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Development of a guide by postgraduate residents on receiving feedback from faculty in the operating theatre at Aga Khan University Hospital

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AGA KHAN UNIVERSITY

Postgraduate Medical Education Programme

Medical College, East Africa

A RANDOMIZED CONTROL TRIAL COMPARING TRAIN OF FOUR RATIO ≥0.9 TO CLINICAL ASSESSMENT OF RETURN OF NEUROMUSCULAR FUNCTION BEFORE ENDOTRACHEAL EXTUBATION ON CRITICAL RESPIRATORY EVENTS IN ADULT PATIENTS UNDERGOING ELECTIVE SURGERY AT THE AGA KHAN UNIVERSITY HOSPITAL, NAIROBI.

By

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A dissertation submitted in part fulfilment of the requirements for the degree Master of Medicine in Anaesthesiology

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Submitted to the Board of Graduate Studies

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In Anaesthesiology

Members of the Dissertations Standard Committee appointed to vet the dissertation of

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Chair, Dissertations Standard Committee

20th May 2015

DEDICATION

This dissertation is dedicated to my loving wife Roselyne Atieno and daughter Barbara Adembesa without whose caring support it would not have been possible, and to all the patients that teach me something new every day.

Abstract

Background

There is increasing evidence that the incidence of postoperative residual paresis after using neuromuscular blockers ranges from 24 to 50% in post anaesthesia care unit and is associated with postoperative complications such as critical respiratory events as evidenced by hypoxia, hypoventilation and upper airway obstruction. Quantitative neuromuscular monitoring (such as the assessment of Train of four (TOF) ratio) and reversal of neuromuscular blockers has been shown to reduce postoperative residual paresis. There are very few outcome studies on effect of residual paresis in Post anaesthesia care unit (PACU). There are no published randomised control trials investigating whether using a TOF ratio ≥0.9 before endotracheal extubation compared to clinical assessment of return of neuromuscular function reduces the incidence of critical respiratory events in PACU.

Primary Objective

To determine whether using TOF ratio ≥0.9 compared to clinical assessment of return of neuromuscular function before endotracheal extubation reduces the incidence of critical respiratory events in PACU

Secondary objectives

To determine incidence and severity of hypoxia in PACU

To determine incidence of upper airway obstruction in PACU

Study Design

Randomised, prospective, double blinded control trial

Setting

Operating theatres of the Aga Khan University hospital Nairobi

Population

Adults, aged 18-65 years ASA physical status I and II undergoing elective surgery under general anaesthesia.

Sample size

168 patients randomised to TOF ratio group and clinical assessment group, 84 per group.

Methods

Patients requiring general anaesthesia for elective surgery with cisatracurium as the muscle relaxant were randomised into 2 groups using computer generated numbers. Group 1 were patients who required a TOF ratio of ≥0.9 before extubation. Group 2 patients were extubated based on clinical assessment of return of adequate neuromuscular function by the anaesthetist as is the standard of practice at the Aga Khan University hospital Nairobi. General anaesthesia was standardised in both groups. Both the investigators and patients were blinded during the study.

Once the patient was transferred to PACU, oxygen saturation (SP02), respiratory rate and any signs of upper airway obstruction as demonstrated by stridor, laryngospasms or requirement of any airway manipulation was recorded for the first 30 minutes. Duration of anaesthesia and surgery was also recorded. Patient demographics were recorded and analysed.

Results

There was no statistical difference between the 2 groups in terms of patient demographics, duration of surgery and anaesthesia and duration since last muscle relaxant was given. In terms of hypoxia on arrival in PACU, the incidence of mild hypoxia (SPO2 90-93%) was 11% in clinical assessment group versus 5% in TOF group P-value 0.149 while severe hypoxia (SPO2 <90%) was 19% versus 10% P-value 0.078. During the first 30 minutes in PACU, the incidence of mild hypoxia (SPO2 90-93%) was statistically significant between the 2 groups (12% in clinical assessment group versus 1% in TOF group, P-value 0.005) while severe hypoxia (SPO2 <90%) was 7% versus 5%, P-value 0.373. The incidence of upper airway obstruction was statistically significant between the two groups (45% in clinical assessment group versus 14% in TOF group P-value<0.0001 for patients requiring airway maneuver, 21% versus 2% P-value <0.0001 for those who required tactile stimulation and 31% versus 12% were snoring, P-value 0.003. Logistic regression analysis revealed TOF group was less likely associated with mild hypoxia (OR 0.09 95% CI 0.01-0.71 P-value 0.023), tactile stimulation (OR 0.09 95% CI 0.02-0.40 P-value 0.002), airway manuever (OR 0.20 95% CI 0.10-0.43 P-value <0.001) and snoring (OR 0.30 95% CI 0.13-0.68 P-value 0.04).

