Incidence and determinants of post-operative neuromuscular blockade in patients undergoing surgery at the University Teaching Hospital, Lusaka, Zambia

By

TINGADANE MUNGA

A dissertation submitted to the University of Zambia in partial fulfilment of the requirements for the award of the Degree of Master of Medicine in Anaesthesia and Intensive Care

THE UNIVERSITY OF ZAMBIA

LUSAKA

2020

DECLARATION

I, Tingadane Munga, do hereby declare that this dissertation presented for the award of the degree of Master of Medicine in Anaesthesia and Intensive Care has not been previously submitted neither in whole or in part at this or any other University.

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CERTIFICATE OF APPROVAL

This dissertation of Dr Tingadane Munga is approved as fulfilling part of the requirements for the award of the degree of Master of Medicine in Anaesthesia and Intensive Care conferred by the University of Zambia.

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ABSTRACT

Background: Anaesthesia provision has advanced significantly over the years. This is in part due to the development of newer, better drugs. Some of these drugs include the muscle relaxants, which paralyze the body. However, drugs, particularly muscle relaxants, are not without fault. Various Western studies have highlighted some adverse effects of some of these drugs, such as post-operative muscle paralysis, leading to infections and death. Despite the routine use of these drugs at the University Teaching Hospital, there is lack of information regarding their potential for post-operative paralysis in the surgical population at this hospital.

Methods: a prospective cross-sectional study was conducted between September 2019 and January 2020 involving adult patients who presented for surgery (elective or emergency) at the University Teaching Hospital theatres. Data was collected from 38 participants regarding their demographics, anaesthetic factors including the type of drug, and surgical factors such as duration of operation. A Train of Four Scanner which measures the level of muscle function was used to determine post-operative paralysis in the participants. The datasets obtained were compared using Mann-Whitney tests, and a multivariable regression model was used to analyse determinants of non-recovery.

Results: post-operative neuromuscular blockade was determined to be present in 13 (34.2%) participants presenting for surgery under general anaesthesia. The risk of residual block increased with increasing age (AOR = 1.2, 95% CI [1.09 – 1.37]; p=0.044), use of pancuronium alone (AOR=2.3; 95% CI [1.21 – 14.9]; p=0.038) or in combination with atracurium (AOR=3.2; 95% CI [1.73-8.41]; p=0.029) and administering reversal agent (AOR = 1.9, 95% CI [1.33 – 5.21]; p=0.048).

Conclusion: Post-operative neuromuscular blockade had an incidence of 34.2% in the study population. It was significantly associated with use of pancuronium, even despite subsequent reversal. In fact, use of neostigmine for reversal was associated with inadequate muscle recovery as determined by the train of four ratio.

DEDICATION

To my wife, Martha, our children Chikondi and Mwangala, and my parents Xaphanaiah T. Munga and Irene M. Kalaluka for your love, companionship and support during this project.

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I would like to recognise the unwavering love and support endowed upon me by my family, particularly my wife, as they accorded me the opportunity to pursue this academic endeavour and dedicated their time and resources toward attaining this goal.

Finally, I would like to thank my God for enabling me with the requisite knowledge, strength and determination to achieve my heart's desire and to use these gifts to serve my fellow man.

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List of Abbreviations and Acronyms

ASA = American Society of Anaesthesiologists

BP = Blood Pressure

GPPF = Graduate Proposal Presentation Forum

mg = milligrams

NMBA = Neuromuscular Blocking Agent

PACU = Post Anaesthesia Care Unit

RNMB = Residual Neuromuscular Block

ToF = Train of Four

ToFR = Train of Four Ratio

UTH = University Teaching Hospital (Lusaka)

CI = Confidence Interval

Definition of Terms

Neuromuscular blockade (NMB): paralysis of the body's voluntary muscles as a result of particular drugs, the neuromuscular blocking agents.

Neuromuscular blocking agents (NMBAs): a class of drugs used in anaesthesia that cause a reversible paralysis of the body's muscles.

Post-operative (= **residual) neuromuscular blockade:** the presence of detectable paralysis of the body's muscles after the operation (i.e. when it is no longer required).

Train of Four (ToF) Ratio: a method of measurement of neuromuscular function using a quantitative neuromuscular blockade monitor, **e.g. TOF Scan**. By attaching the TOF Scan to the skin overlying a nerve, impulses from the device stimulate the nerve and cause four muscle twitches which are then measured by the same device. The ratio of the last to the first twitch is calculated by the device and displayed as the ToF ratio**.** A ToF ratio less than 0.9 is regarded as residual neuromuscular blockade.

American Society of Anaesthesiologists (ASA) Physical Status: a scale used to assess and grade a pre-operative patients' state of health based on the presence or absence of certain disease conditions such as diabetes and high blood pressure (hypertension).

CHAPTER ONE: INTRODUCTION

1.1 Background

The conduct of anaesthesia has evolved from its daring beginnings over several decades. There was recognition of the need to make the patient more comfortable as the surgeon attempts to remove the physical disease from the body. As the anaesthetic techniques evolved over time including the use of equipment such as electronic monitoring and ventilators, there was significant progress with the nature of surgical procedures performed. The art of medicine, and surgery in particular, had been revolutionised. One fundamental component of this revolution was the introduction of newer drugs to facilitate anaesthesia and surgery (Hunter, 2017).

One such group of drugs were the neuromuscular blocking agents (or muscle relaxants) first described some 77 years ago (Griffith and Johnson, 1942). These agents paralyse the body's muscles responsible for voluntary movements. They may have a short, intermediate or long duration of action. They act by competitively inhibiting the action of acetylcholine at the nerve to muscle interface thereby preventing muscle contraction. Acetylcholine is a chemical in the body that acts as a messenger between nerves and muscles. It is produced within the motor nerve and stored in vesicles near the nerve terminals ready for release (Figure 1.1). When the nerve is stimulated by an impulse, the molecules are released and attach to the muscle via specific receptors. From here, they induce end plate potentials which result in electrical changes within the muscle fibres. This causes calcium release from the sarcoplasmic reticulum which interacts with intracellular proteins to induce contraction of the muscle through a process called excitation-contraction coupling (Fletcher, 2011; Wareham, 2005; Pollard, 2005).

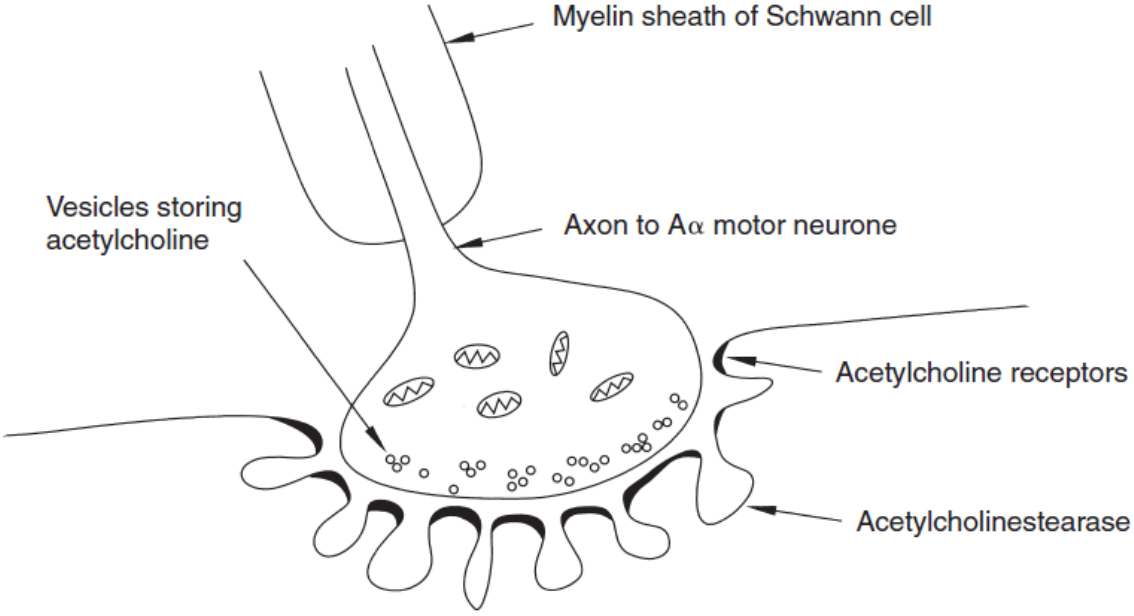

Figure 1.1 showing the structure of the neuromuscular junction, the site of transduction of the nerve impulse to muscle stimulation. Adapted from Pharmacology for Anaesthesia and Intensive Care, 3rd Edition, 2008, Cambridge University Press.

