthesiologists		
ASA PS 1	Normal healthy patient	No organic, physiologic, or psychiatric disturbance; excludes the very young and very old; healthy with good exercise tolerance
ASA PS 2	Patients with mild systemic disease	No functional limitations; has a well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy
ASA PS 3	Patients with severe systemic disease	Some functional limitation; has a controlled disease of more than one body system or one major system; no immediate danger of death; controlled congestive heart failure (CHF), stable angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure; bronchospastic disease with intermittent symptoms
ASA PS 4	Patients with severe systemic disease that is a constant threat to life	Has at least one severe disease that is poorly controlled or at end stage; possible risk of death; unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure
ASA PS 5	Moribund patients who are not expected to survive without the operation	Not expected to survive > 24 hours without surgery; imminent risk of death; multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy
ASA PS 6	A declared brain-dead patient who organs are being removed for donor purposes	

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2nd February 2012

Dr. Mwasaru Nestor Daniel
Dept. of Surgery
School of Medicine
University of Nairobi

Dear Dr Mwasaru

Research proposal: "A study of Post-operative residual paralysis after use of Intermediate Acting Non-depolarizing Neuromuscular Relaxants in the Post-operative care unit of the Kenyatta N. Hospital, Main Operating theatres" (P476/11/2011)

This is to inform you that the KNH/UON-Ethics & Research Committee has reviewed and **approved** your above revised research proposal. The approval periods are 2nd February 2012 – 1st February 2013.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimens must also be obtained from KNH/UON-Ethics & Research Committee for each batch.

On behalf of the Committee, I wish you a fruitful research and look forward to receiving an executive summary of the research findings upon completion of the study.

This information will form part of the data base that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH/UON-ERC

c.c. The Deputy Director CS, KNH
The Principal, College of Health Sciences, UON
The Dean, School of Medicine, UON
The Chairman, Dept. of Surgery, UON
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