Conclusion

There is a lower incidence of critical respiratory events in post anaesthesia care unit with the use of neuromuscular monitoring using TOF ratio ≥0.9 to assess neuromuscular function before endotracheal extubation compared with the use of clinical assessment methods.

LIST OF ABBREVIATIONS

ASA	American Society of Anaesthesiologists
AKUH N	Aga Khan University Hospital Nairobi
BMI	Body mass index
GA	General Anaesthesia
Mcg	Micrograms
mg	Milligrams
mins	Minutes
NMBA	Neuromuscular junction blocking agents
OR	Odds ratio
PACU	Post anaesthesia care unit
PORC	Postoperative residual curarisation
RR	Respiratory rate
S	Seconds
SPO2	Oxygen saturation
TOF	Train of four

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Special thanks to Dr. David Nekyon and Dr. David Odaba for your encouragement and help in my initial stages of refining this study and Dr. Samuel Akech for helping me with data analysis.

To my mother (now late), father and the rest of family, thank you for your prayers and encouragement through this journey.

Finally, to all the patients that agreed to participate in this study, God bless you.

DECLARATION

I declare this dissertation does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university and that to the best of my knowledge it does not contain any material previously published or written by another except where due reference have been made in the text.

The editorial assistance provided to me has in no way added to the substance of my proposal which is the product of my own research endeavours.

Dr Adembesa Isaac

20th May 2015

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Chapter 1: Introduction

Neuromuscular blocking agents (NMBAs) act on nicotinic cholinergic receptors on the skeletal muscle endplate to produce muscle relaxation.
The introduction of neuromuscular blockers in 1942 was an important development in anaesthesia as it ensured muscle relaxation which together with amnesia and analgesia provide balanced anaesthesia as envisaged by John Lundy(1).

Muscle relaxation is required for tracheal intubation and to facilitate surgical procedures as part of balanced anaesthesia (2). If it is not adequately reversed after surgery, residual paresis lead to muscle weakness, respiratory problems, prolonged stay in post anaesthesia care unit (PACU), and delayed recovery (3–5).

Non-depolarizing neuromuscular blocking agents differ in the onset of action, duration of action, metabolic route, potency, adverse effects and cost. An anaesthesiologist is able to choose a neuromuscular blocking agent according to these similarities and differences.

On recovery from muscle relaxation, the anaesthesiologist can assess for return of muscle power using a clinical criteria that includes the ability to lift the head for 5s or hold a tongue depressor between the teeth. These clinical methods are unreliable and may be affected by other factors such as sedation or inability of the patient to follow instructions (6).

When neuromuscular monitoring is used, qualitative methods such as tactile or visual assessment of the degree of neuromuscular block are inaccurate (7). It is therefore clear that in addition to monitoring neuromuscular block clinically, quantitative methods such as acceleromyography, mechanomyography or electromyography should also be used (6).

Acceleromyography has been developed as a simple way to monitor evoked responses in operating theatres. "It measures acceleration of muscle using a piezoelectric ceramic wafer that is strapped on the thumb. When the adductor pollicis is stimulated, the thumb moves and the attached transducer will produce a voltage that is proportional to its acceleration. The voltage can then be converted to an electrical signal that is displayed as twitch response". Studies have shown that acceleromyography is comparable to mechanomyography which is the gold standard of neuromuscular monitoring (8,9).

Ali and colleagues developed in 1970 a Train of four (TOF) pattern of stimulation in an effort to develop a clinical tool to assess neuromuscular block in anaesthetized patient. This pattern of nerve stimulation does not need comparison of evoked potential to a control response obtained before administering a muscle relaxant (6).

A typical pattern of muscle stimulation is noted when a non-depolarizing neuromuscular blocking agent is given. The amplitude of the evoked responses reduces with T4 affected first followed by T3, then T2 and finally T1. This decrease in twitch height is called fade. As the muscle blockade increases, T4 disappears first followed by T3, then T2 and finally T1. During recovery from blockade, the reverse occurs with T1 appearing first followed by T2, then T3 and finally T4 (6). Comparison of T4 twitch height to T1 twitch height gives TOF ratio.

Central muscles like the diaphragm and larynx have faster onset and offset of neuromuscular blockade compared to peripheral muscles such as the adductor pollicis. This is due to good blood supply. Upper airway muscles mirror the central muscles hence monitoring of the peripheral muscle is the best option because recovery of peripheral muscle indicates recovery of

central muscles. The ulnar nerve is chosen because it is a peripheral nerve with a motor component to the adductor pollicis (6).

