

# **The occurrence of residual curarisation in postoperative patients at an academic hospital**

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## **Declaration**

I, Sakeena Hassim declare that this research report is my own work. It is submitted for the admission to the degree of Master of Medicine in Anaesthesiology by the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

..... (Signature of candidate)

Signed on the 15<sup>th</sup> day of March 2016

## Abstract

Postoperative residual curarisation (PORC) resulting from the use of non depolarising muscle relaxants continues to be a significant problem. It is associated with an increase in morbidity and may delay discharge from the recovery room, increasing financial costs. An objective measurement of neuromuscular functioning using an accelerometer is recommended to ensure patient safety. The aim of this study was to describe the occurrence of PORC in the recovery room in patients who have received intermediate acting NDMRs intraoperatively at CHBAH.

This was a prospective, contextual and descriptive study. The study sample included ASA 1 to 3 adult patients who had received an intermediate acting NDMR during elective surgery and had given pre operative consent to participate in the study. Neuromuscular function was monitored using acceleromyography. A TOF **ratio** < 0.9 was defined as having PORC. Data collection took place during December 2014 to February 2015. Data was analysed using descriptive and inferential statistics.

The study sample consisted of 55 patients. Twenty five patients had a TOF **ratio** < 0.9 on arrival in the recovery room. The occurrence of PORC was therefore 45.46%. Intraoperative neuromuscular monitoring was documented to have been done in 3 (5.45%) of the patients. The most frequently used NDMRs were rocuronium 31 (56.36%) and cisatracurium 9 (16.36%). There was no statistically significant differences in the occurrence of PORC relating to the NDMR used ( $p=0.72$ ) but higher percentages were observed with cisatracurium 5 (55.56%). An anticholinesterase as reversal agent was used in 48 (87.27%) of the patients. PORC was significantly more frequent in patients who did not receive an anticholinesterase (85.71 vs. 39.58%,  $p=0.03$ ). Three patients presented with a temperature < 35 °C. Incomplete neuromuscular recovery was more frequent in patients with a temperature < 35 °C, 2 (66.67%) compared to the patients with a temperature  $\geq$  35 °C 23 (44.23%)

PORC remains a clinical problem in the recovery room. To ensure patient safety objective neuromuscular monitoring needs to be performed.

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## Table of contents

Declaration.....	ii
Abstract.....	iii
Acknowledgments.....	iv
Table of contents .....	v
List of tables.....	vii
List of figures .....	ix
Abbreviations .....	x
<b>Chapter 1: Overview of study .....</b>	<b>1</b>
1.1 Background.....	1
1.2 Problem statement.....	4
1.3 Aim of the study .....	4
1.4 Objectives of the study.....	4
1.5 Research assumptions.....	5
1.6 Demarcation of the study field.....	6
1.7 Ethical considerations .....	6
1.8 Research methodology .....	6
1.8.1 Research design.....	6
1.8.2 Study population.....	6
1.8.3 Study sample .....	7
1.8.4 Data collection procedure.....	7
1.8.5 Data analysis .....	8
1.9 Significance of the study .....	8
1.10 Validity and reliability of the study .....	9
1.11 Study Outline.....	9
1.12 Summary.....	9
<b>Chapter 2: Literature review .....</b>	<b>10</b>
2.1 Background.....	10
2.2 Neuromuscular blocking agents.....	10
2.2.1 History .....	10
2.2.2 Classification .....	11
2.2.3 Advantages of muscle relaxants.....	13
2.2.4 Disadvantages of muscle relaxants.....	14
2.2.5 Neuromuscular blocking antagonists.....	14
2.3 Post operative residual curarisation .....	19
2.3.1 Definition of PORC .....	19
2.3.2 Testing of neuromuscular function .....	19
2.3.3 Risk factors for PORC .....	25
2.3.4 Prevention of PORC .....	27
2.3.5 Complications of PORC.....	27
2.3.6 Reported incidence of PORC .....	30
2.4 Summary.....	32
<b>Chapter 3: Research methodology .....</b>	<b>33</b>
3.1 Problem statement.....	33

3.2 Aim of the study .....	33
3.3 Objectives of the study .....	34
3.4 Ethical considerations .....	34
3.5 Research methodology .....	35
3.5.1 Research design.....	35
3.5.2 Study population.....	36
3.5.3 Study sample.....	36
3.5.4 Data collection procedure.....	37
3.5.5 Data analysis .....	39
3.6 Validity and reliability of the study .....	40
3.7 Summary.....	40
<b>Chapter 4: Results and discussion .....</b>	<b>41</b>
4.1 Introduction .....	41
4.2 Sample realisation.....	41
4.3 Results .....	41
4.3.1 Demographics .....	42
4.3.2 Primary objective: document if the TOF ratio was done before administration of an anticholinesterase and extubation by the attending anaesthesiologist.....	42
4.3.3 Primary objective: describe the clinical assessment of neuromuscular function .....	43
4.3.4 Primary objective: describe the occurrence of PORC as determined by the TOF ratio.....	43
4.3.5 Primary objective: describe the occurrence of factors contributing to PORC (hypothermia, NDMR, patients age and use of an anticholinesterase) .....	44
and.....	44
Secondary objective: Compare the factors contributing to PORC (hypothermia, NDMR, patients age and use of an anticholinesterase) with the TOF ratio. ....	44
4.3.6 Secondary objective: compare clinical assessment with TOF.....	49
4.4 Discussion.....	49
4.5 Summary.....	53
<b>Chapter 5: Summary, limitations, recommendations and conclusion.....</b>	<b>54</b>
5.1 Introduction .....	54
5.2 Study summary .....	54
5.2.1 Aim of the study.....	54
5.2.2 Objectives of the study .....	54
5.2.3 Summary of methodology.....	55
5.2.4 Summary of results.....	56
5.3 Limitations of the study .....	56
5.4 Recommendations .....	57
5.4.1 Clinical practice .....	57
5.4.2 Further research .....	58
5.4 Conclusion .....	58
<b>References .....</b>	<b>59</b>
<b>Appendix 1: HREC.....</b>	<b>64</b>

Appendix 2: Postgraduate approval.....	65
Appendix 3: Medical advisory committee .....	66
Appendix 4: Patient information letter.....	67
Appendix 5: Informed consent.....	68
Appendix 6: Data Collection record .....	69

## List of Tables

Table 2.1 Classification of neuromuscular blocking agents according to molecular structure (9).....	12
Table 2.2 Classification of NDMR according to duration of action (9). .....	13
Table 2.3 Modes of neuromuscular stimulation (44, 45).....	20
Table 2.4 TOF ratio associated with specific clinical signs. (7, 12, 15) .....	28
Table 4.1 Clinical parameters .....	43
Table 4.2 The occurrence of PORC with temperature.....	45
Table 4.3 Occurrence of PORC with the different classes of NDMR.....	46
Table 4.4 TOF ratios in both age groups .....	47
Table 4.5 The occurrence of PORC with the use of an anticholinesterase. ...	48
Table 4.6 Clinical assessment against TOF .....	49



## List of figures

Figure 2.1 TOF ratio differences between depolarising and NDMR (49).....	21
Figure 2.2 TOF ratio response pattern (50).....	22
Figure 2.3 TOF Watch® stimulating the ulnar nerve. TOF ratio=0.69 (50).....	24
Figure 4.1 Surgical disciplines from which patients presented .....	42
Figure 4.2 TOF ratio obtained from patients.....	44
Figure 4.3 The use of anticholinesterase and anticholinergic.....	48

## **Abbreviations**

**ASA:** American Society of Anaesthesiology

**CHBAH:** Chris Hani Baragwanath Hospital

**ED:** Effective dose

**NDMR:** Non depolarising muscle relaxant

**PORC:** Postoperative residual curarisation

**TOF:** Train of four

# Chapter 1: Overview of study

In this chapter, a brief overview and summary regarding this research report will be presented. Topics covered include background, problem statement, aims and objectives, research assumptions, demarcation of the study field, ethical considerations, research methodology, significance of the study, validity and reliability and study outline.

## 1.1 Background

Non depolarizing muscle relaxants (NDMR) have been used in anaesthesia since the 1940s (1, 2). The use of an anticholinesterase as an antagonist became routine in the mid 1950s (1, 3). For more than 30 years numerous studies have identified that postoperative residual curarisation (PORC) occurs frequently in patients receiving long acting NDMRs (4-7). This has been shown to be true to a lesser extent for the intermediate acting agents despite the administration of anticholinesterase (4, 8). Intermediate acting NDMRs at  $2 \times \text{ED}_{95}$  (effective dose) typically have a duration of action lasting less than 90 minutes while the longer acting agents have a duration of action greater than 90 minutes. An ED 95 dose is defined as the dose of neuromuscular blocking agent that reduces the twitch height by 95%. (9)

Factors that have been shown to contribute towards PORC include using high doses of NDMRs, long acting NDMRs, administering the anticholinesterase early and hypothermia (10). Patients at a higher risk include those with neuromuscular and respiratory pathology; sleep apnoea as well as obese and elderly patients. NDMRs should therefore be used with caution in these patients (11).

Research has identified that 83% of anaesthetists use their clinical judgement to determine if there is adequate motor function. The parameters most often used include: acceptable minute ventilation, five second hand grip, negative

inspiratory pressures greater than  $-30 \text{ cmH}_2\text{O}$ , the ability to cough and a head lift for more than 5 to 10 seconds. (10, 12)

Optimal conditions for the assessment of these parameters requires that patients be awake, co-operative and without any residual anaesthetic drugs which is normally impossible. Even in an awake patient during the postoperative phase, it is difficult to assess these parameters owing to factors such as pain. (6, 13) This implies that the anaesthetist's assessment is likely to be inaccurate and that the incidence of residual paralysis may be higher than expected. Surveys have shown that anaesthetist estimate the incidence of PORC to be 1%(12).

The recommended method of identifying PORC is with the use of a peripheral nerve stimulator. There are three types of peripheral nerve stimulators that can be used: mechanomyography (isometric contractions measured), electromyography (measures compound action potentials) and with an acceleromyography (measures the acceleration of muscular contractions). Modes of stimulation that can be used include tetanic, post tetanic, double burst and train of four (TOF) stimulation (14). PORC is predominantly identified by measuring the TOF ratio at the adductor pollicis using an acceleromyography and the measurement produced as a ratio of the highest and the lowest twitch height (15). A TOF ratio  $< 0.9$  characterises the current definition of PORC and is associated with numerous complications such as hypoxia, weakness, impaired swallowing and respiratory failure which can result in brain death (8). Consequently, there are delays in discharge from the recovery room, prolonged intubation times and poor patient satisfaction.

Currently there are no published guidelines internationally or locally advocating the routine use of a peripheral nerve stimulator e.g. acceleromyography in the objective assessment of neuromuscular function (12). Recommendations have been made advocating the routine utilisation of peripheral nerve stimulation in the intraoperative period to guide reversal. Anticholinesterase should only be administered once four twitches are present irrespective of fade, to prevent postoperative residual curarisation (16). Fade

is the progressive reduction of twitch height on the application of a TOF ratio stimulus (17).

Anaesthetists in most European countries are of the opinion that after a single intubating dose of  $2 \times \text{ED}_{95}$  of a NDMR of intermediate duration, anticholinesterase is not required after 90 minutes as there is spontaneous recovery (18). A case report by Cladius and Karacan (4) illustrated that the pharmacokinetic principles of the NDMR's are not predictable and the routine administration of an anticholinesterase at the end of surgery may not be correctly timed. Repeated neuromuscular monitoring was carried out and anticholinesterase was administered after 215 minutes when two twitches appeared. Had neuromuscular monitoring not been carried out this patient would have presented to the recovery room with PORC. This case demonstrated that a number of factors contribute to a prolonged blockade and these factors are not always predictable, highlighting the necessity of neuromuscular monitoring. (4)

Administration of an anticholinesterase is not always necessary. Neuromuscular recovery is complete if the TOF ratio  $\geq 0.9$ . TOF ratio can also be used to calculate the dosage of neostigmine thereby limiting its side effects. At times neostigmine dosages as small as 0.015 mg/kg are adequate for complete reversal. (18)

Studies indicate that the incidence of PORC is between 17 and 64% of patients presenting in the recovery room after receiving NDMR. Of these 3% will develop significant morbidity and mortality such as brain injury and death. A further 15% are estimated to develop hypoxia, upper airway obstruction, impaired pharyngeal function, muscle weakness and are at risk for aspiration. (10, 12, 13, 18) The financial implications of prolonged hospital stay and delayed recovery can be exorbitant (7).