The conduct of general anaesthesia usually requires hypnosis, analgesia and muscle paralysis. Optimal neuromuscular blockade assists the anaesthetist to intubate and ventilate a well anaesthetised patient who requires a secured patent airway, and also facilitates delicate surgeries such as laparoscopic procedures. At the end of surgery, this paralysis should be fully reversed allowing the patients to maintain and protect their airway. The drugs used to reverse this paralysis are called anticholinesterases, neostigmine being an example. They act by inhibiting the enzyme that is responsible for metabolising acetylcholine at the neuromuscular junction. This increases the concentration of acetylcholine which then overcomes the inhibition imposed by the neuromuscular blockers (Hunter, 2008). Aside from the individual drug characteristics, the duration of induced paralysis may be influenced by a number of physiological and pharmacological factors. Physiological factors include temperature and serum levels of potassium and magnesium. The pharmacological factors include concomitant use of volatile anaesthetic agents and local anaesthetics.

However, soon after the widespread adoption of the neuromuscular blocking agents (NMBAs) into practice, there was an increased record of deaths following anaesthesia involving their use. A retrospective, multicentre study over 5 years, involving 599,548 anaesthetics reported a postoperative mortality rate 6 times higher in patients who had

received muscle relaxants. It was found that 63% of these deaths were from respiratory failure (Beecher and Todd, 1954). This led to concerns about the safety of their use. It was recognised that monitoring and reversal of neuromuscular blockade were quite useful in improving the level of neuromuscular function and avoiding complications postoperatively.

Monitoring of neuromuscular blockade can be either qualitative or quantitative, the latter being more reliable (Sardesai et al., 2005; Kopman et al., 2018). The Train of Four ratio is a quantitative measurement. By attaching a device (e.g. TOF Scan) to the skin overlying a nerve, impulses from the device stimulate the nerve and cause four muscle twitches which are then measured by the same device. The ratio of the last to the first twitch is calculated by the device and displayed as the ToF ratio. A ratio less than 0.9 is considered residual neuromuscular blockade (Sardesai et al., 2005). Recent publications have shown that despite use of modern monitoring techniques and the use of reversal agents, residual neuromuscular block (RNMB) still occurs in 63.5% of patients (Fortier et al., 2015). The incidence has been documented to be higher when pancuronium is used as muscle relaxant (Berg et al., 2008). This study was set out to investigate the incidence and determinants of post-operative neuromuscular blockade in the adult surgical population at the University Teaching Hospital (UTH), a tertiary level hospital in Lusaka, Zambia.

1.2 Statement of the Problem

From the literature, it is quite clear that residual neuromuscular block is a well-recognised complication associated with anaesthesia, and that it is associated with significant morbidity and mortality. In the sub-Saharan region there is a relatively high postoperative mortality rate, the associated factors with which have not been fully investigated (Biccard et al., 2019). Despite the routine use of neuromuscular blocking agents in operating theatres at the UTH in Lusaka, there is no objective form of monitoring the density of, or recovery from, neuromuscular block. Furthermore, it is not known whether the use of NMBAs is associated with RNMB in this setting. Residual block itself is associated with subjective feeling of weakness and respiratory fatigue. It may be complicated further by aspiration, hypoxia and respiratory failure and may lead to death if unrecognised as UTH recovery rooms are ill equipped to detect complications as they occur due to inadequate monitoring equipment. Anecdotally, in the previous years there have been a number of unexpected deaths in the recovery rooms.

1.3 Study Justification

Post-operative mortality rates in Africa remain persistently high compared to the global average (Biccard et al., 2019). Most of these deaths were attributed to infections, with pneumonia being the second leading cause of death. It is known from studies in high-income settings that RNMB is associated with higher morbidity and mortality. However, there has been no research work done in low-income settings to determine whether RNMB is a problem. In order to ensure adequate recovery from neuromuscular block, some form of objective monitoring is required. Quantitative monitoring using the Train of Four Ratios is reliable and used in the developed world. However, such monitoring is unavailable in resource limited facilities such as UTH. This situation, coupled with the use of long acting muscle relaxants, may predispose the surgical population at UTH to RNMB and its potential complications. A survey highlighted the handicaps in UTH theatre recovery rooms particularly in terms of staffing, monitoring and resuscitation equipment (Anis et al., 2018). Therefore, there is need to investigate this integral component of anaesthetic practice at the UTH. If indeed RNMB is present, identification of the associated risk factors would facilitate protocol development to assist the anaesthetist to mitigate the risks as much as possible and enable more optimal conditions for neuromuscular recovery. The adoption of interventions such as provision of equipment for improved monitoring of patients in the perioperative phase, may lead to early detection and management of common complications, thereby improving surgical outcomes.

1.4 Objectives

1.4.1 General Objective

To investigate the incidence and determinants of residual neuromuscular blockade in adult patients undergoing surgery at UTH.

1.4.2 Specific Objectives

1. To determine the level of neuromuscular blockade on patient arrival in the recovery room.
2. To determine whether patient factors, anaesthetic factors and surgical factors are associated with residual NMB.

1.5 Research Question

What is the incidence of post-operative neuromuscular blockade in patients in the University Teaching Hospital theatre recovery room? What are the factors associated with post-operative neuromuscular blockade?

CHAPTER TWO: REVIEW OF LITERATURE

2.1 Global Overview

2.1.1 Residual Block and Neostigmine

The RECITE study (Fortier et al., 2015) aimed at determining the incidence and severity of residual block across 8 hospitals in Canada. Over 200 data sets were included for analysis and the incidence of RNMB was 63.5% (95% Confidence Interval (CI) 57.4%-69.65) at extubation and 56.5% (95% CI 49.8%-63.3%) on arrival at the post anaesthesia care unit (PACU). More than 70% in each group had received neostigmine for reversal of the block. The researchers concluded that their work demonstrated a high prevalence of RNMB in the immediate post-operative period despite monitoring and use of reversal agents.

A multi-centre study done in the Netherlands investigating the "impact of anaesthetic management characteristics on severe morbidity and mortality" showed that lack of neostigmine reversal (of neuromuscular block) was an independent risk factor for anaesthesia related morbidity and mortality within 24hours (Arbous et al., 2005). Interestingly, another group of researchers found that when used within the clinical dose range, neostigmine provides only partial recovery of muscular function (Donati et al., 2013). Furthermore, their findings indicated that when neostigmine is given during profound block, time to recovery is *not reduced* compared to spontaneous recovery. Current routine clinical practice at UTH is reversal of neuromuscular block with neostigmine (anecdotal, personal experience).