Residual muscle paresis is defined by TOF ratio <0.9 with correlating signs and symptoms of muscle weakness(10). Postoperative residual paresis can be reduced by various techniques. These include avoidance of muscle relaxants with long duration of action, monitoring neuromuscular blockade in the operating room, and using reversal agents after neuromuscular blockade (11).

However, presence of residual paresis is common in early postoperative period even when NMBAs with intermediate duration of action are used, neuromuscular monitoring is done and reversal agents given (3,12,13).

A recent study by Eikermann et al showed that mild degrees of residual muscle paresis (TOF ratios of 0.7-0.9) can be associated with profound impairment of respiratory and pharyngeal muscle function (10). This may be associated with respiratory events and aspiration in PACU. Therefore, complete recovery of muscle function should be present before tracheal extubation to avoid these risks.

PACU critical respiratory event has been defined as "any unanticipated hypoxemia (haemoglobin oxygen saturation < 90%), hypoventilation (respiratory rate <8 breaths/minute) or upper airway obstruction (stridor or laryngospasm) requiring an active or specific intervention (ventilation, airway manipulation, insertion of an oral/nasal airway, opioid or muscle relaxant reversal or tracheal intubation)" (14).

Most studies done globally show that postoperative pulmonary complications come second to postoperative nausea and vomiting in terms of PACU complications (15). This is a patient safety issue considering the critical events involved.

Currently, the American Society of Anaesthesiology task force on post anaesthesia care recommends "assessment of neuromuscular function at emergence from general anaesthesia for patients who have received non-depolarizing neuromuscular blocking agents" (16).

The assumption that correct use of a neuromuscular monitor should reduce the incidence of postoperative residual paresis appears reasonable. Unfortunately, objective neuromuscular monitors that can measure TOF ratio are not available in most operating rooms(17). In addition, outcome studies relating residual paresis with adverse events are limited.

A meta-analysis by Naguib et al demonstrated that the use of a neuromuscular monitor is not associated with a decreased incidence of postoperative residual paresis (17). However, this meta-analysis relied heavily on cohort studies and the authors recommended more randomised control trials on this subject matter.

A recent clinical trial by Murphy et al compared acceleromyographic TOF ratio of 0.8 to qualitative TOF and looked at postoperative residual curarisation (PORC) as the primary objective and hypoxemia and upper airway obstruction as the secondary objective. They showed a reduction in incidence of PORC and respiratory events. However, there study design did not mimick normal clinical practice as the anaesthetists had to adhere to a strict protocol in both groups and there was neuromuscular monitoring in both groups (5).

At the Aga Khan University hospital Nairobi, neuromuscular monitoring is done irregularly in spite of availability of neuromuscular monitors. This is not an unusual clinical scenario in developed and developing countries. The reason for this practice is not due to financial capability but may be due to lack of knowledge among medical staff on availability of other methods of

monitoring neuromuscular blockade. The other reason is often the lack of confirmed data and published research on the topic.

A case series by Adembesa et al in January 2014 involving 10 patients at the Aga Khan University hospital Nairobi showed that the incidence of hypoxemia in PACU was 30%. This study has not been published.

This study aimed to compare whether use of TOF ratio of ≥0.9 to clinical assessment of return of neuromuscular function before endotracheal extubation reduced incidence of critical respiratory events in PACU.

Chapter 2: Literature Review

2.1 Neuromuscular blocking agents (NMBAs)

Use of NMBAs in operating rooms was started by Griffith and Johnson who pioneered use of d-tubocurarine in 1942 (18). However, use of NMBAs as part of anaesthesia was not embraced due to failure to reverse their effect at the end of the anaesthetic. Reversal agents were not given and patients developed respiratory complications (19).

Beecher and Todd in 1954 showed in an observational study that when muscle relaxants were used, there was an appreciable increase in anaesthesia related deaths. They demonstrated high mortality rates when muscle relaxants were used (1:370 anaesthetics) compared to when they were avoided(1:2100 anaesthetics) (19).

Once use of NMBAs became part of general anaesthesia, choice of which agent to use became an issue. Suxamethonium was pioneered in 1952, followed closely by gallamine, dimethyltubocurarine, metocurine and alcuronium in the 1950’s and 1960’s (20).

A number of adverse effects were identified along the way. D-tubocurarine causes hypotension due to histamine release and ganglion blockade. It also causes a prolonged block. Gallamine and alcuronium were withdrawn because they were associated with tachycardia and anaphylactic reactions (21).