## **1.2 Problem statement**

Anaesthetists use NDMRs every day. Practices' regarding the use of neuromuscular blocking agents and their subsequent reversal, or lack thereof, differs among anaesthetists. Common practice in South Africa aimed at identifying residual paralysis is primarily a clinical evaluation (for example: head lift for five consecutive seconds or the ability to cough) (19). Clinical assessment has been shown to over estimate neuromuscular recovery. As a result a high percentage of patients who receive NDMRs may present to the recovery room with residual paralysis. (18)

The failure to prevent, recognise and manage PORC, compromises patient safety and is considered malpractice (10). The occurrence of PORC in the operating theatre recovery room of Chris Hani Baragwanath Academic hospital (CHBAH) is currently unknown.

## **1.3 Aim of the study**

Aim of the study was to describe the occurrence of PORC in the recovery room in patients who have received intermediate acting NDMRs intraoperatively at CHBAH.

## **1.4 Objectives of the study**

The primary objectives of the study were to:

- document if the TOF ratio was done before administration of an anticholinesterase and extubation by the attending anaesthesiologist
- describe the clinical assessment of neuromuscular function
- describe the occurrence of PORC as determined by the TOF ratio
- describe the occurrence of factors contributing to PORC (hypothermia, NDMR, patients age and the use of an anticholinesterase).

The secondary objectives were to:

- compare with TOF ratio with the following clinical parameters:
  - saturation
  - handgrip
  - ability to cough
  - headlift
- compare factors contributing to PORC (hypothermia, NDMR, patients age and the use of an anticholinesterase) with the TOF ratio.

## 1.5 Research assumptions

The following definitions were used in this study.

**Adult:** a patient of the age 18 years and older.

**TOF:** train of four ratio, a supramaximal stimulus of 50 mA and a frequency of 2Hz is applied every 0.5 seconds over a 2 second interval (20). In this study, the TOF ratio will be measured using the ulnar nerve and assessing the adductor pollicis muscle with an accelerometer.

**PORC:** is postoperative residual curarisation which is the presence of clinically significant paralysis postoperatively after using a neuromuscular blocking agent (21). In this study a TOF ratio of between 0.0 to 0.89 will be regarded as PORC.

**Hypothermia:** core body temperature < 35 ° C (22).

**Adequate clinical reversal:** headlift > 5 seconds, handgrip > 5 seconds, oxygen saturation > 90% and having the ability to cough

## **1.6 Demarcation of the study field**

The study took place in the operating theatre recovery room at CHBAH. CHBAH is a 2888 bed central hospital located in Soweto in Johannesburg, Gauteng. It is affiliated to the University of the Witwatersrand and is the referral centre for a number of smaller regional hospitals. The hospital has 25 theatres and approximately 65 000 surgeries are done annually.

## **1.7 Ethical considerations**

Approvals from the relevant authorities were obtained.

Patients were invited to participate in the study the day before surgery. An introduction and detailed explanation including a patient information letter was given to the patient. Informed written consent was obtained from all study patients.

The study was conducted in accordance with the Declaration of Helsinki (23) and the South African Good Clinical practice guidelines (24).

## **1.8 Research methodology**

### **1.8.1 Research design**

A prospective, contextual and descriptive research design was used.

### **1.8.2 Study population**

The study population included ASA 1 to 3 patients who had undergone elective surgery and received an intermediate acting NDMR.



### 1.8.3 Study sample

In consultation with a statistician a sample size of 55 patients was determined. A convenience sampling method was employed for this study.

Inclusion criteria for this study were as follows:

- adults 18 years and older
- ASA 1 to 3 patients
- surgery for an elective procedure
- received an intermediate acting NDMR intraoperatively
- extubated postoperatively.

Exclusion criteria for this study were as follows:

- patients who did not consent
- no access to either ulnar nerve
- patients who were unable to understand English.

### 1.8.4 Data collection procedure

On arrival to the operating theatre recovery room, once the anaesthetist responsible for the patient had signed the patient off as being adequately recovered, the TOF ratio was recorded by the researcher.

The researcher used an accelerometer. Electrodes were placed over the ulnar nerve on the volar aspect of the wrist and the acceleration sensor was connected to an unrestricted thumb. Clinical assessment of neuromuscular function such as the ability to sustain a head lift, handgrip strength, the ability to cough, and pulse oximetry was carried out as these parameters are most commonly employed. Data was captured on a standardised data capture record. During the study period if a patient was found to have PORC, the researcher contacted the anaesthetist responsible for the patient and remained with the patient until the anaesthetist arrived.

### 1.8.5 Data analysis

Data was captured using Microsoft Office Excel® data spread sheets. Data was analysed with the assistance of a biostatistician using STATISTICA, version 12.5.

## **1.9 Significance of the study**

Surveys have shown that anaesthetist estimate the incidence of PORC to be 1% or less and that more than 62% reported that they never use a monitor to assess neuromuscular function, 28% of the respondents to the survey reported using neuromuscular monitoring occasionally and only 9.7% used it routinely. (6, 12)

In the literature the incidence of PORC ranges from 17 to 64%. The complications of PORC are significant and have a negative impact on morbidity and mortality and thus patient safety. Complications from PORC include hypoxia, upper airway obstruction, impaired pharyngeal function, muscle weakness and the risk of aspiration. Delays in leaving the recovery room have significant cost implications. (10, 18)

The financial implications of prolonged hospital stay and delayed recovery can be exorbitant. The failure to prevent, recognise and manage PORC, compromises patient safety and is considered malpractice. (10)

The study is significant as it could potentially contribute to changing practice and improving patient safety resulting in better outcomes for postoperative patients at CHBAH.

## **1.10 Validity and reliability of the study**

Measures were taken to ensure validity and reliability of this study.

## **1.11 Study Outline**

The following chapters are presented in this study:

- Chapter 1: Overview of the study
- Chapter 2: Literature review
- Chapter 3: Research design and methodology
- Chapter 4: Results and discussion
- Chapter 5: Summary, limitations, recommendations and conclusion.

## **1.12 Summary**

This chapter provided a brief overview and summary regarding this research report. Topics covered included introduction and background, problem statement, aims and objectives, research assumptions, demarcation of the study field, ethical considerations, research methodology, significance of the study, validity and reliability and a study outline.

The literature review is presented in the following chapter.

## **Chapter 2: Literature review**

In this chapter, various concepts of neuromuscular blocking agents and PORC are reviewed from the literature. In the first section, a brief overview on the history and pharmacology of the neuromuscular blocking agents is presented. Thereafter, PORC will be discussed in detail. The testing of neuromuscular function to identify PORC will be discussed. Risk factors for the development of PORC are examined next. Important principles regarding the prevention of PORC will then be evaluated. In the following section the consequences of PORC on patient's quality of life and functioning will be addressed. The prevalence of PORC according to various international studies will be considered.

### **2.1 Background**

Anaesthesia produces a reversible loss of consciousness. "It is characterised by hypnosis, analgesia, amnesia, immobility, ensuring haemodynamic stability, and reducing the stress response". Immobility is usually achieved with lower levels of anaesthesia by the co-administration of curare type neuromuscular blocking agent. Neuromuscular blockade plays an important role in providing adequate operating conditions. (25)

### **2.2 Neuromuscular blocking agents**

#### **2.2.1 History**

Neuromuscular blocking agents have been described since the sixteenth century when European explorers noticed that the indigenous population in the Amazon killed their prey by paralysing them using the sap of the rubber plant *Chondrodendron tomentosum* (1). Curare was introduced into anaesthesia in 1942, in Montreal Canada, by Griffith and Johnson (26, 27). The first clinical use of curare (intocostrin) was on a patient undergoing an

appendectomy (27). Initial recommendations advocating the use of an anticholinesterase (e.g. pyridostigmine) to antagonise the residual block was “when clinically indicated” (28).

It was in the mid 1950s that the use of an anticholinesterase became routine because of the increasing numbers of inadequate recoveries, postoperatively (28). A retrospective study by Beech and Todd (28, 29) in 1954 revealed that the anaesthetic mortality rate was six times greater when a neuromuscular blocking agent was utilised. In this study the major cause of death with the use of curare was cited as cardiac arrest, which occurred within 10 minutes of administration. The average dose of suxamethonium was 197mg which is higher than current dosing practices- this may be the cause of cardiac arrest. Prior to the use of curare the only way to achieve adequate relaxation was the use of deep inhalational agents which were poorly tolerated by elderly and ill patients with an ASA score greater than three (26).

### 2.2.2 Classification

Neuromuscular blocking agents consist of two major groups recognised by their mechanism of action: depolarising and non depolarising. Depolarising muscle relaxants e.g. suxamethonium, exert their effects by binding to the acetylcholine receptors on the motor end plate. This results in the depolarisation of the motor end plate. It also prevents repolarisation and thus further depolarisation. NDMRs competitively occupy receptors on the motor end plate, thereby preventing acetylcholine from binding to the receptors. (9, 30).

Under normal physiological conditions only a fraction of the available receptors are needed to generate a muscular contraction. There is no detectable block until 75 to 80 % of receptors are occupied. To produce complete block i.e. complete paralysis, approximately 90 to 95 % of receptors

must be occupied. Therefore adequate muscle relaxation corresponds to a narrow range of 85 to 90% receptor occupancy. (30, 31)

NDMR's can be further sub classified according to their molecular structure (benzylisoquinolones and aminosteroids) as seen in Table 2.1 or according to their duration of action (short, intermediate and long acting) as shown in Table 2.2. Controversy over cisatracurium exists. Cisatracurium may be considered an intermediate-acting muscle relaxant but this is only if twice the ED 95 is given. However, if the recommended intubation dose of cisatracurium (i.e. 3 × ED 95) is routinely used, cisatracurium will then be classified as a long-acting agent (i.e. clinical duration > 60 min) with a potential influence on the development of respiratory complications. (9, 32)

**Table 2.1 Classification of neuromuscular blocking agents according to molecular structure (9)**

<b>Depolarising</b>	<b>Non depolarising</b>	
	<b>Aminosteroids</b>	<b>Benzylisoquinolones</b>
Suxamethonium	Rocuronium Vecuronium Pancuronium	Atracurium Cisatracurium Mivacurium Doxacurium Alcuronium

**Table 2.2 Classification of NDMR according to duration of action (9).**

<b>Short acting</b>	<b>Intermediate acting</b>	<b>Long acting</b>
Mivacurium	Atracurium Rocuronium Vecuronium	Cisatracurium Pancuronium Alcuronium Doxacurium

### 2.2.3 Advantages of muscle relaxants

Griffith et al (28) published a case series approximately 70 years ago on the use of non depolarising agents in abdominal surgery and stated:

*“It seems to us, as the result of these preliminary clinical investigations, that the curare may prove to be a drug that will occasionally be of great value, and will give us a means of providing the surgeon rapidly with excellent muscle relaxation at critical times during certain operations”.*

Neuromuscular blocking agents facilitate endotracheal intubation, provide optimal operating conditions and produce adequate circumstances for ventilation. They permit the current practice of balanced anaesthesia: analgesia, hypnosis and muscle relaxation with fewer side effects on the cardiovascular and respiratory systems. Prior to the introduction of neuromuscular blockers, muscle relaxation was achieved using a deep anaesthetic technique. This resulted in the majority of patients developing hypotension, arrhythmias, hypoxia, laryngospasms and bronchospasm. (26, 30)

Endotracheal intubation and some surgeries, require an intense neuromuscular blockade to prevent movement. Examples where any movement during surgery could be detrimental include neurosurgical,

ophthalmic and cardiothoracic procedures (33). There should be no response to TOF ratio when an intense blockade is required (15, 34).

#### 2.2.4 Disadvantages of muscle relaxants

Specific complications are based on individual classes of drugs.

Suxamethonium is a depolarising muscle relaxant and is well known for its complications, which include malignant hyperthermia, scoline apnoea, bradycardia, hyperkalaemia and muscle pain. The NDMRs have side effects that are agent specific e.g. pancuronium causes tachycardia and hypertension and atracurium stimulates histamine release and is associated with anaphylactoid and anaphylactic reactions. (9, 30)

Neuromuscular blocking agents have no analgesic or anaesthetic activity and therefore an ineffectual anaesthetic technique can result in intraoperative awareness. This predisposes patients to developing posttraumatic stress disorder. The use of a neuromuscular blocking agent in an unanticipated difficult airway can result in brain injury and even death (26). Failure to intubate and ventilate when a NDMR has been given will result in the patient not being ventilated and as a consequence the patient becomes hypoxic resulting in hypoxic brain injury or death. (35, 36)

Inappropriate use of neuromuscular blocking agents can result in residual paralysis in the postoperative period and is associated with a number of complications that will be discussed in more detail later in the chapter.