2.1.2 Residual Block and Pancuronium

Studies have demonstrated that critical respiratory events (hypoxia, airway obstruction) were more common in patients who had Train of four (ToF) ratios < 0.7 and were less common or did not occur in patients who had recovered to ToF ratio > 0.7 (Berg et al., 1997; Murphy et al., 2008). Berg's study randomised patients to receive pancuronium, vercuronium or atracurium. The researchers discovered that the long acting agent i.e. pancuronium, was

associated with higher incidence of RNMB and that patients within that group developed pulmonary complications during a six day follow up. A similar study done some years later (Murphy et al., 2003) made the same association between use of pancuronium and risk of RNMB. More recently, an association has been demonstrated between the use of an intermediate-acting muscle relaxant and the development of pneumonia post-operatively during a 30 day follow–up. The risk of developing pneumonia was two times higher in patients who did not receive neostigmine for reversal (Dmochowski et al., 2016). This illustrates a concerning link between the use of NMBAs and RNMB with potentially life threatening pulmonary complications. There is, however, no data available for Zambia in this regard.

2.1.3 Assessment of Residual Block

The use of clinical methods to detect RNMB has consistently been shown to be unreliable as these methods tend to be quite subjective and inaccurate. A meta-analysis of 24 trials involving 3375 patients (from 1979 to 2005) could not provide evidence that the use of qualitative monitoring reduced the incidence of RNMB and its subsequent complications (Naguib et al., 2007). A similar report published a year earlier also documented the inability of clinicians using nerve stimulators (a qualitative method) to exclude RNMB (Fortier et al., 2006). In addition, Kopman subjected 10 healthy volunteers to paralysis with mivacurium (a short acting muscle relaxant) whilst awake. Their neuromuscular function was then monitored and 3 subjects were able to achieve a five second head lift (thought to be a clinical marker of good neuromuscular activity) at ToF Ratios less than 0.6 (Kopman et al., 1997). These findings underscore the need for an objective approach to patient monitoring particularly in this era of day case procedures. There is a large body of evidence for the use of quantitative monitoring methods such that a consensus document from leading experts has highlighted it and other recommendations for practitioners who use neuromuscular blocking agents (Kopman et al., 2018). As a quantitative measurement, the Train of Four is calculated from the ratio of the forth twitch height to the first twitch height measured by the scanner device. This provides an unambiguous, objective measurement which aids the anaesthetist to safely extubate the patient. Such devices are unavailable in a low resource centre such as UTH hence anaesthetists heavily rely on the clinical parameters to assess for return of neuromuscular function.

2.2 Regional Overview

Within the sub-Saharan region, there is a paucity of data on this subject. From a study in Durban, South Africa, 70 patients were monitored for RNMB and the researchers documented a 35.7% incidence of inadequate neuromuscular recovery (Invernizzi et al., 2016). The African Surgical Outcomes Study (ASOS) across 25 countries (including Zambia) involving over 11,000 patients revealed some startling statistics on surgical outcomes. Despite having surgical patients who were younger (mean age 38.5 years) and fitter (ASA 1-2) than the global average, the post-operative mortality was more than twice the global average (Biccard et al., 2019). Thus, steps to improve on perioperative care of the patient in an effort to avoid preventable deaths are imperative. One of the recommendations was improved surveillance of these patients in the perioperative phase. Locally, data from a yet to be published study indicated a perioperative mortality rate of 0.85% at the University Teaching Hospitals, but this was not stratified into intra-operative or post-operative deaths (Nchimunya, 2019).

CHAPTER THREE: METHODOLOGY

3.1 Study Design

This study was designed as a prospective cross-sectional study involving a group of patients who were to have surgery under general anaesthesia**.**

3.2 Population

The study population was adult patients that underwent surgery at the University Teaching Hospitals (UTH) operating theatres. UTH is the largest referral centre in Zambia and currently has three adult operating theatre complexes, comprising a total of 14 operating rooms. There was a rotation of data collection among the three sites.

3.3 Study Sample

The study recruited participants at or above the age of 18 years who presented for either emergency or elective surgery who would receive a NMBA. Participants were recruited in the waiting area, before their operation. They were given information regarding the study (Appendix I), and if willing to proceed, informed consent (Appendix II) was obtained. Participants with a myopathy and those with a known or suspected allergy to NMBAs were excluded from the study.

Sample size: $N= [Z^2 \times P (1-P)] \div (E)^2$ where:

N = Sample required

Z = Z Score 1.96 when using a 95% CI

P = proportion of morbidity (estimated at 35% from Durban)

E = confidence interval, using 0.05, gives

N=101

3.4 Sampling Technique

Consecutive sampling was implemented. There was a rotation of patient selection among the three complexes i.e. the emergency theatre (phase five), the elective theatre (phase three) and the obstetrics and gynaecology theatre (at C block). Within a theatre, all consented participants arriving in the recovery room had an assessment of neuromuscular function. The sampling technique was suitable for the purposes of this study as it provided a rapid yet comprehensive method of participant recruitment.

3.5 Data Collection Tools

The patients' anaesthetic record/chart was used to obtain data regarding the types, doses and timings of the neuromuscular blocking drugs used for the operation as well as other anaesthetic information. This was entered into data capture forms (appendix III) which also had sections for surgical and some patient details. A ToF scan **(IDMED TOFSCAN SN: 15-641)** was used to obtain a train of four ratio which would indicate the level of neuromuscular blockade. All data was then entered into spreadsheet software for storage and coding.

3.6 Data Collection Procedure and Timeline

A quantitative neuromuscular blockade monitor **(IDMED TOFSCAN SN: 15-641)** was used to assess the level of post-operative neuromuscular block by measuring a Train of Four (ToF) ratio following ulnar nerve stimulation using the device. This was performed **by the principle investigator** on participants in the theatre recovery room at the time of arrival, and at 10 and 20 minutes after arrival. The information obtained was documented on the data capture forms (Appendix III). Non identifying participant demographics were obtained to assist in data analysis. The anaesthetic records were also reviewed to obtain data regarding ASA status, NMBA used, total dose and timing of last dose, use of reversal agent (including timing and dose), documented difficulties post extubation (including need for re-intubation), and total duration of procedure. The data collection phase was planned to run for 12 weeks, but ran for about 20 weeks due to logistical challenges primarily relating to recruitment as very few patients received NMBAs, and not all were willing to participate in the study.

3.7 Data Analysis Strategy

Categorical data was displayed as proportions. Continuous variables were displayed as means with standard deviation (normally distributed data) or medians and Inter-quartile Range (IQR) (if not normally distributed) and compared using Mann-Whitney tests. A multivariable regression analysis model was used to assess the correlation between the risk factors and residual block, as well as rule out confounders. A statistician assisted in performing the analyses using STATA (Version 15, StataCorp, Texas, USA).

3.8 Dissemination

The results of this study will be shared within the department of anaesthesia (U.T.H.) with a view to influence training and practice standards. The results will also be shared with the larger scientific community to grow the current knowledge and understanding of the neuromuscular blocking agents.

3.9 Ethical Considerations

3.9.1 **Approval**: Ethical Approval was sought from University of Zambia Biomedical Research Ethics Committee (**REF No. 130-2019**) (appendix IV). Permission to carry out the study was also obtained from the UTH management.

3.9.2 **Informed Consent**: Participation in this study was entirely voluntary. The participant could withdraw at any time during the study without a reason, and there would be no consequences to their routine standard of care. The purpose of this study and the techniques involved were explained to the participants in writing (appendix I) and verbally. Informed Consent (appendix II) was obtained from the willing participants prior to their transfer into the operating room. Participant information was kept strictly confidential.

3.9.3 **Risks and Benefits**: There were no direct benefits to the participant per se, except in the instance where residual block was significant, this was addressed for the participants' safety. Standard treatments were used for these participants; no new interventions were instituted. It is hoped that information obtained will be used to mitigate risk of residual block in future. The stimulating device was optimized to minimize the possibility of participant discomfort.

3.10 Limitations

The study was carefully designed and performed, however, some limitations were identified.

The principle investigator acting in dual roles as investigator and anaesthetist led to delays in attending to other post-operative participants initially recruited due to the need to treat or follow up established post-operative blockade. This significantly affected the study sample size. It may have also led to some bias in intra-operative drug selection.