Pancuronium is an aminosteroidal NMBA and is metabolised in the liver. This was considered advantageous as the previous NMBA's were eliminated by the kidneys. However, pancuronium has vagolytic and sympathomimetic effects hence causes tachycardia and hypertension (20,21).

Vecuronium and atracurium, intermediate acting NMBAs, were introduced in the 1980's and provide reliable neuromuscular blockade of 25-30 minutes duration (20). Vecuronium shares similar structure with pancuronium but lacks the sympathomimetic effects (20).

Atracurium, a benzylisoquinolinium agent, is metabolised in the body by a pH dependent process called Hoffman elimination. This is a non-organ dependant metabolism (21). This was considered a better agent than pancuronium.

However, atracurium releases histamine especially when given rapidly and in large doses. When metabolised, it produces laudanosine which is eliminated through the kidneys. Accumulation of these metabolites especially at high concentrations produces seizures. Vecuronium is reliable but has active metabolites and interacts with some drugs. It also requires reconstitution before use and its onset of action is takes several minutes (21).

More new agents were introduced in the 1990's. These include mivacurium, rocuronium, pipecuronium and doxacurium (20). Pipecuronium and doxacuronium are long acting agents and are unavailable in Kenya. Mivacurium, a benzylisoquinolinium agent, has a short to intermediate acting duration and is metabolised by plasma pseudocholinesterases. It releases histamine when given rapidly and at high doses and thus is usually given as an infusion. It is associated with prolonged blockade in patients with atypical or defective pseudo cholinesterase (20).

Rocuronium is aminosteroidal in structure and intermediate acting in duration. However, its main advantage is its fast onset of action (21). It is metabolised in the liver and does not release histamine (21).

More recently, cisatracurium, an isomer of atracurium, with similar metabolism to atracurium but with less release of histamine and laudanosine was introduced into practice (20). Sagir et al showed that cisatracurium is the safest non-depolarizing neuromuscular blocker to use in the elderly people compared to rocuronium and vecuronium though has slow onset of action (22).

2.2 Incidence of residual neuromuscular block

Traditionally, train of four ratio ≥0.7 has been considered to reflect adequate neuromuscular function recovery because it is associated with the ability to maintain 5s head lift and a return of adequate ventilatory function (23,24).

Viby-Mogensen et al demonstrated in 1979 that when patients were examined in the recovery room after surgery, many showed residual neuromuscular blockade. They studied 72 adult patients who had received gallamine, d-tubocurarine, or pancuronium for muscle relaxation. Neostigmine was given at the end of anaesthesia to 67 patients. TOF ratio was ‹0.7 in 42% and 24% of the 68 awake patients were unable to lift head for 5 seconds (25).

Kopmann et al showed that a TOF ratio of ≤0.7 is associated with "functional impairment of the muscles of the pharynx and upper oesophagus predisposing to regurgitation and aspiration" (26).

However, according to Kopmann, Yee and Neumann, "normal vital muscle function including pharyngeal function requires the TOF ratio at the adductor

pollicis to recover to ≥0.9" (26). Thus, residual paresis is defined by a TOF ratio ‹0.9.

A study by Debeane and colleagues found that "45% of patients had residual paresis (train of four (TOF) <0.9) in the postoperative recovery room after single intubating dose of intermediate acting drugs atracurium, vecuronium or rocuronium (12). Neuromuscular block was not antagonised in this study and neuromuscular monitoring was not done".

A meta-analysis by Naguib et al showed an overall incidence of postoperative residual paresis of 52%. They analysed studies done between 1979 and 2005 (17).

Murphy et al also demonstrated an incidence of residual paresis of 32% in PACU in patients who had reversal with anticholinesterase neostigmine (27).

2.3 Role of reversal drugs to reduce residual paresis

General opinion favours administration of anticholinesterases at emergence from general anaesthesia. However, some anaesthetists avoid giving reversal drugs due to their side effects such as tachycardia, bradycardia, heart block and increased risk of postoperative nausea and vomiting.

Tramer et al in a systematic review demonstrated that incidence of postoperative nausea and vomiting and the need for antiemetics does not increase with the use of neostigmine (28,29). Incidence of residual paresis, however, increases if neostigmine is not given (28).

Using the appropriate dosage of the reversal drug matched to the degree of blockade should reduce potential side effects associated it (28).

Neostigmine should therefore be administered depending on the degree of blockade. 30-40 micrograms per kilogram body weight for mild blockade to maximum of 70micrograms per kilogram for dense block (30).