#### 2.2.5 Neuromuscular blocking antagonists

Complete neuromuscular function post surgery is desirable unless postoperative ventilation is deemed necessary (8). Anticholinesterases are agents administered to increase the concentration of acetylcholine at the neuromuscular junction (9, 17). The increase in acetylcholine results in the



competitive antagonism of NDMR at the neuromuscular junction (35). It can only be used for NDMR and is not to be used for the depolarising agent suxamethonium, as it has the opposite effect with suxamethonium i.e. enhances the neuromuscular block (1). The anticholinesterases are administered with an anticholinergic (e.g. glycopyrolate or atropine) to prevent the side effects associated with the activation of muscarinic receptors. Due to the limited availability of edrophonium in South Africa and the long onset time for pyridostigmine, neostigmine is the primary anticholinesterase used. The preferred anticholinergic is glycopyrolate as it does not cross the blood brain barrier. (9)

Side effects encountered with the use of neostigmine include arrhythmias, dry mouth, nausea and vomiting, bronchospasm, severe bradycardia and asystole (18). It has also been reported that neostigmine increases intraluminal pressure in the bowel and can compromise intestinal anastomoses (28).

Patients with complete recovery (TOF ratio  $\geq 0.9$ ) from NDMR do not require reversal. Complete recovery can only be assessed with TOF ratio and not with clinical parameters. Clinical parameters are not accurate in identifying the presence of recovery. (18)

Before an anticholinesterase (e.g. neostigmine) is administered the anaesthetist has to identify whether spontaneous recovery is sufficient to allow reversal. The effectiveness of anticholinesterase administration is directly dependant on the degree of spontaneous recovery. (26) Objective assessment of recovery can be performed by using an accelerometer to assess the TOF ratio (5, 33). The result obtained can be used to calculate the dosage of anticholinesterase needed to successfully reverse neuromuscular block consequently reducing the probability of side effects (37). Complete recovery is defined as a TOF ratio of 1, therefore if a patient has a TOF ratio of 0.7 the amount of antagonist needed to achieve a TOF ratio of 1 will be less than that needed by a patient with a TOF ratio of 0.3. (18, 34)

An antagonist is administered to reduce PORC, however a study conducted in Portugal (2013) found a 15% higher incidence of PORC in patients who had received a reversal agent. No neuromuscular monitoring was utilized to determine how much antagonist was actually needed. This study does not mention when the antagonist was administered in relation to spontaneous recovery. (37)

Neostigmine has a ceiling effect and as a result it is unable to reverse profound blockade as it increases the concentration of acetylcholine but has no direct effects on the NDMR's. The maximum dosage of neostigmine is 60 to 80 mcg/kg and above this further increases in anticholinesterase will not produce greater antagonism. Increasing the concentration of acetylcholine at the neuromuscular junction will only improve neuromuscular function if approximately 20% of receptors are not bound to a NDMR's, therefore with profound blockade where 100% of the receptors are occupied, neostigmine will have no effect. (1)

Time constraints and pressure on the anaesthetist to wake a patient up instantaneously after surgery often results in neostigmine being administered too early resulting in PORC (21, 38). Additionally, administering reversal when adequate recovery is present can result in muscle spasm. Increasing acetylcholine at the neuromuscular junction in the absence NDMR presence will result in excessive motor end plate depolarisation. These spasms can also cause muscle weakness in the postoperative period with a normal TOF ratio. (18, 33)

Sugammadex is a new reversal agent that has recently become available in South Africa and is expected to change current anaesthetic practice and therefore will be discussed in greater detail. (21, 39)

Sugammadex is a modified  $\gamma$  cyclodextrin, which are cyclic oligosaccharide carbohydrates. They have a ring structure with a hydrophilic surface facilitating its solubility in water. It retains the ability to bind to complex hydrophobic molecules within its central core. The nominated  $\gamma$  means that it

contains eight glucose units. (39) It is the leading selective relaxant binding agent indicated to antagonise the neuromuscular blockade of aminosteroidal NDMR's induced during general anesthesia.(1).

The reason for its lack of affinity towards the benzylisoquinolones is owing to the size of its inner cavity and its structural design for the correct hydrophobic steroidal skeleton. The affinity for other steroidal drugs like cortisone, hydrocortisone and aldosterone to sugammadex is 140 times less than that of rocuronium. Drugs identified as having the ability to displace rocuronium and vecuronium from sugammadex are toremifene and flucloxacillin. (40)

A prompt reversal of profound neuromuscular blockade is needed in an emergency situation as in a "cannot intubate, cannot ventilate" scenario. In these circumstances the use of an anticholinesterase is contraindicated, as it has no effect in reversing profound blockades. Based on studies on human volunteers reversal of profound blockade can be achieved using higher dosages of sugammadex. (38, 39) Doses of 16 mg/kg are recommended for reversing an intense block (no twitch on TOF count) and complete reversal is achieved in less than three minutes. Recovery using sugammadex is consequently faster than spontaneous recovery from suxamethonium. (40)

The molecular weight of sugammadex is 2178. It has an osmolality ranging between 300 and 500 mOsmol/kg and a pH of 7.5. The blood brain barrier penetration (< 3 %) and placental transfer (< 6%) are considered nominal. Protein binding is low. (1) Sugammadex rapidly encapsulates free aminosteroidal NDMRs, forming a stable and inactive complex which prevents the pharmacological action of the aminosteroidal NDMRs at the neuromuscular junction (39). This produces a diffusion gradient between concentrations in the plasma and in the tissues. NDMRs from the tissue thus enter the plasma and are encapsulated by sugammadex even further. It binds to rocuronium with a high affinity and with a slightly lower affinity to vecuronium. (40)

The encapsulated complex is excreted by the kidney. It is alleged to have no intrinsic activity and has no direct effects on cholinergic transmission. (38, 40) Teratogenicity or genotoxicity has not been demonstrated in animals. Sugammadex produces a faster and more predictable recovery compared to neostigmine. The ability to efficiently and rapidly reverse very deep levels of neuromuscular blockade provides an advantage over neostigmine. Inhalational agents, which ordinarily prolong recovery times, do not influence the efficacy of sugammadex. (40, 41)

The majority of side effects observed in the phase II and III studies were nonspecific, including nausea, hypotension, coughing, movement and a dry mouth. The incidence of a prolonged QT interval was identified to be comparable to the placebo group. A prolonged QT interval is observed with several agents used in anesthesiology therefore its significance is uncertain. (40, 41) Sugammadex has been used in the management of rocuronium induced anaphylaxis, however there are case studies of sugammadex also causing allergic reactions (40, 42). Hypersensitivity reactions have caused delays in obtaining FDA approval in the United States of America (42). The manufacturer of sugammadex recommends that special caution be exercised when using sugammadex in patients with decreased hepatic and renal function and in obstetric patients. Sugammadex is a new drug and limited studies have been done on a variety of patients to accurately determine its side effect profile. (27, 38)

Dose recommendations of sugammadex depend on the intensity of blockade. The presence of four twitches requires 2 mg/kg, two twitches 4 mg/kg and with the absence of twitches up to 16 mg/kg (38, 43). As is evident by the dosing protocols, the depth of neuromuscular block has to be assessed or an inappropriate dose of sugammadex could be administered which would cause a residual block or recurarisation following the administration sugammadex. There is an economic barrier to the wide introduction of sugammadex in South Africa. Further trials considering the cost-effectiveness should therefore be conducted. (11, 21, 43)

## **2.3 Post operative residual curarisation**

### 2.3.1 Definition of PORC

PORC is defined as the presence of persistent paralysis after emergence from general anaesthesia with neuromuscular blocking drugs especially the NDMRs. The first definition of PORC was set at a TOF ratio < 0.7, this has now been changed to TOF ratio < 0.9, as it has been shown that residual paralysis above 0.7 is problematic and produces a number of complications (21).

### 2.3.2 Testing of neuromuscular function

Clinical assessment of residual paralysis comprising of head lift of 5 to 10 seconds, five second handgrip, adequate minute ventilation and negative inspiratory pressures greater than -30 cmH<sub>2</sub>O, is still used by clinicians as indicators of adequate muscle function recovery (7, 12). The evaluation of a muscular response to an electrical stimulus is considered more sensitive and specific for an accurate assessment. Table 2.3 explains the modes of stimulation that can be used including tetanic, post tetanic, double burst and TOF ratio stimulation. (44)

**Table 2.3 Modes of neuromuscular stimulation (44, 45).**

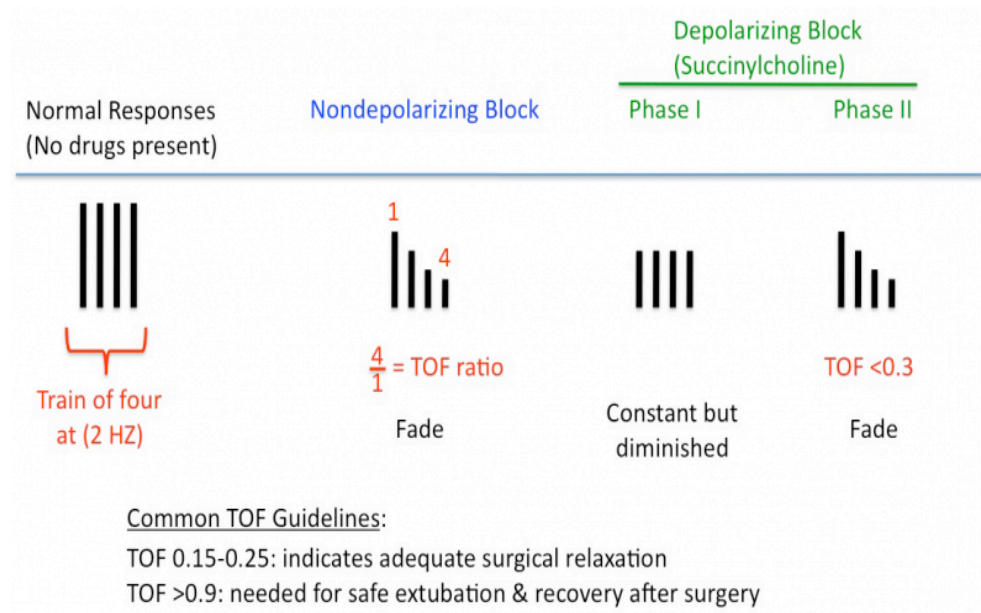
<b>Type of stimulation</b>	<b>Frequency used</b>	<b>Duration</b>	<b>Indication</b>
<b>Single twitch</b>	0.1 Hz	0.2 sec	Induction
<b>Tetanus</b>	50 Hz	5 sec	No clinical use
<b>Post tetanic count</b>	50 Hz	2 sec	Intense block
<b>Double burst</b>	50 Hz	40 msec	Residual curarisation
<b>TOF</b>	2 Hz	2 sec	Intraoperative and postoperative

The TOF ratio is the most frequently used mode of nerve stimulation. A supramaximal stimulus of 50 mA and a frequency of 2 Hz is applied every 0.5 seconds over a two second interval (46). This is repeated every 10 to 15 seconds. The effect detected is known as the TOF count or ratio. TOF count is the number of twitches observed after stimulation. A count of four is required before reversal can be administered. (43, 47, 48) The TOF ratio divides the amplitude of the fourth response by the amplitude to the first response (fade) i.e.

$$\text{TOF ratio} = \frac{T_4}{T_1}$$

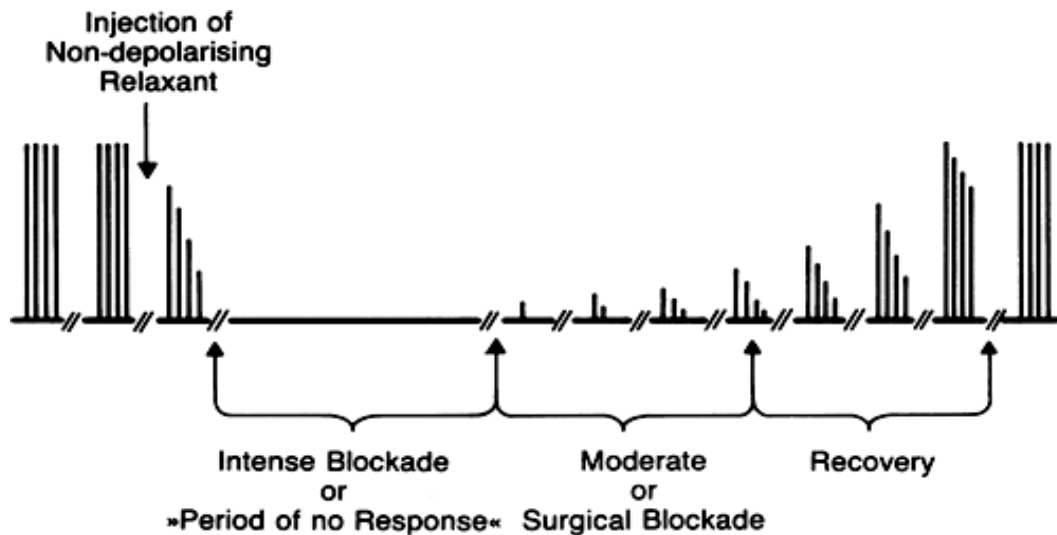
In a patient that has not received any NDMR, the TOF ratio should be 1, the height of the first and the fourth twitch being the same. If a depolarising muscle relaxant is used, (e.g. suxamethonium) the amplitude of all four twitches is decreased but the TOF ratio is still 1 as the first and fourth twitch

are of equal height, unless a phase two block develops resulting in the development of fade. This is illustrated in Figure 2.1.