Another factor limiting the participant sample was that most anaesthetic machines had no ventilator capabilities which significantly reduced the number of patients administered the NMBAs. Additionally, there were stock outs of NMBAs lasting several days and therefore, new participants could not be recruited during those phases.

Missing data (drug doses, use of reversal agent) from the anaesthetic charts resulted in some participants being excluded from the study due to insufficient characteristics obtained for analysis.

The study was conducted on a limited number of participants, at a single centre and the results thereof may not be generalized to other centres within the country or region.

CHAPTER FOUR: RESULTS

This chapter presents the findings of the study in the form of figures and tables, in accordance with the study objectives. The general objective was to investigate the incidence and determinants of post-operative neuromuscular blockade in adult patients undergoing surgery at UTH.

The specific objectives were to determine the level of neuromuscular blockade on patient arrival in the recovery room, and to determine whether patient factors, anaesthetic factors and surgical factors were associated with post-operative NMB (i.e. non-recovery from paralysis).

4.1: Baseline demographic of the study participants

In this study there were a total of 38 participants. The median age of the participants was 45 years (IQR, 38 - 53). Majority 25 (65.8%) of the participants were female. The median body mass index (BMI) was 22.5 kg/m^2 (IQR, 19.5 – 27.5) as shown in Table 4.1.

Table 4.1: Baseline demographics of study participants

Variable		
Age (years)*	45 (IQR, 38 - 53)	
BMI (kg/m^2)*	22.5 (IQR, 19.5 – 27.5)	
	Category	Frequency (%)
Sex	Female	25 (65.8)
	Male	13 (34.2)

*median and interquartile range reported; IQR= interquartile range, BMI = Body Mass Index

4.2: Clinical characteristics of the study participants

In this study participants with renal dysfunction were 5 (13.2%) and those with liver dysfunction were only 3 (7.8%). When participants physical status was assessed using the American Society of Anaesthesiologists (ASA) score, majority 16 (42.1%) were in mild disease (ASA 2), and only 1 (2.6%) was in life threatening condition (ASA 4) as shown in Table 4.2.

Table 4.2: Clinical characteristics of the study participants

Variable	Category	Frequency (%)
Renal dysfunction	No	33 (86.8)
	Yes	5 (13.2)
Liver dysfunction	No	35 (92.1)
	Yes	3 (7.9)
ASA classification	Fit (ASA 1)	11 (28.9)
	Mild disease (ASA 2)	16 (42.1)
	Severe disease (ASA 3)	10 (26.30
	Life threatening (ASA 4)	1 (2.6)

ASA = American Society of Anaesthesiologists

4.3: Description of Anaesthetic characteristics

In this study, majority 33 (86.8%) of the cases were attended by registrars, 3 (7.9%) by junior trainees and only 1 (2.6) was by a consultant. The median concentration of atracurium drug was 1.28 mg/BMI (IQR, 1.04 – 1.4) and the median concentration of pancuronium was 0.19 mg/BMI (IQR, 0.18 – 0.21). In most 27 (71.2%) participants a reversal drug was used after the procedure as shown in Table 4.3.

Table 4.3: Description of Anaesthetic Characteristics

Variable		
Atracurium (mg/BMI)*	1.28 (IQR, 1.04 – 1.4)	
Pancuronium (mg/BMI)*	0.19 (IQR, 0.18 – 0.21)	
	Categorical	Frequency (%)
Reversal drug	No	11 (28.9)
	Yes	27 (71.1)
Doctors seniority	Junior	3 (7.9)
	Registrar	33 (86.8)
	Senior registrar	1 (2.6)
	Consultant	1 (2.6)

*median and interquartile reported; BMI = body mass index; IQR = interquartile range

4.4: Description of Surgical Characteristics

The median duration of the operation procedure was 2 hours (IQR, 1.5 – 3). Majority 34 (89.5%) of the operations were electives. Most 21 (55.3%) of the operations were general surgery, 11(28.9%) gynaecology, 2 (5.3%) maxillofacial and the rest were 1 each (2.6%) as shown in Table 4.4.

Table 4.4: Description Surgical Characteristics

Variable		
Duration of procedure (hours)*	2 (IQR, 1.5 – 3)	
Urgency of operation	Emergency	4 (10.5)
	Elective	34 (89.5)
Specialty	General surgery	21 (55.3)
	Gynaecology	11 (28.9)
	Maxillofacial	2 (5.3)
	Neurosurgery	1 (2.6)
	Obstetrics	1 (2.6)
	Orthopaedics	1 (2.6)
	Urology	1 (2.6)

*median and interquartile range reported; IQR= interquartile range

4.5: Description of participants' post-operative neuromuscular function

After the operation procedure, 25(65.8%) recovered from paralysis (ToFR > 0.9) as shown in Table 4.5.

Table 4.5: Frequency of recovery and non-recovery

Variable	**Frequency (%)**
Recovered	25 (65.8)
Non-recovered	13 (34.2)

4.6: Association between the non-recovered participants and independent variables

When association between non-recovery and independent categorical variables was determined, there was significant association between use of reversal drug with non-recovery (p=0.037) and muscle paralysis drug (NMBA) used and non-recovery (p=0.010). As for the other variables, there was no significant association as shown in Table 4.6.

Table 4.6: Association between non-recovered and independent variables

Variable	Recovered (%)	Non-recovered (%)	P-value
Sex			
Female	15 (60)	10 (40)	0.297
Male	10 (76.9)	3 (23.1)	
Renal dysfunction			
No	21 (63.60)	12 (36.4)	0.472
Yes	4 (80)	1 (20)	
Liver dysfunction			
No	24 (68.6)	11 (31.4)	0.217
Yes	1 (33.3)	2 (66.7)	
ASA classification			
Fit	9 (81.8)	2 (18.20)	0.333
Mild disease	10 (62.5)	6 (37.5)	
Severe disease	6 (60)	4 (40)	
Life threatening	0 (0)	1 (100)	
Muscle paralysis drug			
Atracurium	15 (88.2)	2 (11.8)	0.011
Pancuronium	4 (44.4)	5 (55.6)	
Atracurium/ pancuronium	4 (36.4)	7 (63.6)	
Doctors seniority			
Junior	2 (66.7)	1 (33.3)	0.775
Registrar	21 (63.6)	12 (36.4)	
Senior registrar	1 (100)	0 (0)	

Consultant	1 (100)	0 (0)	
Urgency			
Emergency	2 (50)	2 (50)	0.482
Elective	23 (67.7)	11 (32.4)	
Reversal drug			
No	10 (90.9)	1 (9.1)	0.024
Yes	14 (51.9)	13 (48.2)	

Note: Fisher's exact test was used due to small numbers in some cells

4.7: Comparison of age between participants who recovered and those who did not recover

When age of participants was compared between those who recovered to those who did not, the median age for those who recovered was 41 years (32 – 49.5) compared to those that did not recover 49.5 years (45 – 53) and the difference was statistically significant (p=0.01) as shown by the dot plot in Figure 4.1. Mann-Whitney test was used to determine the difference.