Sugammadex, a synthetic cyclodextrin analogue selectively binds aminosteroidal NMBAs and reverses neuromuscular block through chemical encapsulation. The encapsulation results in immediate decrease in plasma concentration of aminosteroidal NMBA and subsequent decrease in concentration at the motor endplate. Hence, sugammadex causes "rapid and complete reversal of rocuronium induced neuromuscular block" (31).

2.4 Consequences of residual paresis

Large data based studies identify intraoperative use of muscle relaxants and residual paresis as risk factors for anaesthetic-related morbidity and mortality (19,23).

Incomplete neuromuscular block is most likely to affect sensitive muscle groups such as the upper airways, pharynx and proximal oesophageal sphincters. This can lead to lack of coordination during swallowing and breathing leading to aspiration and adverse respiratory events.

Berg et al in a randomized clinical trial showed that "incomplete neuromuscular recovery during the early postoperative period may result in acute respiratory events (hypoxemia and airway obstruction), unpleasant symptoms of muscle weakness, longer postanesthesia care unit stays, delays in tracheal extubation, and an increased risk of postoperative pulmonary complications" (32).

Eriksson and colleagues showed that at TOF≤0.7, "chemoreceptor sensitivity to hypoxia is decreased leading to inadequate ventilatory response to hypoxia" (33).

An editorial by Kopmann concurs with a study by Murphy et al which demonstrated residual blockade is associated with hypoxemia and upper

airway obstruction. However, he points out that the investigators did not mimick normal clinical practice in their study design (5,34).

Sauer et al demonstrated that residual paresis is associated with adverse respiratory events in patients who were not reversed with neostigmine (4).

2.5 Neuromuscular block monitoring

Clinical assessment of the return of neuromuscular function includes voluntary muscle function tests such as hand grasp, tongue protrusion, sustained eye opening and the ability to lift the head for 5 seconds and clench teeth. Respiratory function tests include vital capacity, inspiratory force, peak expiratory flow rate can also be used (35). However, clinical tests are not sensitive or specific and thus, minimal residual paresis cannot be accurately ruled out (36).

It is therefore important to note that as much as a TOF ratio of ≥0.9 is taken to reflect sufficient recovery, it is not possible either by clinical assessment or qualitative peripheral nerve stimulation to exclude clinically significant residual blockade (5). Often even experienced observers cannot appreciate fade with TOF ratios as low as 0.1-0.2 (24).

Wide adoption of peripheral nerve stimulation using train of four ratio has been due to ability of this monitor to quantify neuromuscular blockade without the need for comparison with control response (7).

Although lack of tactile estimation of fade after TOF stimulation, double-burst stimulation, and 100Hz 5second tetanic stimulation is considered adequate recovery, absence of fade does not correlate with the TOF ratio. It is impossible to qualitatively evaluate a TOF ratio with sufficient certainty to

exclude residual paresis. Therefore tactile assessment of TOF ratio is not reliable (7,37).

A recent meta-analysis involving 24 studies (3375 patients) by Naguib et al found that intraoperative assessment of TOF response using a conventional nerve stimulator did not influence the incidence of postoperative residual paralysis (17).

Avram et al in a recent study demonstrated that quantitative method of neuromuscular function assessment using acceleromyography reduces the incidence of postoperative residual paralysis (5).

Ideally, accurate and objective data on the degree of neuromuscular paralysis can be obtained by measuring the force of muscle contraction by mechanomyography. This is the gold standard for neuromuscular monitoring but it is mainly used in research laboratories due its bulky nature.

Acceleromyography is based on the Newton's second law which states that "force is equal to mass multiplied by acceleration". Muscle acceleration has a linear correlation with the force of contraction. Studies show there is a good correlation between acceleromyography and mechanomyography (9).

Chapter 3: Justification of the study

Neuromuscular blockers are used frequently during general anaesthesia as part of balanced anaesthesia and to facilitate tracheal intubation.

To avoid postoperative residual paresis, use of intermediate or short acting muscle relaxants together with neuromuscular monitoring and reversal using neostigmine or sugammadex is recommended (38).

A study by Murphy et al showed that neuromuscular monitoring using quantitative acceleromyography minimises incomplete neuromuscular recovery compared to conventional Train Of Four (5). In this trial 185 patients undergoing elective surgical procedures were randomised to two groups. No hypoxemia or upper airway obstruction was observed in the acceleromyographic group. However, in this trial a TOF ratio of ≤0.8 was used to determine residual paresis in patients who were awake in PACU. Accuracy of acceleromyography in awake patients has been questioned (39).