**Figure 2.1 TOF ratio differences between depolarising and NDMR (49).**

NDMR reduce the TOF ratio and the reduction is inversely proportional to the degree of paralysis. The number of elicited twitches indicates the degree of receptor occupancy. Disappearance of T4, T3, T2, T1 corresponds to 75%, 80%, 90% and 100% occupancy. Therefore even with a TOF ratio > 0.9 70 % of receptors may still be occupied. (5, 15, 48) Figure 2.2 below illustrates the TOF ratio response pattern of NDMRs.



**Figure 2.2 TOF ratio response pattern (50).**

Advantages of using TOF ratio as compared to the other modes of stimulation include that a control value does not need to be recorded for an accurate assessment of residual block, unlike a single twitch where a control twitch is needed for comparison. It is also less painful than tetanic stimulation for a post tetanic count and can be used in an awake patient. Bailliard et al (51) found that 3.5% of the patients sampled remembered the use of the TOF ratio in the recovery room and that the degree of discomfort scored < 3 on the Visual Analogue Pain Scale. An additional advantage is that monitoring can be performed frequently unlike tetanic stimulation, which eventually produces an exaggerated and inaccurate response. (15)

The most prevalent site of nerve stimulation is the ulnar nerve and the adductor pollicis is assessed for a response. The choice of nerve used needs to fulfil certain criteria. It must have a motor element, it must be close to the skin and lastly the muscular contraction elicited must be visible. Optimal stimulation requires that the electrodes be applied on the volar side of the wrist. The negative electrode is placed 1 cm proximal to the point at which the proximal flexion crease of the wrist crosses the flexor carpi ulnaris tendon. The positive electrode is placed 2 to 3 cm proximal to the negative electrode. When the adductor pollicis cannot be assessed the facial nerve is stimulated and motor responses in the corrugator supercilli is utilised instead.(15)



Different muscles have different sensitivity profiles to neuromuscular blocking agents. The diaphragm is the least sensitive and therefore recovers the fastest from blockade while the adductor pollicis is one of the last muscles to recover (16). To accurately assess laryngeal muscle recovery the most accurate muscles to assess are the orbicularis oculi or corrugator supercilli (muscles around the eye) as they have a similar sensitivity profile to the laryngeal muscles. The reason for the difference in sensitivity profile is largely unknown with possible reasons including different muscle fibres, blood supply, innervation and muscle temperature. (15)

Kopman et al (18) demonstrated that the clinical parameters stated previously correlate with a TOF ratio of between 0.4 and 0.8. Tactile or visual assessment of the TOF ratio is no longer considered acceptable as it can simply detect residual paralysis of a TOF ratio of < 0.4. Objective and quantitative measurements are required to increase the sensitivity of this test in identifying residual paralysis. (26)

Neuromuscular monitoring in the clinical setting can be performed with a mechanomyography (isometric contractions measured), electromyography (measures compound action potentials) and with an acceleromyography (measures acceleration). Acceleromyography uses Newton's second law of motion i.e.

$$\text{force} = \text{mass} \times \text{acceleration.}$$

Mass is constant therefore force is directly proportional to the acceleration. (14) Figure 2.3 illustrates an accelerometer (TOF Watch) commonly used in clinical practice. The gold standard currently is the mechanomyography, however its heavy weight prevents its use routinely in clinical practice. A study by Viby-Mogensen and Claudius (4) in 2008 proposed that acceleromyography is as useful as mechanomyography (grade B evidence). They did suggest that the TOF ratio should be 0.9 or even higher to exclude PORC (4).



**Figure 2.3 TOF Watch® stimulating the ulnar nerve. TOF ratio=0.69 (50).**

There is conflicting evidence regarding the effectiveness of intraoperative neuromuscular monitoring in reducing PORC (11). Despite the conflicting data a TOF ratio initially set at 0.7, but now agreed at 0.9, is considered to correlate with sufficient clinical recovery of muscle function (26). Residual paralysis cannot be prevented by neuromuscular monitoring but it does alert the anaesthetist to the problem so that appropriate management can be applied, e.g. delay reversal until four twitches are present and extubate only when TOF ratio > 0.8. It can also guide the anaesthetist as to how much reversal should be given taking into account the ceiling dose of neostigmine. (21, 46)

A TOF ratio of > 0.9 does not mean that all the acetylcholine receptors are available for potentiating an action potential. However there are now enough receptors to facilitate adequate muscular function. A study by Baumuller et.al (52) found that the administration of sugammadex, after a TOF ratio of > 0.9 was established, did not produce any clinical difference in neuromuscular recovery.

### 2.3.3 Risk factors for PORC

Patients who receive multiple boluses or a continuous infusion of NDMRs are at a higher risk of PORC. The risk is higher because larger cumulative doses of the NMDA's are administered over a short period as compared to a single appropriately calculated dose when a bolus dose regime is used. The incidence is thought to be higher in patients with organ dysfunction as this alters the pharmacokinetic properties of the drug.(7, 25) Dosing of NDMR's is according to the ideal body weight and therefore obese patients may also present with an increase risk of developing PORC if the total body weight is used (9).

Hypothermia has also been shown to lengthen the duration of action of the NDMRs as their metabolism is reduced with decreasing temperatures. Core temperatures  $< 36^{\circ}\text{C}$  result in a decrease in blood viscosity and thus a decrease in blood flow. In addition enzymatic function is slower at lower temperatures. (26, 30, 53)

Heier et al (54) found that the clearance of vecuronium decreased by 10% for every  $1^{\circ}\text{C}$  drop in core body temperature. A core body temperatures below  $32^{\circ}\text{C}$  is associated with an increased potency of NDMR's however these temperatures are rarely encountered in routine surgery.

Ageing is accompanied by numerous physiological changes including a decrease in renal and hepatic blood flow resulting in a decline of function. This has an impact on the pharmacodynamics and pharmacokinetics of NDMR's in the elderly population. Ageing is also associated with anatomical changes such as a reduction in the number of motor neurons in the spinal cord, a loss of muscle fibres and a decrease in the size of type two muscle fibres. However the difference in the pharmacological behaviour of NDMRs has been demonstrated to be primarily from the physiological changes (55). Pietraszewski et.al (32) found that 90% of all elderly patients ( $> 65$ years) had

residual paralysis when neuromuscular monitoring was not used. Elderly patients were twice as likely to develop residual paralysis when compared to younger patients.

Magnesium is frequently used in anaesthesia to prevent hypertension and arrhythmias and is occasionally used as a bronchodilator. Magnesium also potentiates the effects of NDMRs by the antagonism of calcium at the presynaptic terminal of the neuromuscular junction, reducing the release of acetylcholinesterase. (9, 56, 57)

Pinard et al (56) found that administration of magnesium in patients undergoing cardiac surgery resulted in an increase in the duration of neuromuscular blockade of cisatracurium by 30 to 35 minutes. A study at the University of Cape Town found administering magnesium to rats after an anaesthetic, during which rocuronium was used, decreased the TOF ratio by 52.5% to 19.4% despite apparent full neuromuscular recovery (TOF ratio >0.9). The use of magnesium resulted in recurarisation (58).

The increasing pressure for quick turnover of surgical cases may also shorten the time between the administration of reversal and endotracheal extubation. The current practice of extubating five minutes after administering an anticholinesterase is a potentially unsafe practice as insufficient time has passed for the adequate return of neuromuscular function. (7)

In addition some anaesthetists do not routinely administer an anticholinesterase if spontaneous ventilation with adequate tidal volumes (6 ml/kg) develops before the end of surgery (12, 59). This predisposes to the development of PORC as adequate tidal volumes are achieved with a TOF ratio < 0.4 (12, 21).

#### 2.3.4 Prevention of PORC

Four steps are supported to prevent PORC: avoid long acting NDMRs, prevent hypothermia as it delays recovery, anticholinesterase administration only after spontaneous recovery is identified by the presence of four visible twitches on the TOF ratio and reversal should be administered in any patient with a TOF ratio < 0.9 (16, 26).

Neuromuscular blocking agents should be avoided unless absolutely necessary (60). Patients with co-morbid illnesses need drug dose titration to effect, as the pharmacokinetic and pharmacodynamics properties of the NDMRs are often altered (6). NDMR drug selection should be determined according to the duration of surgery and the patient's pharmacokinetic profile.

Avoid repeated boluses, particularly towards the end of surgery.

Neuromuscular monitoring should guide both intraoperative and postoperative assessments of muscle function (53). Delay extubation and reversal in patients with intense blockades until spontaneous recovery is evident. It should be noted that spontaneous recovery does not mean that there is no residual paralysis as different muscle groups recover at different rates from NDMR. In some countries, it is a common practice not to give reversal if there is spontaneous recovery. This is considered bad practice and affects patient safety. Reversal should only be omitted when objective assessments using an acceleromyograph or mechanomyograph is used and a TOF ratio  $\geq 0.9$  is found. (60)

#### 2.3.5 Complications of PORC

Murphy et al (59) identified numerous side effects of PORC including a higher risk of aspiration, upper airway obstruction, depressed hypoxic drive, subjective muscle weakness and pharyngeal muscle weakness with impaired swallowing.

A review by Ghai et al (15) concluded that there is a good correlation between the clinical observation and TOF ratio but the relationship between TOF ratio and the signs and symptoms of PORC differs among patients Table 2.4 categorises which signs are found at a specific TOF.

**Table 2.4 TOF ratio associated with specific clinical signs. (7, 12, 15)**

<b>TOF</b>	<b>Signs and symptoms</b>
<b>TOF ratio &lt; 0.4</b>	Inability to lift head or arm Tidal volume can be normal Vital capacity and negative inspiratory pressures are decreased
<b>TOF ratio &lt; 0.6</b>	Head lift for three seconds Eyes open wide Able to stick out tongue Vital capacity and negative inspiratory pressures are reduced
<b>TOF ratio &lt; 0.8</b>	Head lift for five seconds Grip strength 60% of normal Vital capacity and negative inspiratory pressures are normal Diplopia or facial weakness

As a result of PORC, there are delays in discharge from the operating theatre recovery room. A study by Butterly et.al (61) found that patients with PORC (TOF ratio < 0.9) had a mean operating theatre recovery room length of stay of 323 minutes compared to those without PORC who stayed on average about 243 minutes. Although in their study the length of stay in the recovery room was particularly long, it does demonstrate that the presence of PORC delays discharge from the operating theatre recovery room. This has

significant economic consequences as the operating theatre recovery room can be fully occupied preventing further admissions. (61)

Profound muscle weakness produces anxiety in the majority of patients, this can have long term psychological effects including depression and post traumatic stress disorder (10). Patients in recovery will often complain of “feeling weak” or “difficulty seeing or speaking” as a consequence of diplopia and weakness of the oral cavity muscles (18, 19).

Murphy et al (59) performed a study focused on patients subjective experiences compared to the TOF ratio. Patients complained of general weakness, difficulty in opening eyes and lifting head, difficulty in tracking objects, blurry vision, difficulty in speaking and muscle weakness. Results of the study showed that 54 to 91% of patients with a TOF ratio  $< 0.9$  complained of the above symptoms, compared to 9 to 45% of patients in the TOF ratio  $\geq 0.9$  group. The possible causes of muscle weakness in the group with a TOF ratio  $\geq 0.9$  include residual effects of inhalational agents, hypothermia, electrolyte imbalances, prolonged immobility and an inflammatory response to perioperative stressors. The clinical evaluation of PORC is often difficult because of the effects of intraoperative anaesthetic drugs, shivering, analgesia and pain. The multifactorial aetiology of muscle weakness presents a limitation to the above study.