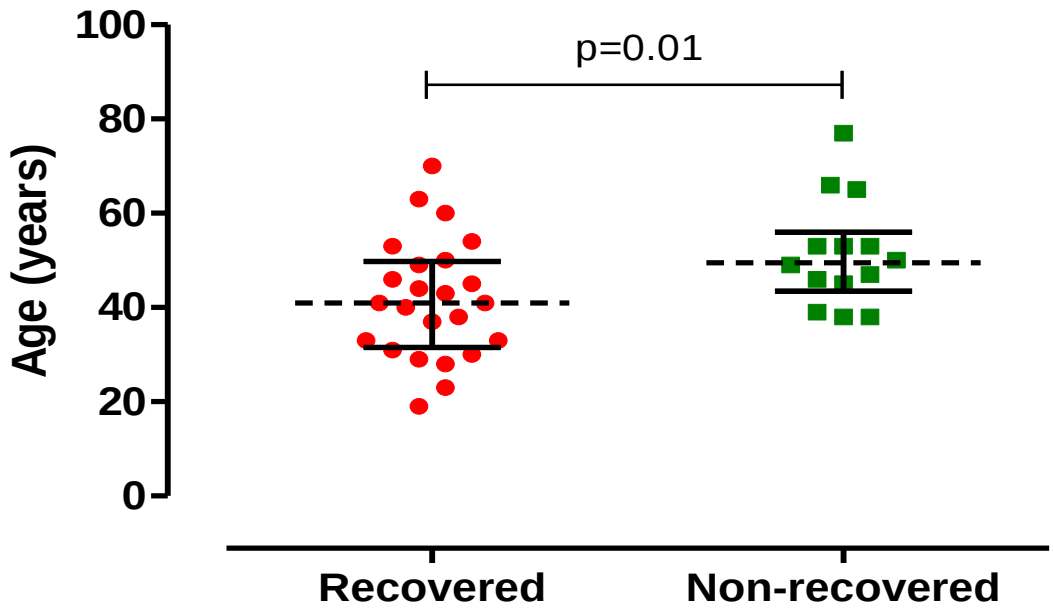

Figure 4.1: Comparison of age between participants who recovered and those who did not recover.

4.8: Comparison of BMI between participants who recovered to those who did not

When BMI was compared between participants who recovered to those who did not, the median BMI for those who recovered was 22.5 kg/m^2 (19.5 - 26.4) compared to those who did not recover 22.6 kg/m^2 (19.5 – 30.6) and there was no statistical difference (p=0.855). The Mann-Whitney test was used to determine the difference as shown by the Box and Whisker plot in Figure 4.2.

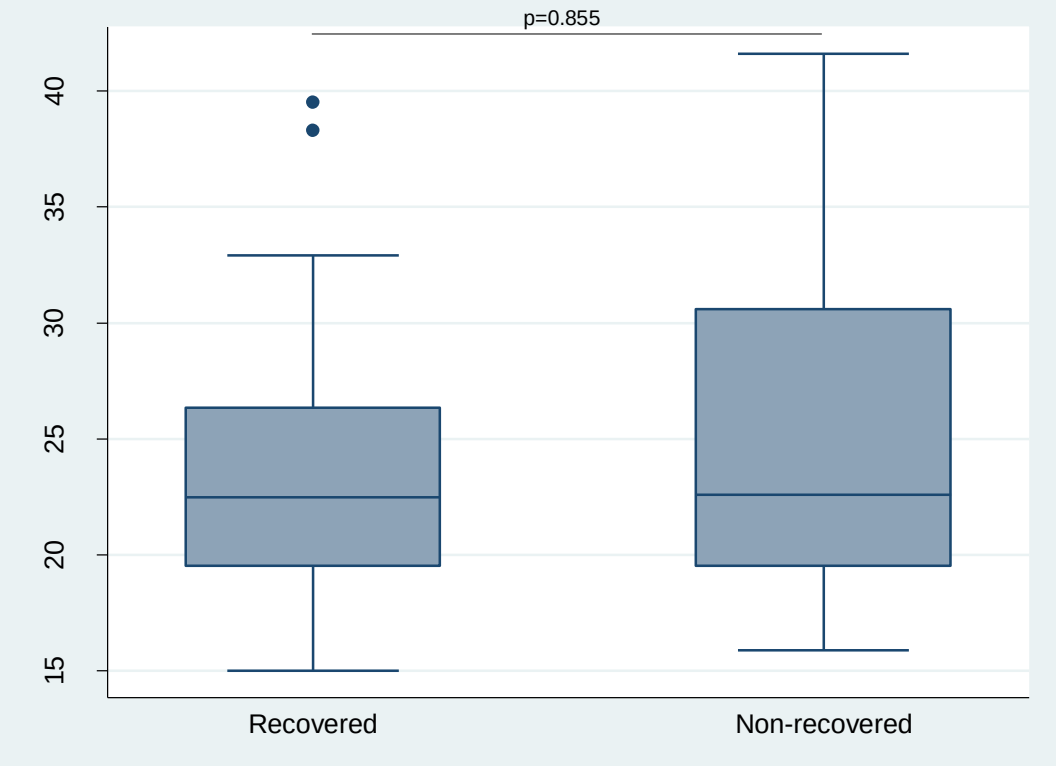

Figure 4.2: Comparison of BMI between participants who recovered to those who did not

4.9: Comparison of Atracurium between participants who recovered and those who did not recover

When the atracurium concentration was compared between participants who recovered to those who did not, the median atracurium concentration for those who recovered was 1.3 mg/BMI (0.99 – 1.3) significantly lower compared to those who did not recover 2.84 mg/BMI (2.4 – 3.3) and there was statistically significant difference (p=0.031). The Mann-Whitney test was used to determine the difference as shown by the Box and Whisker plot in Figure 4.3.

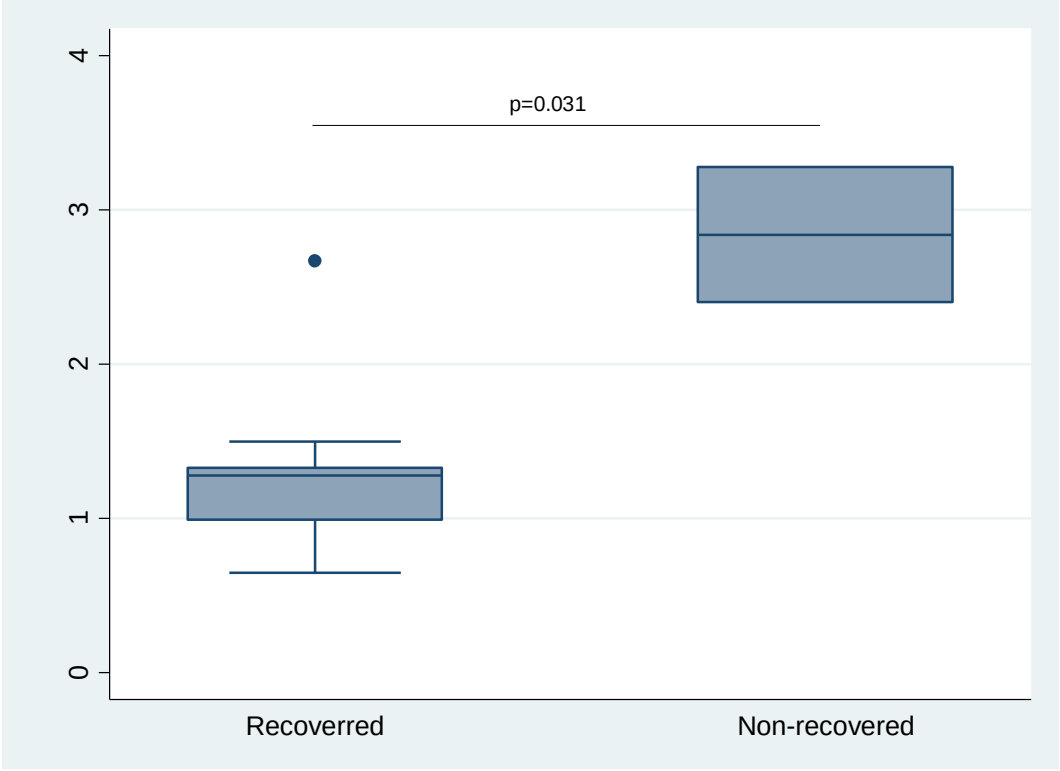

Figure 4.3: Comparison of Atracurium concentration between participants who recovered to those who did not recover.