Eikermann et al showed that TOF ratio≤0.9 is associated with upper airway obstruction (10).

Berg et al demonstrated that residual block is associated with postoperative pulmonary complications (32).

However, a meta-analysis by Naguib et al, analysed data from 24 studies (13 randomized and 11 observational studies), and could not demonstrate reduction in incidence of postoperative residual curarisation with intraoperative neuromuscular monitoring. However, this analysis over-relied on cohort studies and therefore confounding could have influenced the final analysis. The authors noted that use of intermediate acting muscle relaxants does not reduce incidence of postoperative residual block and were concerned with the low use-rate of even simple qualitative nerve stimulators for neuromuscular monitoring (17).

There is no clinical trial that compares TOF ratio≥0.9 to clinical assessment of return of neuromuscular function before endotracheal extubation on critical respiratory events in PACU.

At the Aga Khan University hospital and indeed throughout the East, Central and Southern African region, neuromuscular monitoring is not done routinely. An unpublished study by Mwasaru et al at Kenyatta National hospital showed an incidence of 50% of residual paresis in PACU using TOF ratio ‹0.9.

3.1 Aim of study

To determine whether using TOF ratio ≥0.9 compared to clinical assessment of return of neuromuscular function before endotracheal extubation reduces the incidence of critical respiratory events in PACU

3.2 Research question

Does neuromuscular monitoring using TOF ratio≥0.9 compared to clinical assessment of return of neuromuscular function before endotracheal extubation reduce critical respiratory events in PACU?

3.3 Alternative hypotheses

There is a decrease in the incidence of critical respiratory events in PACU when neuromuscular monitoring using TOF ratio ≥0.9 is used before endotracheal extubation compared to clinical assessment of return of neuromuscular function.

Chapter 4: Objectives

4.1 Primary objective

To determine whether using TOF ratio ≥0.9 compared to clinical assessment of return of neuromuscular function before endotracheal extubation reduces the incidence of critical respiratory events in PACU

4.2 Secondary objectives

To determine incidence and severity of hypoxia in PACU

To determine incidence of upper airway obstruction in PACU

Chapter 5: Methodology

5.1 Study design

Double blinded prospective randomized control trial

5.2 Study Period

Data collection: 22 May to 31 November 2014

Data Analysis: December 2014

5.3 Study Population and setting

The Aga Khan University hospital Nairobi is a private tertiary not-for-profit hospital with a bed capacity of 280 beds and postgraduate medical education programmes in various disciplines was the setting of the study.

The study population included all adults aged between 18 and 65 years undergoing elective surgery at Aga Khan University hospital Nairobi.

Since Nairobi is a cosmopolitan city, the patients served by the hospital cut across most racial groups present within the country. Patients were recruited from the pre-anaesthesia clinics, which run on a daily basis, wards and day-care unit.

5.4 Eligibility criteria

5.4.1 Inclusion criteria

Adults, aged 18-65 year American society of anaesthesiology (ASA) physical status I and II undergoing elective surgery under general anaesthesia.

5.4.2 Exclusion criteria

1. ASA status III and above

2. Pregnant women

3. Patients with neuromuscular diseases

4. Patients on medications that interfere with neuromuscular junction function. For example, magnesium sulphate and aminoglycosides

5. Patients with renal, hepatic or respiratory diseases

6. Patient refusal to take part in the study

7. Patients with BMI >30

8. Patients allergic to cisatracurium

9. Patients undergoing brain surgery

10. Children and the elderly

5.5 Sample size and sample calculation

A sample size of 168 patients (84 per group) was sufficient to demonstrate 11% difference in the incidence of hypoxia and upper airway obstruction between the TOF ratio group and clinical assessment group at 95% confidence level and a power of 80%.

A study by Murphy et al showed the incidence of hypoxemia was 21% in conventional TOF and 0% in the acceleromyographic group while incidence of upper airway obstruction was 11.6% in the conventional TOF group compared to 0% in the acceleromyographic group (5).

I therefore hypothesize there will be a difference of at least 11% between the TOF ratio group and clinical assessment group.