A study performed in Germany in 2006 by Eikermann et al (62) induced a partial neurological blockade (TOF ratio between 0.5 to 0.8) in 10 healthy young males volunteers. The volunteers were kept spontaneously breathing. An MRI was performed to identify the upper airway dimensions; electromyography was used to measure the force of contractions of the genioglossus muscle and spirometry was used to measure lung volumes. These tests were all performed on different days. Results from this study showed a 10 to 20% decrease in inspiratory volumes and an increase in the anterior posterior upper airway diameter during forced inspiration. A decrease in genioglossus activity was also identified. There were no effects on lung volumes and upper airway size during expiration, which is expected, as

expiration is primarily a passive movement. This study suggests that a residual block that does not produce respiratory symptoms (e.g. desaturation) still results in impaired upper airway dimensions and function. (62, 63)

The common of effects of PORC are usually seen 24 to 48 hours after surgery, these include atelectasis and pneumonia and are usually treated by surgeons. As a consequence many anaesthesiologists do not recognise that PORC continues to be a danger long after the patient has left theatre. (32, 64)

### 2.3.6 Reported incidence of PORC

One of the first studies looking at the incidence of PORC was done by Viby-Mogensen et al (65) in 1979. All patients tested received a long acting NDMR. They used a TOF ratio of  $< 0.7$  and found that 42% of patients had residual block despite having clinical recovery. (10) If the new criterion of a TOF ratio  $< 0.9$  had been used the incidence would have been 72% (21).

A study done in South Africa reported a 42.9% occurrence of PORC (TOF ratio  $< 0.9$ ) in a hospital in Bloemfontein in 2004. These results are similar to those attained by Viby-Mogensen et al (65) 25 years earlier. (19)

In 2011, a multicentre study in Portugal aimed at identifying the incidence of PORC, reported that 26% of patients presented to the recovery room with a TOF RATIO  $< 0.9$ , 66.6% had been given reversal. A higher incidence of residual paralysis was found in patients who had received reversal (30%) compared to those who had not (17%). It is postulated that the reason for this is that reversal is avoided by many because of its side effect profile, therefore when used it was possibly for rapid reversal. (37).

Despite the use of intermediate acting NDMR's and the use of reversal the estimated incidence of PORC ranges from 17 to 36% and can be as high as 64% in some institutions (10, 12, 18). It has also been postulated that



approximately 40% of patients will develop at least one hypoxaemic episode in the recovery room and that these occur within the first 20 minutes after admission (64). Routine neuromuscular monitoring has been advocated as a means of reducing the incidence of PORC and therefore hypoxaemic episodes (16).

Administration of neostigmine after surgery does not always ensure complete restoration of patient's muscle strength. Neostigmine in the absence of a neuromuscular block (TOF ratio  $\geq 0.9$ ), will impair upper airway volumes, genioglossus muscle function and diaphragmatic function. A study by Grosse-Sundrup (25) postulated that the administration of neostigmine in the absence of a residual block could lead to muscle weakness (acetylcholine accumulation at the motor end plate results in spasm). In light of this information, the need for intraoperative neuromuscular monitoring is further highlighted. (7, 25)

A review article by Murphy et al (44) identified the majority of studies conducted from 1979 to 2013 have demonstrated that the incidence of PORC (using objective neuromuscular monitoring) remains high despite the introduction of intermediate acting NDMR. Most anaesthetists still believe that clinically significant muscle weakness is an infrequent event (44, 66).

A survey conducted in 2011 indicated that anaesthetists estimated the incidence of PORC to be 1% or less. This survey was sent to American and European anaesthetists and 80% responded that they had never seen clinically significant residual paralysis. (12)

Evidence suggests that PORC impairs clinical recovery and has a negative impact on patient safety. Clinical studies have shown through objective measures that a TOF ratio  $< 0.9$  reduces upper airway volumes, causes airway obstruction, hypoxemic events and postoperative pulmonary complications. In light of the research done it has been recommended that neuromuscular monitoring be performed routinely to reduce the incidence of PORC and improve patient safety. (7, 53) Patient perceived quality of

recovery is an important measure of patient safety and research has shown that most patients will complain of uncomfortable symptoms of muscle weakness with a TOF ratio < 0.8 (44). Some authors have even advocated that the use of an acceleromyograph should become a standard of care similar to pulse oximetry (11, 28).

The use of neuromuscular monitoring has been shown to reduce the incidence of PORC from between 38.1 to 67% (14). An assessment of practice found that the majority of anaesthetists do not use neuromuscular monitoring, either because they feel that clinical signs are adequate or because of a lack of equipment availability at some institutes (12). Tsai et al (67) concluded that neuromuscular monitoring is an evidence based practice, it is non invasive and has little risk. Their recommendation was that this measurement should be performed in theatre before extubation to ensure patient safety.

## **2.4 Summary**

An in-depth discussion on various subjects has been presented in the literature review regarding NDMR and PORC. In the first section, a brief overview of the history and pharmacology of neuromuscular blocking agents was provided. Thereafter, PORC was discussed in detail. The testing of neuromuscular function to identify PORC was discussed. Risk factors for the development of PORC were examined next. Important principles regarding the prevention of PORC was then evaluated. The consequences of PORC on patient's quality of life and functioning was addressed. The prevalence of PORC according to various international studies was considered.

The following chapter deals with the research methodology of this study.

## **Chapter 3: Research methodology**

The problem statement, aim and objectives of the study, ethical considerations, research methodology and validity and reliability of the study are discussed in this chapter.

### **3.1 Problem statement**

Anaesthetists use NDMRs every day. Practices' regarding the use of neuromuscular blocking agents and their subsequent reversal, or lack thereof, differs among anaesthetists. Common practice in South Africa aimed at identifying residual paralysis is primarily a clinical evaluation (for example: head lift for five consecutive seconds or the ability to cough) (19). Clinical assessment has been shown to over estimate neuromuscular recovery. As a result a high percentage of patients who receive NDMRs may present to the recovery room with residual paralysis. (18)

The failure to prevent, recognise and manage PORC, compromises patient safety and is considered malpractice. (10) The occurrence of PORC in the operating theatre recovery room of Chris Hani Baragwanath Academic hospital (CHBAH) is currently unknown.

### **3.2 Aim of the study**

Aim of the study was to describe the occurrence of PORC in the recovery room in patients who have received intermediate acting NDMRs intraoperatively at CHBAH.

### **3.3 Objectives of the study**

The primary objectives of the study were to:

- document if the TOF ratio was done before administration of an anticholinesterase and extubation by the attending anaesthesiologist
- describe the clinical assessment of neuromuscular function
- describe the occurrence of PORC as determined by the TOF ratio
- describe the occurrence of factors contributing to PORC (hypothermia, NDMR, patients age and the use of an anticholinesterase).

The secondary objectives were to:

- compare with TOF ratio with the following clinical parameters:
  - saturation
  - handgrip
  - ability to cough
  - headlift
- compare factors contributing to PORC (hypothermia, NDMR, patients age and the use of an anticholinesterase) with the TOF ratio.

### **3.4 Ethical considerations**

Approval to conduct the study was obtained from the Human Research Ethics Committee (Medical) (Appendix 1) and the Post Graduate Committee of the University of Witwatersrand (Appendix 2). Permission from the Medical Advisory Committee of CHBAH was also acquired. (Appendix 3)

Patients were invited to participate in the study the day before surgery. An introduction and detailed explanation including a patient information letter (Appendix 4) was given to the patient. Informed written consent (Appendix 5) was obtained from all study patients who agreed to take part. The patient information letter and informed consent was written in a manner that was clear to the intended patients.

During the study period if a patient was found to have PORC, the researcher contacted the anaesthetist responsible for the patient and remained with the patient until the anaesthetist arrived.

All information regarding individual participants was recorded anonymously and kept confidential. Records will be stored in a secure place for six years.

The study was conducted in accordance with the Declaration of Helsinki (23) and the South African Good Clinical practice guidelines (24).

### **3.5 Research methodology**

#### **3.5.1 Research design**

A research design determines what methods are used find subjects, collect and analyse data, and interpret results. It can therefore be described as the blueprint for the study. (68) A prospective, contextual and descriptive research design was used.

A prospective study is one where the variables are measured during the time the study takes place (69, 70). This study was prospective as the data was collected when the study took place.

Context refers to the setting for an event, the “small scale world” (68). This study was conducted contextually in the recovery room of operating theatres at CHBAH.

A descriptive research design is used to observe, describe and document occurrences as they happen in real life situations (70). This study was descriptive as it described the occurrence of PORC in patients who have received intermediate acting NDMRs.

### 3.5.2 Study population

The study population included ASA 1 to 3 patients who had undergone elective surgery and received an intermediate acting NDMR.

### 3.5.3 Study sample

#### **Sample size**

Sample size is determined not just by the nature of the design study but also by the degree of precision required. Other factors that have to be taken into consideration when determining the sample size include precision of the data collection instrument, heterogeneity of the population and the incidence of the type of participant in the population. The more precise the data collection instrument is the smaller the sample size needed. Increasing demographic variables require increasing sample size. (68, 70, 71)

Sampling describes the process of selecting a group of people with whom one wants to conduct the study. This subset of the population aims to represent the population in its entirety. (70)

Studies have identified that the average incidence of PORC ranges from 17 to 64% (48, 60, 64). It was estimated by the anaesthetists at CHBAH that the occurrence of PORC was about 20%. In consultation with a biostatistician using STRATA 12.5, it was postulated that 20% of our patients compared to an average of 40% of patients in the literature would have PORC, with a 5% level of confidence and 90% power, we needed 55 patients.

## **Sampling method**

A convenience sampling method will be employed for this study as a whole population study is limited by consent from participants and the possibility that the entire population will not be available or fulfil the inclusion criteria at the time of sampling. Convenience sampling can be considered as availability sampling as it entails choosing subjects that are readily available as participants for the study. This continues until an available sample size is reached. A disadvantage of this sampling method is that the data may not truly represent the population. (68) A convenience sampling method was employed for this study.

## **Inclusion and exclusion criteria**

Inclusion criteria for this study were as follows:

- adults 18 years and older
- ASA 1 to 3 patients
- surgery for an elective procedure
- received an intermediate acting NDMR intraoperatively
- extubated postoperatively.

Exclusion criteria for this study were as follows:

- patients who did not consent
- no access to either ulnar nerve
- patients who were unable to understand english.

### **3.5.4 Data collection procedure**

Data was collected on days convenient for the researcher. This ensured that routine anaesthetic practice did not change while data was collected.

Preoperative consent was obtained from all ASA 1 to 3 patients booked for elective surgery. Consent was obtained the day before in the ward. Patients were invited to take part in the study. Patients who agreed received a patient information letter (Appendix 4) and informed written consent (Appendix 5) was obtained. The patient information letter and informed consent was written in a manner that is clear to the intended patients.

The intraoperative management of the patient was at the discretion of the responsible anaesthetist i.e. if a NDMR was used or not; if neuromuscular function was monitored intraoperatively and/or if a reversal agent was used. The anaesthetist managing the patient intraoperatively was not alerted to the fact that neuromuscular monitoring would occur in the recovery room.

On arrival to the operating theatre recovery room, once the anaesthetist responsible for the patient had signed the patient off as being adequately recovered, the TOF ratio was recorded by the researcher before accessing the anaesthetic record to ascertain which NDMR had been used.

The researcher used an accelerometer. The accelerometer used was a TOF Watch® SX, produced by Organon, was on loan from the Department of Anaesthesiology and calibrated prior to use by local manufacturers. No further calibrations were done between patients. The TOF Watch® SX was exclusively used for research purposes.

Electrodes of the accelerometer were placed over the ulnar nerve on the volar aspect of the wrist and the acceleration sensor was connected to an unrestricted thumb. The negative electrode was placed 1 cm proximal to the point at which the proximal flexion crease of the wrist crosses the flexor carpi ulnaris tendon. The positive electrode was placed 2 to 3 cm proximal to the negative electrode. A submaximal stimulus of 30 mA was applied and the accelerometer generated a ratio. This current intensity will induce only a fraction of fibres in a given nerve bundle. This would therefore reduce the twitch height but the ratio measured between the twitches remains the same (31). Measurements were repeated every 20 seconds until three



measurements were obtained. The average of these three measurements was used as the TOF ratio.

Clinical assessment of neuromuscular function such as the ability to sustain a head lift and handgrip, the ability to cough, and oxygen saturations were carried out as these parameters are most commonly employed.