4.10: Comparison of pancuronium between participants who recovered and those who did not recover

When the pancuronium concentration was compared between participants who recovered to those who did not, the median pancuronium concentration for those who recovered was 0.19 mg/BMI (0.18 – 0.2) compared to those who did not recover 0.21 mg/BMI (0.18 – 0.21) and there was no statistically significant difference (p=0.852). The Mann-Whitney test was used to determine the difference as shown by the Box and Whisker plot in Figure 4.4.

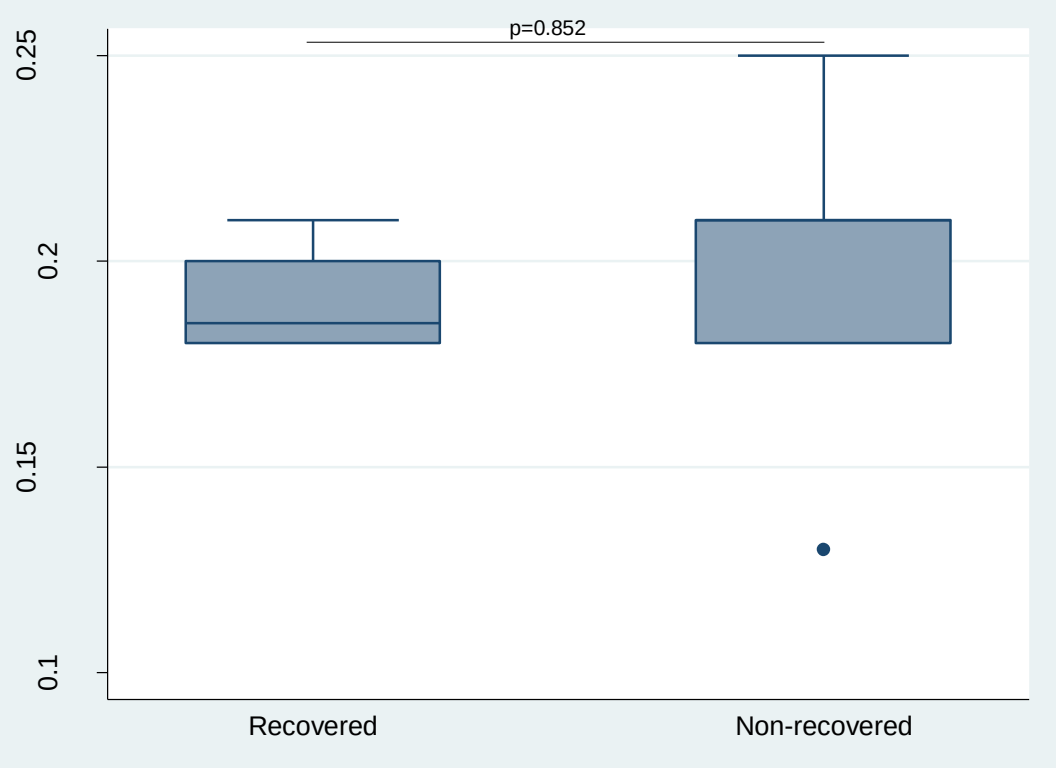

Figure 4.4: Comparison of pancuronium concentration between participants who recovered to those who did not

4.11: Comparison of duration of the operation between participants recovered and those who did not recover

The median duration of participants who recovered was 2 hours (1.4 – 3.3) compared to those that did not recover 2 hours (1.5 – 2.7) and there was no statistically significant difference (p=0.617). The Mann-Whitney test was used to determine the difference as shown by the dot plot in Figure 4.5.

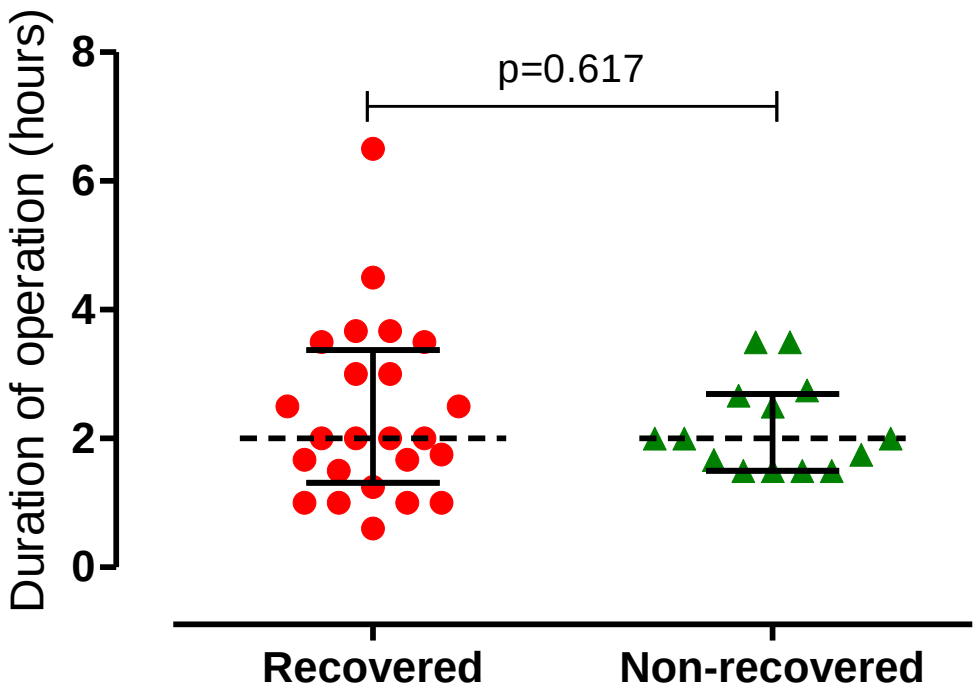

Figure 4.5: Comparison of duration of operation between participants who recovered to those who did not recover.

4.12: Multivariable regression analysis for determinants of non-recovery

In the multivariable regression model, only those variables with p=0.25 (25%) were included in the final model. For age, every one unit increase in age (year) was associated with 1.2 increase in odds (AOR = 1.2, 95% CI [1.09 – 1.37]; p=0.044) of non-recovery and was significant. The use of muscle paralysis drugs, for pancuronium the odds of non-recovery were 2.3 times higher (AOR=2.3; CI [1.21 – 14.9]; p=0.038) compared to those who received atracurium, and for those who received a combination of atracurium and pancuronium the odds were 3.2 higher compared to those who received atracurium. Similarly, those who received reversal drug (neostigmine) the odds of non-recovery were almost twice higher (AOR = 1.9, 95% CI [1.33 – 5.21]; p=0.048) and this association was significant as shown in Table 4.7.

Table 4.7: multivariable regression analysis for the determinants of non-recovery

Variable	AOR	95% CI	P-value
Age	1.2	1.09 – 1.37	0.044
Liver dysfunction			
No	Ref.		
Yes	1.05	0.21 – 27.3	0.412
Muscle paralysis drug			
Atracurium	Ref.		
Pancuronium	2.3	1.21 – 14.9	0.038
Pancuronium/Atracurium	3.2	1.73 – 8.41	0.029
Reversal drug			
Not given	Ref.		
Given	1.9	1.33 – 5.21	0.048

AOR= adjusted odds regression; Ref = reference category, CI = Confidence Interval

CHAPTER FIVE: DISCUSSION

The median age among the study participants was 45 years (IQR 38-53), and there were nearly twice as many female (n=25) participants owing to the selection bias at the "C block" theatre for obstetrics and gynaecology. Most participants were relatively healthy (ASA 1 and 2) presenting for elective surgery. These demographics are similar to findings of the ASOS study which determined the mean age as 38.5 years, with ASA status 1 and 2. Nonetheless, despite having these seemingly reassuring patient characteristics, post-operative morbidity and mortality are much higher in this region when compared to the global average (Biccard et al., 2019).