The sample size formula to compare two proportions is:

$$n = \left(\frac{z_{1-\alpha}\sqrt{2\bar{p}(1-\bar{p})} + z_{\beta}\sqrt{p_1(1-p_1) + p_2(1-p_2)}}{\delta} \right)^2$$

Where n=84 patients per arm

$Z_{1-\alpha}$=Significance level 0.05

Z_{β} = Power of study 80%

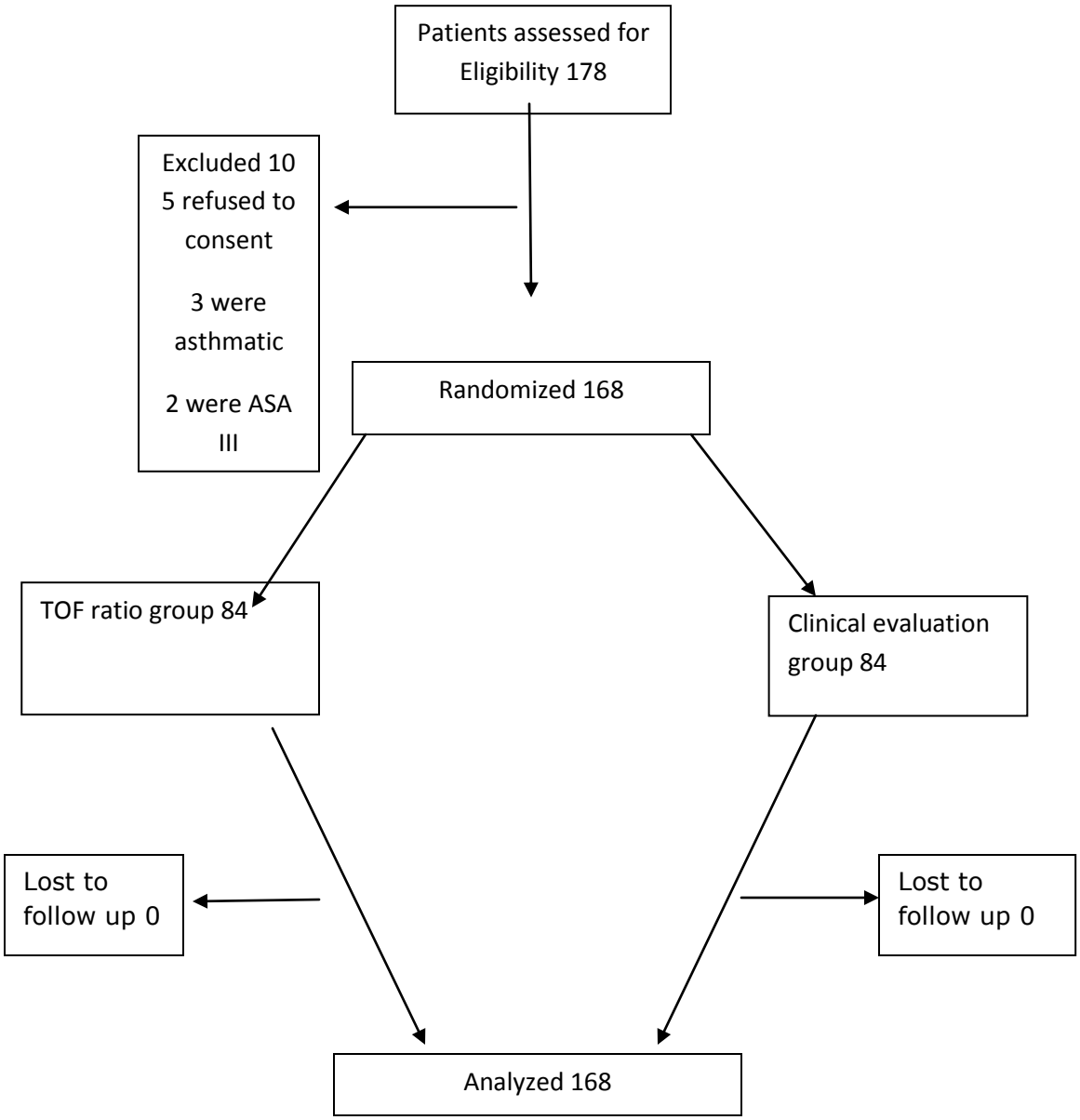
p_1, p_2= Proportions of TOF ratio and clinical assessment group

δ= Difference between the proportions-11

5.6 Recruitment procedure

The primary investigator reviewed prospective subjects at the pre-anaesthetic clinic, ward and day-care unit. Patients were informed of the nature of the study and recruited if eligibility criteria were met. Eligible patients received written and oral explanations on the purpose and nature of the study. The patients who gave written informed consent were enrolled into the study and their files tagged with a special colour sticker for ease of identification.

Figure 1: Flow diagram of patient distribution



5.7 Randomization and Blinding

Simple randomization was generated by the statistician using a computer program. Each of the random numbers was sequentially assigned to either;

Group 1: TOF ratio

Group 2: Clinical assessment

These numbers were sealed in envelopes and delivered to the anaesthetist administering general anaesthesia.