The following data was captured on a data capture record (Appendix 6):

- demographic data
  - age
  - gender
  - surgery
  - duration of surgery
  - drug names
- TOF ratio measurements intraoperatively, if available
- TOF ratio measurements done by the researcher in recovery room
- clinical assessments
  - head lift
  - handgrip
  - cough
  - oxygen saturation.
  - body temperature.

If a patient was found to have PORC, the researcher contacted the anaesthetist responsible for the patient and remained with the patient until the anaesthetist arrived.

### 3.5.5 Data analysis

Data was captured using Microsoft Office Excel<sup>®</sup> data spread sheets. Data was analysed with the assistance of a biostatistician and using STATISTICA, version 12.5. Frequencies and percentages were used to summarise the

results. Continuous variables were summarised using means and standard deviations if normally distributed and median and ranges if not normally distributed.

### **3.6 Validity and reliability of the study**

Validity has been defined as “a measure of the truth or accuracy of a claim” (70). Reliability is represents a consistency of the measure achieved (69).

Validity and reliability of this study was ensured by:

- choosing an appropriate study design
- using appropriate data gathering techniques
- the researcher being the only data collector
- the sample size being determined with assistance of a biostatistician
- the data being analysed in consultation with a biostatistician
- using a calibrated accelerometer
- using the same accelerometer on all patients.

### **3.7 Summary**

A detailed explanation of the research methodology has been presented in this chapter under the headings of study design, study population and study sample (including study size, sampling method, inclusion and exclusion criteria), description of data collection procedures, and the planned statistical analysis of the data.

The following chapter details the data analysis and discussion of the results of the study.

## **Chapter 4: Results and discussion**

### **4.1 Introduction**

This chapter contains the results according to the objectives and the discussion thereof. The primary objectives of the study were to:

- document if the TOF ratio was done before administration of an anticholinesterase and extubation by the attending anaesthesiologist
- describe the clinical assessment of neuromuscular function
- describe the occurrence of PORC as determined by the TOF ratio
- describe the occurrence of factors contributing to PORC (hypothermia, NDMR, patients age and the use of an anticholinesterase).

The secondary objectives were to:

- compare with TOF ratio with the following clinical parameters:
  - saturation
  - handgrip
  - ability to cough
  - headlift
- compare factors contributing to PORC (hypothermia, NDMR, patients age and the use of an anticholinesterase) with the TOF ratio.

### **4.2 Sample realisation**

Data was collected over a period of three months (December 2014 to February 2015) and 55 patients were included in the study.

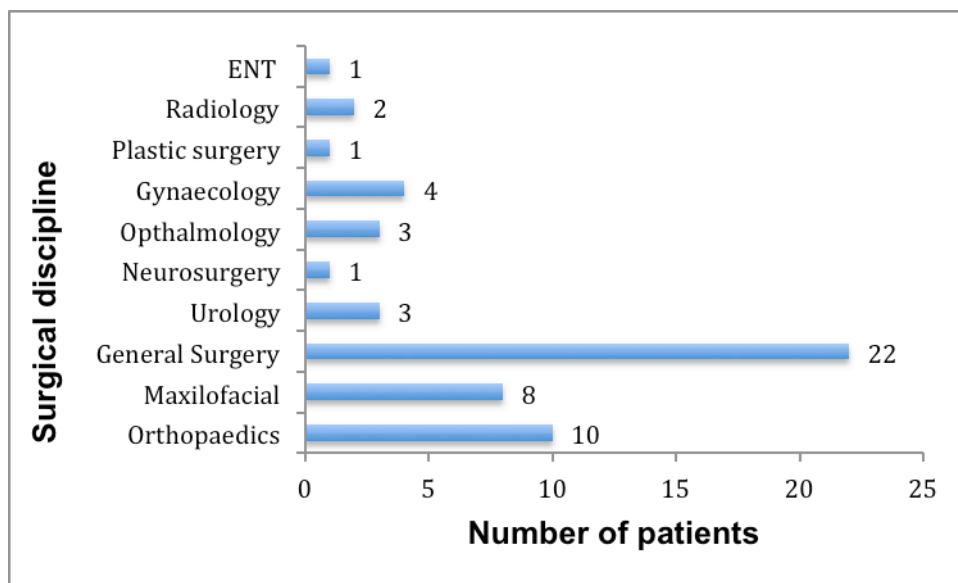
### **4.3 Results**

Results are presented rounded off to two decimal points. Where appropriate, primary and secondary objectives will be presented together for ease of reading.

#### 4.3.1 Demographics

Of the 55 patients, 30 (54.54%) were male. The mean age of patients assessed was 43.9 years (SD 15.80), ranging from 20 to 79 years.

Twenty two (40%) of the patients presented for elective general surgery. Figure 4.1 exhibits the range of surgical disciplines from which patients presented.



**Figure 4.1 Surgical disciplines from which patients presented**

4.3.2 Primary objective: document if the TOF ratio was done before administration of an anticholinesterase and extubation by the attending anaesthesiologist

Of the 55 patients, 3 (5.45%) according to the anaesthetic chart had received intraoperative neuromuscular monitoring. However the exact stimuli utilised and responses elicited were not recorded. It was also not evident whether the

use of neuromuscular monitoring intraoperatively changed practice in the administration of a reversal agent and extubation criteria.

#### 4.3.3 Primary objective: describe the clinical assessment of neuromuscular function

Parameters utilised in this study to describe clinical assessment of adequate neuromuscular function include the oxygen saturation  $\geq 90\%$ ; the ability to hold a hand grip for  $\geq 5$  seconds; (grip strength was not assessed) the ability to cough and to lift the head for  $\geq 5$  seconds.

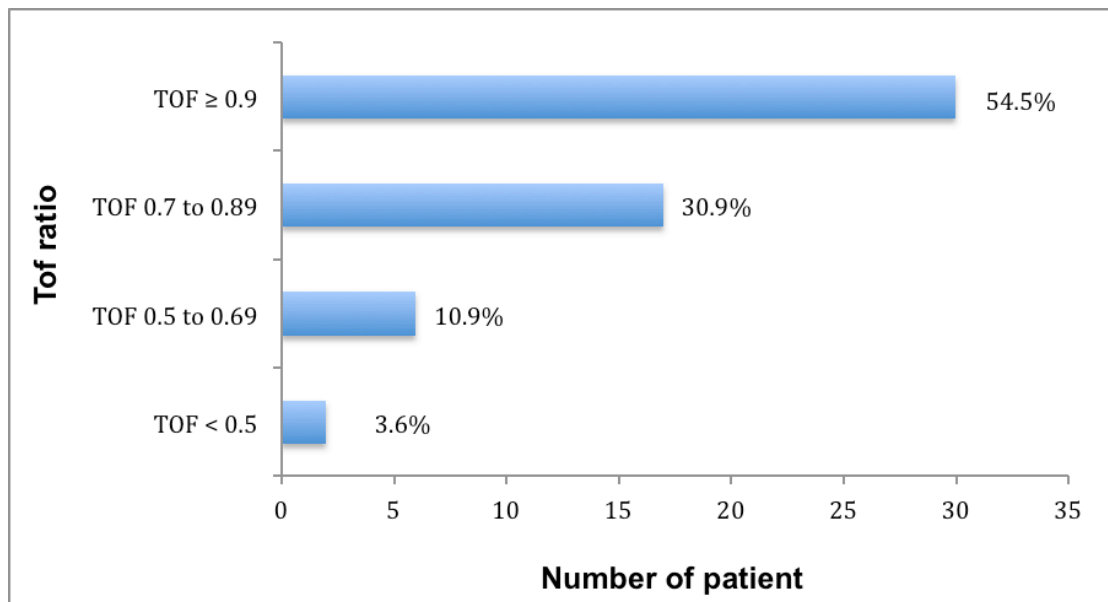
Supplemental oxygen was placed by the attending anaesthetist and whether placed routinely or as a therapeutic measurement was not determined by the researcher. Oxygen saturation ranged from 85 to 100% with a mean of 96.3% (SD 2.86). Forty two (76.36%) of the 55 patients were placed on supplemental oxygen in the recovery room. One (1.82%) patient on supplemental oxygen had a saturation  $< 90\%$ . The clinical parameters of patients assessed are presented in Table 4.1.

**Table 4.1 Clinical parameters**

<b>Parameter</b>	<b>Adequate n (%)</b>	<b>Inadequate n (%)</b>
<b>Saturation</b>	54 (98.18)	1 (1.82)
<b>Handgrip</b>	46 (83.63)	9 (16.37)
<b>Ability to cough</b>	51 (92.73)	4 (7.27)
<b>Headlift</b>	44 (80)	11 (20)

#### 4.3.4 Primary objective: describe the occurrence of PORC as determined by the TOF ratio

Out of the 55 patients, 25 (45.46%) patients fulfilled the criteria for PORC with a TOF ratio  $< 0.9$ . The TOF ratios obtained from patients is shown in Figure 4.2



**Figure 4.2 TOF ratio obtained from patients**

4.3.5 Primary objective: describe the occurrence of factors contributing to PORC (hypothermia, NDMR, patients age and use of an anticholinesterase)

and

Secondary objective: Compare the factors contributing to PORC (hypothermia, NDMR, patients age and use of an anticholinesterase) with the TOF ratio.

## Hypothermia

Temperature within the study sample was normally distributed, with a mean of 36.28 °C (SD 0.88), a minimum of 34.1 °C and a maximum of 38.4 °C.

Table 4.2 presents the occurrence of PORC with temperature.

**Table 4.2 The occurrence of PORC with temperature**

	<b>Temp ≥ 35</b> n (%)	<b>Temp &lt; 35</b> n (%)	<b>Total</b> n (%)
<b>TOF RATIO&lt;</b> <b>0.9</b>	23 (41.82)	2 (3.64)	25 (45.46)
<b>TOF RATIO≥</b> <b>0.9</b>	29 (52.72)	1 (1.82)	30 (54.54)
<b>Total</b>	52 (94.54)	3 (5.46)	55 (100)

**\*p=0.59**

Of the 55 patients, 3 (5.46%) patients had a temperature of < 35 °C and were therefore hypothermic. Of those who were hypothermic 2 (66.67%) had PORC and 23 (44.23%) of those with a temperature above 35 °C presented with PORC.

A Fisher's exact was applied to determine if temperature in the patients with PORC differed from the patients without PORC. The p value of 0.59 was considered not significant.

## **NDMR**

The occurrence of PORC in each of the intermediate NDMRs used is shown in Table 4.3. Rocuronium was the most frequently used NDMR with 31 (56.36%) of 55 patients having received it.

**Table 4.3 Occurrence of PORC with the different classes of NDMR**

	<b>Atracurium</b> n (%)	<b>Cisatracurium</b> n (%)	<b>Rocuronium</b> n (%)	<b>Vecuronium</b> n (%)	<b>Total</b> n (%)
<b>TOF ratio &lt; 0.9</b>	2 (3.63)	5 (9.09)	15 (27.27)	3 (5.45)	25 (45.56)
<b>TOF ratio ≥ 0.9</b>	5 (9.09)	4 (7.27)	16 (29.09)	5 (9.09)	30 (54.54)
<b>Total</b>	7 (12.72)	9 (16.36)	31 (56.36)	8 (14.54)	55 (100)

**\*p = 0.72**

Of those that had received rocuronium 15 (48.39%) of the 31 patients presented with a TOF ratio < 0.9. Cisatracurium was the second most commonly used NDMR, 9 patients received cisatracurium and 5 (55.56%) of them developed PORC. Eight patients received vecuronium and 3 (37.50%) developed PORC. Atracurium was the least used NDMR with 7 patients having received it and 2 (28.57%) of them developed PORC.

A Freeman-Halton extension of the Fisher exact test was applied to the above data and yielded a p-value of 0.72. The result is therefore not statistically significant.

### **Patient age**

Patients between 18 and 80 years of age were included in data analysis. Forty five (81.81%) of the patients were < 60 years old and 10 were ≥ 60 years old. Table 4.4 identifies the TOF ratios within the two age groups.