The study results showed that 13 (34.2%) of the participants had not recovered their muscle function as demonstrated by the Train-of-Four ratio (ToFR). This finding is quite similar to the results from a Durban study where 25 (35.7%) of the participants had residual neuromuscular block (ToFR <0.9) (Invernizzi et al., 2016). The 13 participants were then treated using standard doses of neostigmine (with atropine) and by 20 minutes, only 3 (7.8%) had evidence of post-operative (or residual) neuromuscular blockade (RNMB). The assessment of neuromuscular function should ideally be performed prior to extubation of the trachea, so as to ensure optimal airway and breathing functions. However, these results stated were obtained from the recovery room (PACU). The U.T.H. recovery facilities are poorly stocked with monitoring and resuscitative equipment (Anis et al., 2019), and the recovery room staff may be preoccupied with other functions assigned to them.

Patient demographic and clinical variables were assessed for association with RNMB. There was no statistically significant association with sex (p=0.297), renal dysfunction (p=0.472), liver dysfunction (p=0.217), ASA class (p=0.333) or BMI (p=0.855). The lack of statistical significance of these factors may be accounted for by the limited datasets. However, there was a significant association with age. The median age of the participants with optimal muscle function post-operatively was 41 years, while the median age for patients with RNMB was 49.5 (p=0.01). When further subjected to regression models, every one unit increase in age (i.e. year) was associated with 1.2 increase in odds (AOR = 1.2, 95% CI [1.09 – 1.37]; p=0.044) of non-recovery of muscle function. This could be related to impaired synthetic and metabolic functions associated with advancing age along with comorbidities or chronic drug/alcohol use.

In this study participants received either atracurium (n=17) or pancuronium (n=8) or both (n=13). The median dose of atracurium administered was 1.28mg/kgm^{-2} (IQR 1.04-1.4), while that of pancuronium was 0.19mg/kgm^{-2} (IQR 0.18-0.21). There was a positive correlation between the dose of atracurium and RNMB. The participants that had RNMB had received significantly higher drug doses (2.84 mg/kgm^{-2}) compared to those that recovered adequate muscle function (1.3mg/kgm^{-2}), suggesting a dose dependent relationship (p=0.031). As per analysis, pancuronium dosages did not differ significantly in patients who achieved adequate muscle recovery when compared to those who did not (0.19mg/kgm^{-2} vs 0.21mg/kgm^{-2}). This finding may indicate that RNMB associated with pancuronium is independent of the dose (p=0.852).

When logistic regression models were applied against atracurium, it was revealed that pancuronium had over twice the odds of RNMB (AOR=2.3; CI [1.21 – 14.9]; p=0.038), whereas administering both of these drugs carried an even greater risk of RNMB (AOR=3.2; 95% CI [1.73-8.41]; p=0.029). Older studies on pancuronium (Berg, 1997; Murphy et al., 2003; Murphy et al., 2008) have highlighted the problems with this drug, such as pulmonary complications resulting from RNMB; hence it is logical that most middle and high income countries have relegated pancuronium from current practice.

This study also found a statistically significant correlation between the use of a reversal agent (neostigmine) and sub-optimal muscle recovery (AOR = 1.9, 95% CI [1.33 – 5.21]; p=0.048) as determined by the ToFR. This may be due to the 'ceiling effect' of neostigmine when given during profound neuromuscular blockade (Donati et al., 2013) whereby it will prevent the enzymatic breakdown of acetylcholine but does not displace the NMBA, meaning the muscle does not regain function. It was found that of the twenty-seven participants that received the reversal agent, nearly half did not achieve recovery. In a Canadian study, a notable concern from the investigators was the lack of recovery of muscle function (53.5% in PACU) despite administering reversal agents (70% of participants) and use of neuromuscular monitoring (Fortier et al., 2015).

The role of neostigmine has come under scrutiny in recent years. There is conflicting data regarding its actual effects when used as an antagonist to NMBAs. Data from an American research group (Eikermann et al., 2015) appears to link its use to the development of post-operative pulmonary complications, including pneumonia, while European researchers (Arbous et al., 2005; Dmochowski et al., 2016) found that omitting antagonism was

independently linked to the same complications. Hence the need for a robust randomised trial to resolve these ambiguous results. In addition, the cholinergic effects are well documented and do account for the undesired side effects associated with neostigmine, which require prophylactic anticholinergic therapy. Sugammadex, a cyclodextrin, is a relatively newer alternative reversal agent which has shown superior efficacy in antagonising neuromuscular blockade, without the cholinergic effects seen with neostigmine and others in that class. It is, however, limited in this role because it is only selective for the aminosteroidal NMBAs (Hunter, 2017).

The majority of cases (86.8%) were undertaken by anaesthetic registrars (post-primary specialist trainees) and this is a reflection of the prevailing staffing levels of the anaesthesia department during the study period. There is usually one consultant available to supervise clinical work within a theatre complex, with registrars situated in specific operating theatres. Sometimes, there may be no direct supervision of anaesthetic practice which may compromise the quality of care owing to poor judgement when the consultant is unavailable. However, the study demonstrated no statistically significant correlation between anaesthetist grade and RNMB.

Most participants were undergoing elective surgery (89.5%), with the majority being general surgery operations (55.3%). The surgical procedures had a median duration of two hours (IQR 1.5 - 3). The findings could not demonstrate any statistically significant correlation between RNMB and the urgency of procedure ($p=0.482$) or its duration ($p=0.617$).

Thus, the study found that as regards determinants of post-operative neuromuscular block, age was a significant patient factor, whereas dose of atracurium, use of pancuronium and use of reversal were significant anaesthetic factors. As anaesthesia plays a crucial role in successful outcomes and patient satisfaction across surgical specialties, improving efficiency in anaesthesia can yield substantial benefits for hospitals and health systems. Such development can only be attained by continued research and development of various relevant aspects of anaesthetic practice.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

Perioperative care is an important aspect of the surgical experience. In order to provide holistic care to surgical patients thereby optimising comfort and safety, consideration of all factors cardinal to achieving successful outcomes is vital. One frequently overlooked area is post-operative muscle function. The investigation revealed that 34.2% of the participants had Train-of-Four ratios consistent with residual paralysis. Risk of RNMB increased with age. Further, findings of this study provide empirical evidence to support the use of the shorter acting muscle relaxants (atracurium) in appropriate doses, and avoiding the use of pancuronium with the usual follow up of a reversal agent (antagonist), both of which were found to have a significant association with post-operative muscle paralysis.

6.2 RECOMMENDATIONS

- Larger multi-centre studies are required to establish the pattern of post-operative neuromuscular blockade in low resource settings and thus formulate local policy and guidelines on the use of neuromuscular blocking agents in these environments.

- The potential link to post-operative morbidity and mortality associated with NMBAs and use of neostigmine merits further investigation.

- NMBAs should be appropriately selected and considered carefully with the patient, anaesthetic and surgical factors in mind.

- There is need to consider steps to improve on perioperative care of the patient in an effort to avoid preventable morbidity, such as improved surveillance through improved levels of monitoring e.g. pulse oximetry and blood pressure, and staffing.

- Enhance multidisciplinary collaborative governance thereby improving theatre supply chains to match targeted theatre output.

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APPENDICES

APPENDIX I: INFORMATION SHEET

RESEARCH TITLE: INCIDENCE AND DETERMINANTS OF POST-OPERATIVE RESIDUAL NEUROMUSCULAR BLOCKADE IN PATIENTS UNDERGOING SURGERY AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA

My names are Dr Tingadane Munga. I am a master's degree student in anaesthesia and critical care with the University of Zambia. I am conducting a study on the residual effects of some of the drugs you will receive during anaesthesia for your operation.