**Table 4.4 TOF ratios in both age groups**

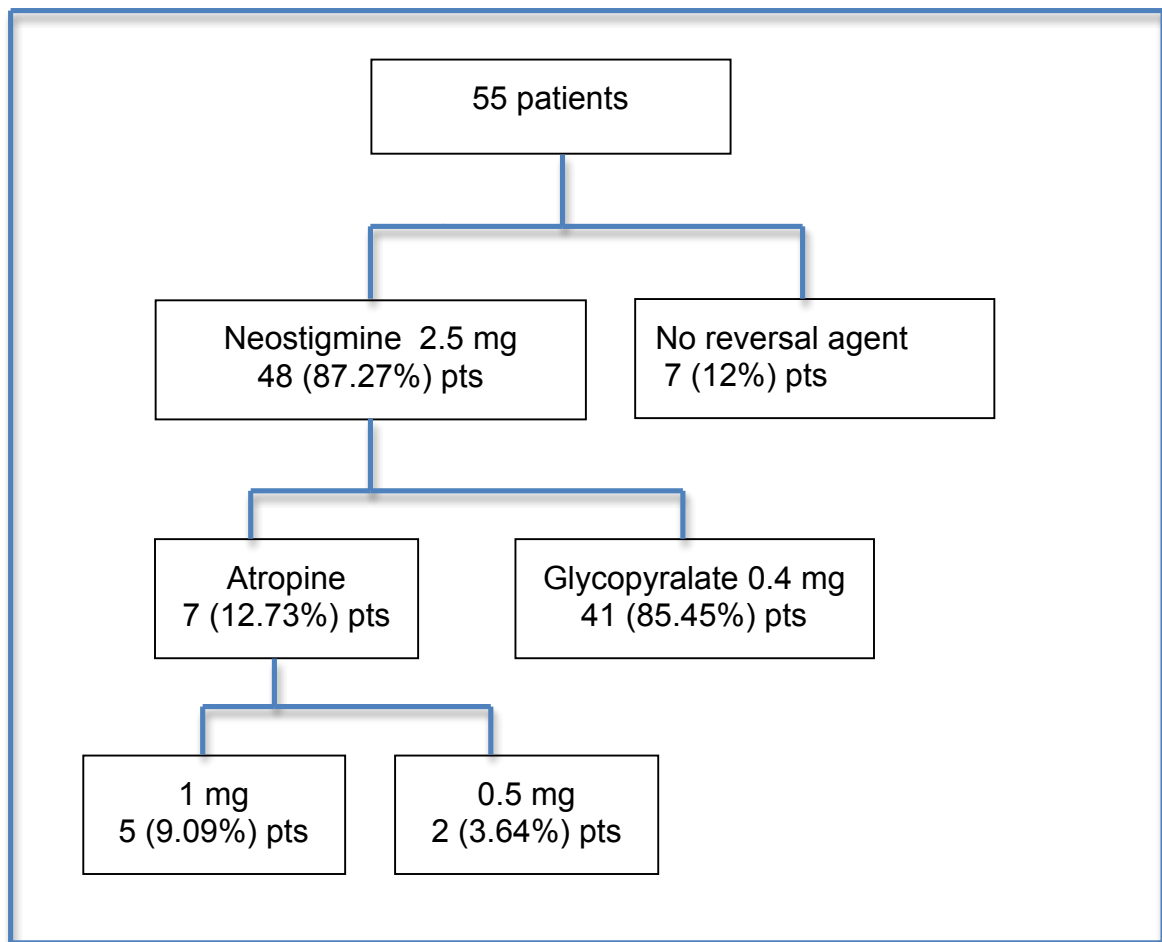
	<b>&lt; 60</b> n (%)	<b>≥ 60</b> n (%)	<b>Total</b> n (%)
<b>TOF ratio &lt; 0.9</b>	21 (38.18)	4 (7.28)	25 (45.46)
<b>TOF ratio ≥ 0.9</b>	24 (43.64)	6 (10.90)	30 (54.54)
<b>Total</b>	45 (81.82)	10 (18.18)	55 (100)

**\*p = 0.49**

A Fishers exact test was not statistically significant with a p value of 0.49

### **Use of an anticholinesterase**

Neostigmine is currently the only reversal agent available at CHBAH. At the time of data collection there was a shortage of the anticholinergic glycopyralate and as a consequence this may have impacted on the results. Figure 4.3 illustrates the practice of anticholinesterase and anticholinergic use.



**Figure 4.3 The use of anticholinesterase and anticholinergic**

The occurrence of PORC in patients that received an anticholinesterase can be seen in Table 4.5.

**Table 4.5 The occurrence of PORC with the use of an anticholinesterase.**

	Received n (%)	Did not receive n (%)	Total n (%)
<b>TOF ratio &lt; 0.9</b>	19 (34.55)	6 (10.91)	25 (45.46)
<b>TOF ratio ≥ 0.9</b>	29 (52.72)	1 (1.82)	30 (54.54)
<b>Total</b>	48 (87.27)	7 (12.73)	55 (100)

**\*p = 0.03**

Of the 55 patients, 48 (87.27%) received a reversal agent and 19 (39.58%) of them subsequently presented with PORC. Seven (12.73%) patients did not receive an anticholinesterase and 6 (85.71%) of them presented with PORC.

A Fishers exact test yielded a p value of 0.03 which is considered statistically significant. Therefore there is an association between the use of an anticholinesterase and PORC.

#### 4.3.6 Secondary objective: compare clinical assessment with TOF

Table 4.6 compares the clinical assessment with the TOF. Passing the clinical assessment meant that they could lift their heads for  $\geq 5$  seconds sustain a handgrip  $\geq 5$  seconds, able to cough and maintain oxygen saturations  $\geq 90\%$  with or without supplemental oxygen. A TOF ratio of  $\geq 0.9$  was considered adequate reversal.

**Table 4.6 Clinical assessment against TOF**

	<b>Clinical assessment pass n (%)</b>	<b>Clinical assessment fail n (%)</b>
<b>TOF ratio &lt; 0.9</b>	20 (36)	5 (9)
<b>TOF ratio <math>\geq 0.9</math></b>	24 (44)	6 (11)

**\*p = 0.63**

A Fishers exact test was performed comparing the clinical assessment against the TOF ratio results. The p value was 0.63 was considered not significant.

## 4.4 Discussion

This study aimed to describe the occurrence of PORC in the recovery room in patients who have received an intermediate acting NDMR intraoperatively at CHBAH. This study was executed in conditions of daily practice at CHBAH. At the time of data collection intermittent drug shortages of glycopyralate and atracurium were present. This study provides data on the prevalence of

residual paralysis in the recovery room, which has not previously been assessed at CHBAH. The occurrence of PORC was found to be 45.46%. Research done internationally over the last 30 years has identified that the average incidence of PORC ranges from 17 to 64% (10, 12, 18). A study performed at Universitas Hospital in Bloemfontein in 2004, produced a prevalence of 42.9% when a TOF ratio  $< 0.9$  was used and only 17.1% if a TOF ratio  $< 0.8$  was used. A TOF ratio  $< 0.8$  was the diagnostic criterion for PORC in 2004 (19). These results are similar to the results achieved in this study.

Estimates of the occurrence of PORC vary widely in the literature. This may be due to different patient demographics, practices of using reversal agents and the use of intraoperative neuromuscular monitoring. The occurrence of PORC found is still high considering that one of the first studies to identify the incidence was done by Viby-Mogensen et al (65) in 1979. All patients tested in their study received a long acting nondepolarising neuromuscular blocker. They used a TOF ratio of  $< 0.7$  as the diagnostic criterion and found that 42% of patients had residual block despite having adequate recovery clinically. (65) If the new criterion of a TOF ratio  $< 0.9$  had been used the incidence would have been 72% (21).

It is essential to consider why the occurrence of PORC is still regarded as being relatively infrequent even though several studies (11, 19) including this research report have shown that PORC is a common occurrence. Many anaesthetist still rely on clinical parameters to exclude PORC which has been shown to be inaccurate (6, 8). The side effects of PORC with a TOF ratio  $> 0.7$  are not usually life threatening and may therefore be perceived as less important (7).

Results from the secondary objectives should be interpreted with caution, as the sample size was not calculated to power the comparisons.

Of the 55 patients included in this study, 44 (80%) passed the clinical assessment done by the researcher. Of these 44 patients, 20 (36%) who were

clinically assessed to be reversed had a TOF ratio  $< 0.9$ . A further 6 (11%) of the 55 patients failed the clinical assessment done by the researcher and had a TOF ratio  $\geq 0.9$ . A comparison between objective testing using the TOF ratio and the subjective clinical assessment was not statistically significant. The parameters used in this study are those commonly employed by most anaesthetists in the recovery room at CHBAH to determine if patients are ready for discharge. Other parameters such as measuring the negative inspiratory pressure are not routinely used, as there are no pressure gauges available for this measurement in CHBAH recovery room.

Two (3.64%) of the 55 patients had a TOF ratio  $< 0.5$ . These patients required supplemental oxygen in the recovery area and one of them nonetheless had a saturation of  $< 90\%$ . These 2 (3.64%) patients passed all other clinical parameters tested in the study. According to the literature patients with a TOF ratio  $< 0.6$  should be able to present with a head lift and handgrip for three seconds, open eyes wide and stick out their tongue but the vital capacity and negative inspiratory pressures are reduced (7, 12, 15).

The selection of NDMR played no statistically significant role in the development of PORC. However patients who received cisatracurium presented with a higher percentage of PORC relative to the total number of patients that received cisatracurium i.e. 5 (55.56%) out of the 9 patients that received cisatracurium presented with PORC. On further observations 1 of the 2 patients that presented with a TOF ratio  $< 0.5$  had received cisatracurium.

Maybauer et.al (66) found a higher incidence of PORC in patients who received cisatracurium when compared to rocuronium. This is in keeping with findings in this study where 55.56% of all patients who received cisatracurium developed PORC compared to 48.39% of those who received rocuronium. The dosing of cisatracurium is known to influence its duration of action and at  $3 \times ED_{95}$  it acts as a long acting NDMR. Dosages of drugs were documented on the anaesthetic records however the weights of patients were not, as a result no conclusions could be drawn on the impact of cisatracurium on PORC.

The administration, or lack thereof of an anticholinesterase was found to contribute to the development of PORC. Of the 55 patients included in data analysis 48 (87.3%) received an anticholinesterase as a reversal agent and 7 (12.7%) did not. Of the 7 that did not receive an anticholinesterase, 6 (86%) were found to have PORC. This is in keeping with results found in the literature. The reduction in the occurrence of PORC is further reduced when timing of administration of an anticholinesterase is determined by neuromuscular testing (21, 38).

The occurrence of PORC is higher in patients who had a temperature  $< 35^{\circ}\text{C}$  (66.67%) compared to the patients with a temperature  $\geq 35^{\circ}\text{C}$  (44.23%). This result is not statistically significant. A review article by Heier et.al (54) where the duration of action of NDMR and recovery time was increased by the reduced elimination rate. A  $2^{\circ}\text{C}$  reduction in core body temperature can increase the duration of action of NDMRs by as much as 100%.

The occurrence of PORC in patients over 60 years of age was not found to be higher than in younger patients. Pietraszewski et.al (32) found that 90% of all elderly patients ( $\geq 65$ ) had residual paralysis when neuromuscular monitoring was not used. Elderly patients were twice as likely to develop residual paralysis when compared to younger patients.

The dosing practices of NDMRs including the dose per kilogram, timing and frequency of administration play a vital role in the development of PORC (7, 66). Other factors which may also increase the occurrence of PORC including commonly used drugs like magnesium were not included as part of data collection and therefore their impact on the occurrence of PORC is unknown. Magnesium is a calcium antagonist; this reduces the release of acetylcholine from the presynaptic terminal of the neuromuscular junction resulting in prolonged neuromuscular blockade.

The introduction of sugammadex has the potential to significantly reduce the occurrence of PORC. The costs associated with the impact of inadequate

reversal including prolonged hospital stay and patient morbidity outweigh the cost of sugammadex. The single exit price for an ampoule of sugammadex is one thousand and two hundred rand compared to neostigmine which is five rand for a 2,5 mg vial. A review article by Paton et al(72) looked at the cost effectiveness of sugammadex when compared to neostigmine. Although sugammadex is more expensive than neostigmine it has the ability to reverse profound neuromuscular blockade by encapsulating and removing the aminosteroidal NDMR from the neuromuscular junction unlike neostigmine which has a ceiling dose effect. This means that the patient spends less time in theatre waiting for neuromuscular recovery thereby reducing theatre costs. Sugammadex can also prove to be life saving in situations where an unanticipated difficult airway is encountered consequently the benefits far outweigh the cost.

This study identified that the occurrence of PORC at CHBAH is still high as 45.46% of all patients who presented to the recovery room had a TOF ratio < 0.9. Neuromuscular monitoring was recorded as having been done in 5.45% of the study sample. The values of neuromuscular monitoring were not recorded on the anaesthetic chart and it is not known if neuromuscular monitoring changed the anaesthetic practice intraoperatively. The perceived incidence of PORC by anaesthetists at CHBAH is unknown, but founded on results obtained in this study it is underestimated.

## **4.5 Summary**

In this chapter the results and discussion of the results were presented. In the following and final chapter the summary, limitations, recommendations and conclusion will be addressed.

# **Chapter 5: Summary, limitations, recommendations and conclusion**

## **5.1 Introduction**

In this chapter, the aim and objectives, a study summary, the limitations, recommendations and conclusion will be presented.

## **5.2 Study summary**

### 5.2.1 Aim of the study

The aim of this study was to describe the occurrence of PORC in the recovery room in patients who have received intermediate acting NDMRs intraoperatively at CHBAH.

### 5.2.2 Objectives of the study

The primary objectives of the study were to:

- document if the TOF ratio was done before administration of an anticholinesterase and extubation by the attending anaesthesiologist
- describe the clinical assessment of neuromuscular function
- describe the occurrence of PORC as determined by the TOF ratio
- describe the occurrence of factors contributing to PORC (hypothermia, NDMR, patients age and the use of an anticholinesterase).

The secondary objectives were to:

- compare with TOF ratio with the following clinical parameters:
  - saturation
  - handgrip
  - ability to cough



- headlift
- Compare factors contributing to PORC (hypothermia, NDMR, patients age and the use of an anticholinesterase) with the TOF ratio.

### 5.2.3 Summary of methodology

This study was a prospective, contextual and descriptive study on a sample that consisted of ASA 1 to 3 adult patients who had received an intermediate acting NDMR during elective surgery and were subsequently extubated.

In consultation with a biostatistician it was estimated that a sample of 55 patients was needed. A convenience sampling method was used. Potential patients were identified and invited to participate in the study and given an information letter (Appendix 4). Those agreeing were consented (Appendix 5). Patients were excluded from the study if they did not consent, if there was an inability to use either ulnar nerve during testing and if they did not understand English.

Patients were assessed in the recovery room once they had been discharged by the their attending anaesthetist. A TOF Watch® accelerometer was used to test the TOF ratio using either ulnar nerve on the volar aspect of the wrist. Clinical parameters tested included the ability to sustain a head lift and handgrip, the ability to cough, oxygen saturation and temperature. Details regarding the anaesthetic were obtained from the anaesthetic record and recorded on the data collection record. Data was collected from December 2014 to February 2015. Using Microsoft Excel® 2010, data was captured onto spread sheets. Statistical analyses were done using STATISTICA version 12.5. A p value < 0.05 was considered significant.

#### 5.2.4 Summary of results

Of the 55 patients in the study, 25 (45.46%) had a TOF **ratio** < 0.9 which fulfills the criterion for PORC. Intraoperative neuromuscular monitoring was documented to have been done in 5.45% of the study sample. Hypothermia did not statistically contribute to the development of PORC ( $p=0.2$ ) and neither did the type of NDMR used ( $p=0.72$ ). However a high percentage of patients who were hypothermic presented with PORC (66.67%) i.e 2 of the 3 patients that were hypothermic had a TOF **ratio** < 0.9. Patients who received cisatracurium had a higher occurrence of PORC with 55.56% having a TOF **ratio** < 0.9. Patients older than 60 years were not found to have a higher risk of developing PORC ( $p=0.49$ ). The use of an anticholinesterase in reducing the occurrence of PORC was identified however it did not completely reduce the risk ( $p=0.03$ ). Seven of the 55 patients in the study did not receive an anticholinesterase and 6 (85.71%) of them subsequently presented with PORC. Clinical assessment of adequate neuromuscular function did have any association with the TOF **ratio** objective testing.

### 5.3 Limitations of the study

The study is contextual and therefore results may not be generalisable to other institutions, however the results have the potential to improve clinical practice at CHBAH.

The dosing practices of NDMRs towards developing PORC is important. This study did not collect data on the weight of patients prior to surgery and the dose per kilogram, frequency and timing of administration of NDMRs was not collected. The duration of surgery was noted however timing of last dosages was not evident on anaesthetic records and therefore could not be analysed to determine if it contributed to developing PORC.

This study was not powered to determine if contributing factors like temperature, NDMR, patients age and use of anticholinesterase increased the risk of developing PORC.

Pulse oximetry of patients were recorded but whether oxygen was placed routinely or as a treatment measure was not identified and as such no associations can be made on whether patients who had a TOF **ratio** < 0.9 had a higher prevalence of low oxygen saturations.

Clinical parameters tested are those that are commonly employed in CHBAH, however other parameters can also be used such as inspiratory pressures which may be better at clinically assessing adequate neuromuscular function.

A supramaximal stimulus of 50 mA is recommended for testing using an accelerometer but because of the degree of pain associated with 50 mA a submaximal stimulus of 30 mA was used as in previous studies.

Drug shortages at the time of data collection include glycopyrralate and atracurium and therefore may not reflect usual practices at CHBAH.

## **5.4 Recommendations**

### 5.4.1 Clinical practice

Intraoperative neuromuscular monitoring has the potential to decrease the occurrence of PORC by increasing the awareness and the diagnosis of PORC. Accelerometers should be available in all theatres and neuromuscular monitoring should become routine. Drug dosing practices should be guided by the results obtained from intraoperative neuromuscular monitoring and by patient factors such as age, body mass index and temperature. Utilise NDMRs only when necessary and preferably not for short cases.

Anticholinesterase as a reversal agent should only be administered once four twitches are elicited on a TOF count. Delay extubation and keep patients sedated if the TOF **ratio** < 0.9.

#### 5.4.2 Further research

Should the above mentioned recommendations be implemented at CHBAH, it is recommended that their effectiveness be followed up. Further research adequately powered to identify the contributing factors of PORC is also needed. Dosing practices of NDMRs in relation to the weight of the patient, duration of surgery and timing of the last dose towards the development of PORC also needs to be researched. Research to identify the patient related complications as a consequence of PORC is also recommended to highlight short term and long term effects.

### 5.4 Conclusion

The prevalence of PORC found in this study remains a clinically significant problem. Of interest was the finding that the majority of patients were clinically reversed but 45.46 % still had PORC. This study also found that the use of an anticholinesterase contributed to reducing the risk of developing of PORC but did not reduce the occurrence of PORC. The duration of surgery, NDMR's used, age and temperature of the patients did not show any statistical significance in contributing to the occurrence of PORC.

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# Appendix 1: HREC



R14/49 Dr Sakeena Hassim and Dr Sean Chetty

## HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

### CLEARANCE CERTIFICATE NO. M140360

**NAME:** Dr Sakeena Hassim and Dr Sean Chetty  
**(Principal Investigator)**

**DEPARTMENT:** Anaesthesiology  
Chris Hani Baragwanath Academic Hospital

**PROJECT TITLE:** The Occurance of Residual Curarisation in Postoperative Patients at an Academic Hospital

**DATE CONSIDERED:** 28/03/2014

**DECISION:** Approved unconditionally

**CONDITIONS:**  
**SUPERVISOR:** Helen Perrie

**APPROVED BY:**   
\_\_\_\_\_  
Professor P Cleaton-Jones, Chairperson, HREC (Medical)

**DATE OF APPROVAL:** 23/05/2014  
This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

#### **DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

\_\_\_\_\_  
Principal Investigator Signature

\_\_\_\_\_  
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

## Appendix 2: Postgraduate approval



Faculty of Health Sciences  
Private Bag 3 Wits, 2050  
Fax: 027117172119  
Tel: 02711 7172040

Reference: Ms Thokozile Nhlapo  
E-mail: [thokozile.nhlapo@wits.ac.za](mailto:thokozile.nhlapo@wits.ac.za)

26 May 2014  
Person No: 0301708T  
PAG

Dr S Hassim  
P O Box 8394  
Die Heuwel  
1042  
South Africa

Dear Dr Hassim

**Master of Medicine: Approval of Title**

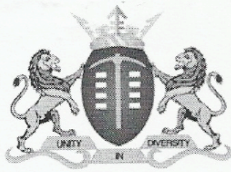
We have pleasure in advising that your proposal entitled *The occurrence of residual curarisation in post operative patients at an academic hospital* has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.

Yours sincerely

A handwritten signature in cursive script, appearing to read 'Sandra Benn'.

Mrs Sandra Benn  
Faculty Registrar  
Faculty of Health Sciences

## Appendix 3: Medical advisory committee



**GAUTENG PROVINCE**

HEALTH  
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE  
CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

### PERMISSION TO CONDUCT RESEARCH

Date: 25 August 2014

TITLE OF PROJECT: The occurrence of postoperative residual curarisation in postoperative patients at an academic hospital

UNIVERSITY: Witwatersrand

Principal Investigator: S Hassim

Department: Anaesthesiology

Supervisor (If relevant): H Perrie


Permission Head Department (where research conducted): Yes

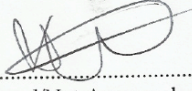
Date of start of proposed study: Aug 2014

Date of completion of data collection: December 2015

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Hospital. The CEO /management of Chris Hani Baragwanath Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- the Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- the MAC will be informed of any serious adverse events as soon as they occur
- permission is granted for the duration of the Ethics Committee approval.

  
.....  
Recommended  
(On behalf of the MAC)  
Date: 25 August 2014

  
.....  
Approved/Not Approved  
Hospital Management

Date: 25/08/14

## Appendix 4: Patient information letter

Hello,

My name is Sakeena Hassim. I am a doctor currently specialising at Wits University. As part of the course requirement, I am expected to conduct research and would like to invite you to take part in my study. The title of my study is: **The occurrence of residual curarisation in postoperative patients at an academic hospital.**

During your operation, you will be given medicine to make your muscles weak. This medicine will help the doctor to do the operation. At the end of the operation, the doctor will check that your muscles are strong enough again so that you can breath on your own. If they are not strong enough the doctor will give you medication to make them strong again. I would like to check if your muscles are strong enough for you to breath when you get to the recovery room after your operation. To do this I will use a little machine that will give you a light shock on your wrist. You will feel this but it will be not painful and you might not remember this. I will also ask you to squeeze my hand, to lift your head up for a short while, to cough and I will take your temperature. If I find that your muscles are not strong enough I will stay with you and ask someone to go and fetch the doctor that put you to sleep for your operation so that he can check you again.

You do not have to take part in this study if you do not want to, or you can decide to take part and then change your mind and this will not affect your treatment in anyway. If you decide to take part in my study I will keep all your information anonymous, meaning that no one will know that you took part as I will not record your name anywhere. Also your information will be locked away safely and only my supervisors and I will be able to see it.

The study has obtained approval from the Human Research Ethics Committee of the University of the Witwatersrand. If you have any questions, please feel free to ask me. You will be given a copy of this form to keep. If you have any questions later on, you can contact me on 011 933 9334 or the Chairman of the Ethics Committee on 011 717 1234.

Thank you for reading this letter.

Yours sincerely

Dr Sakeena Hassim  
[zakke77@yahoo.com](mailto:zakke77@yahoo.com)

## **Appendix 5: Informed consent**

### **Informed consent form**

YOU ARE MAKING A DECISION WHETHER OR NOT TO PARTICIPATE. YOUR SIGNATURE INDICATES THAT YOU HAVE DECIDED TO PARTICIPATE, HAVING READ THE INFORMATION PROVIDED ABOVE AND HAVING YOUR QUESTIONS ANSWERED TO YOUR SATISFACTION.

**Print name of participant:** \_\_\_\_\_

**Signature of participant:** \_\_\_\_\_

**Hospital number:** \_\_\_\_\_

**Study Number:** \_\_\_\_\_

**Print name of researcher/person taking consent:** \_\_\_\_\_

**Signature of researcher/person taking consent:** \_\_\_\_\_

**Date (dd/mm/yy):**

## Appendix 6: Data Collection record

Study number:

Date:

### Demographics

Gender:

<b>Male</b>	<b>Female</b>
-------------	---------------

Age:

Discipline:

TOF Ratio

Measurements:

--	--	--

### Clinical Parameters of adequate neuromuscular function:

Headlift	sec	
Handgrip	sec	
Saturation	%	
Ability to cough	YES	NO

Clinical Parameters:

O2 Facemask	litres/min
Temperature	° C

**Anaesthetic Drugs used, time and dosage:**

<b>Drug</b>		
<b>Atracurium</b>		
<b>Cisatracurium</b>		
<b>Rocuronium</b>		
<b>Vecuronium</b>		
<b>Neostigmine</b>		
<b>Atropine</b>		
<b>Glycopyrralate</b>		
<b>Maintenance</b>		
Was neuromuscular monitoring used	YES	NO
Duration of anaesthetic		