The drugs I am studying are the muscle relaxants. They are used to facilitate placement of the breathing tube and the performance of surgery by paralyzing the bodys' muscles. The muscle relaxing effects of these drugs are no longer needed after the operation and so they are reversed using other drugs (eg. neostigmine). In this study, I want to measure whether this reversal is complete. I will use a device called a ToF scanner to assess the level of muscle paralysis after your operation. It will be attached to your hand where it will stimulate some muscles to react. This reaction will be measured and displayed, indicating the level of muscle function. The test may be uncomfortable but not painful.

Your participation in this study is entirely voluntary. You will not receive any compensation. You are free to withdraw from the study at any time, even without a reason. There will be no consequences to your standard care during this or future operations. You are also free to ask questions related to the study or anaesthesia in general. There are no direct benefits for you as a participant except where the residual blockade is significant, this will be treated for your safety using standard medication. It is hoped that the patterns associated with better recovery can be identified and used to limit the unwanted effects of these drugs that are used for many operations every day.

Your identity will be concealed and any other personal information obtained for this study will be kept strictly confidential and used for research purposes only. The records on paper will be kept under lock and key and the electronic data will be password protected, accessible by the researcher only.

You will be given a written consent to acknowledge your understanding of this study and your participation in it. This information will be read to you if you are unable to do so. For any queries or clarifications please contact me, Dr Tingadane Munga, 0973262532, UTH

Department of Anaesthesia, P/bag RW1X, Lusaka. Alternatively, you may contact the University of Zambia Biomedical and Research Ethics Committee, Ridgeway Campus, P. O. BOX 50110, Lusaka.

APPENDIX II: CONSENT FORM

I,……

have been given information about this study on the incidence and determinants of residual neuromuscular block. I can confirm that I understand the information provided and I have had the opportunity to ask questions which have been answered to my satisfaction. I understand that by signing this form, I do not waive my rights and that I may withdraw from participation from the study at any point. I, therefore, voluntarily consent to participation in this study:

Name: …….. Age: ……

Signature/thumbprint:……Date:.……

STATEMENT BY RESEARCHER

I have read out and explained the participant information and I have provided answers concerning the study and its methods to the best of my ability. I can confirm that the participant has not been coerced into this study and that their participation is voluntary. I have further provided my contact details and those of the Ethics Committee to the participant should they so wish to contact the aforementioned regarding this study.

Name: ……

Signature and Date: …….

WITNESS

I have witnessed the reading of the information sheet and consent. I confirm that the participant has had the opportunity to ask questions and has freely given consent for the study.

Name:……

Signature and date:……..

APPENDIX III: DATA CAPTURE FORM

PATIENT DETAILS

Index no.		
Age		
Sex	M	F
Weight		
Height		
Education level	1. nil	
	2. primary	
	3. secondary	
	4. tertiary	
Magnesium therapy	Yes	No
If on therapy indicate dose and time of last dose		
ASA score		
Documented renal dysfunction	Yes	No
Documented liver dysfunction	Yes	No

ANAESTHETIC INFORMATION

Anaesthetist grade:

Non physician	Junior trainee	Registrar	Senior registrar	Consultant

Neuromuscular agents used (separate boluses with commas):

Drug	suxamethonium	pancuronium	atracurium	vecuronium	other
Dose (mg)					
Time given					

Volatile Agent Used:

Agent	Halothane	Isoflurane	Sevoflurane
(tick)			

Time of extubation: …….

Reversal agent given (circle): yes / no

Name, timing and dose of reversal agent (if yes to above):

……..…….

Any adverse events post extubation (list):

1. ……
   ……..
2. ……
   ……
3. ……
   ……

ToF ratio	On arrival	At 10 minutes	At 20 minutes

Dose of reversal agent in recovery:……..

Patient vitals: BP: ……. Heart Rate: ……Temperature: ……

SURGERY DETAILS

Theatre (tick)	C block	Phase 3	Phase 5
Specialty			
Procedure			
Urgency (tick)	Elective	Semi emergency	Emergency
Duration	Start:	Finish:	Total length (hours)

APPENDIX IV: ETHICS APPROVAL LETTER

UNIVERSITY OF ZAMBIA
BIOMEDICAL RESEARCH ETHICS COMMITTEE

Telephone: 260-1-256067
Telegrams: UNZA, LUSAKA
Telex: UNZALU ZA 44370
Fax: + 260-1-250753
Federal Assurance No. FWA00000338

Ridgeway Campus
P.O. Box 50110
Lusaka, Zambia
E-mail: unzarec@unza.zm
IRB00001131 of IORG0000774

22nd July, 2019.

REF. No. 130-2019

Dr. Munga Tingadane,
University of Zambia,
Department of Anaesthesia,
P.O Box 50110,
Lusaka.

Dear Dr. Tingadane,

RE: "INCIDENCE AND DETERMINANTS OF POSTOPERATIVE RESIDUAL NEUROMASCULAR BLOCKADE IN PATIENTS UNDERGOING SURGERY AT THE UNIVERSITY TEACHING HOSPITAL, LUSAKA" (Ref. No. 130-2019)

The above-mentioned research proposal was presented to the Biomedical Research Ethics Committee on 18th July, 2019. The proposal is **approved**. The approval is based on the following documents that were submitted for review:

a) **Study proposal**
b) **Questionnaires**
c) **Participant Consent Form**

APPROVAL NUMBER : REF. 130-2019

This number should be used on all correspondence, consent forms and documents as appropriate.

- **APPROVAL DATE : 22nd July 2019**
- **TYPE OF APPROVAL : Standard**
- **EXPIRATION DATE OF APPROVAL : 21st July 2020**
  After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the UNZABREC Offices should be submitted one month before the expiration date for continuing review.
- **SERIOUS ADVERSE EVENT REPORTING**: All SAEs and any other serious challenges/problems having to do with participant welfare, participant safety and study integrity must be reported to UNZABREC within 3 working days using standard forms obtainable from UNZABREC.
- **MODIFICATIONS**: Prior UNZABREC approval using standard forms obtainable from the UNZABREC Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the UNZABREC using standard forms obtainable from the UNZABREC Offices.

- **NHRA:** Where appropriate, apply in writing to the National Heath Research Authority for permission before you embark on the study.
- **QUESTIONS**: Please contact the UNZABREC on Telephone No.256067 or by e-mail on unzarec@unza.zm.
- **OTHER**: Please be reminded to send in copies of your research findings/results for our records. You're also required to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study. Use the online portal: unza.rhinno.net for further submissions.

Yours sincerely,

Sody Mweetwa Munsaka, BSc., MSc., PhD
CHAIRPERSON
Tel: +260977925304
E-mail: s.munsaka@unza.zm

APPENDIX V: GRADUATE PROPOSAL PRESENTATION APPROVAL

UNIVERSITY OF ZAMBIA

SCHOOL OF MEDICINE

Telephone : +260211252641
Telegram: UNZA, Lusaka
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P.O Box 50110
Lusaka, Zambia

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7 June 2019

Dr. Tingadane Munga
UNZA, School of Medicine
C/O Department of Surgery
LUSAKA

Dear Dr. Munga

RE: GRADUATE PROPOSAL PRESENTATION FORUM

Following the presentation of your proposal entitled **"Incidence and Determinants of Postoperative Residual Neuromuscular Blockade in Patients Undergoing Surgery at the University Teaching Hospitals, Lusaka"** your supervisor has confirmed that the necessary corrections to your research proposal has been done.

You can proceed and present to the Research Ethics.

Yours faithfully,

Dr. P. Machona
ASSISTANT DEAN, POSTGRADUATE

cc: Head, Department of Surgery

UNIVERSITY OF ZAMBIA
SCHOOL OF MEDICINE
- 7 JUN 2019
ASSISTANT DEAN (PG)
P.O. BOX 50110, LUSAKA.