All anaesthesia residents and anaesthetists administering general anaesthesia were sensitized and trained on how to use the acceleromyographic nerve stimulator machine (TOF- Watch^{R} SX, Organon).

The principal investigator, research assistants and patients were not aware of the groups assigned.

5.8 Informed consent

Informed consent was obtained by the Primary investigator after a detailed explanation of the nature of the study and any queries were addressed with the patient. In case an enrolled and consented patient withdrew consent, the next consecutively randomized patient was to be selected as a replacement. The Consent form used is shown in Appendix III

5.9 Anaesthetic procedure

General anaesthesia was standardized in the patients enrolled in the study.

Upon entering theatre, the anaesthetist administering general anaesthesia was given a sealed envelope containing the group the patient had been randomised.

In the TOF ratio group, 2 surface electrodes were placed over the ulnar nerve at the wrist after cleansing and rubbing the skin with an alcohol solution. The acceleration transducer was then attached on the volar aspect of the distal phalanx of the thumb. Current selected was 50mA for all the patients in this group (TOF watch^{R} SX, Organon). This was done after the patient was under anaesthesia.

Intraoperative monitoring included non-invasive blood pressure, electrocardiography, pulse oximetry, capnography and core temperature monitoring via a nasopharyngeal temperature probe.

Intravenous induction was done with 2mcg/kg of fentanyl, 2-2.5mg/kg propofol, and 0.2mg/kg of cisatracurium. Orotracheal intubation was done after two to three minutes of bag ventilation and thereafter ventilation was controlled with a tidal volume of 6 to 8mls/kg, respiratory rate was varied to maintain end-tidal carbon dioxide between 30-35mmHg.

Anaesthesia was maintained by isoflurane 1-2% in oxygen and air to maintain oxygen saturations above 98%. End tidal isoflurane was adjusted to keep blood pressure within 20% of baseline values. Any drop in blood pressure below this recommended level was corrected with 3-6mg boluses of ephedrine. Muscle relaxation was maintained with 0.05mg/kg of cisatracurium boluses every 30 to 45 minutes as is the routine practice in our hospital. Last top-up of muscle relaxant was at least 30 minutes before end of anaesthesia.

Patients received standard analgesia of morphine 0.1mg/kg, paracetamol 15mg/kg and with a non-steroidal anti-inflammatory agent unless contra-indicated. Ondansetron 4mg with or without dexamethasone 8mg was given to all patients as prophylaxis against postoperative nausea and vomiting.

Patients were kept warm by warm blankets, infusion of warm fluids and ambient theatre temperature of 24^0C. Core temperature was maintained above 35^0C.

During reversal, isoflurane and air were switched off and patient was put on 100% oxygen. Oropharyngeal suctioning was done. Neostigmine 50micrograms/kilogram to a maximum of 5mg and atropine 20microgram/kilogram were given.

In the TOF ratio group, the patient required a TOF ratio ≥0.9 before being extubated and transferred to post anaesthesia care unit.

In the clinical assessment group, the patient required head lift for at least 5 seconds, tidal volume 4-6ml/kg with a regular respiratory rate of at least 12 breaths or coughing or pulling on the orotracheal tube before being extubated and transferred to post anaesthesia care unit. This is the routine practice in our hospital.

The patient was then transferred to PACU when the anaesthetist was comfortable with their clinical status. During transport, no oxygen was given. This is routine practice in our hospital.

Once the patient got to PACU, a pulse oximeter was connected by the investigator who was blinded to the study and baseline SPO2 recorded. After that, all the patients received oxygen 6L/minute via the Hudson mask as is the practice in the hospital. Sustained SPO2 < 90% for at least 5 seconds with a good pulse oximetry waveform was considered severe hypoxemia while SPO2 90-93% mild hypoxemia.

SPO2 was recorded continuously for 30 minutes. Any features of airway obstruction such as stridor, laryngospasms, airway manipulation by chin lift, jaw thrust or requirement of an oral airway or tactile stimulation or re-intubation, were recorded.

5.10 Data collection procedure and tools

Data was collected by the principal investigator or research assistant in the PACU using the data collection form (Appendix I). The collected data was counterchecked for complete entry by the principal investigator and then entered into an MS-Excel data base.

5.11 Data storage

All the raw data in this study was filed in box files which were stored in a locked filing drawer. In addition, all the sheets were checked to confirm completeness before being filed. The processed data was saved in a compact disc (CD) and copies were kept in the supervisor's office.

5.12 Statistical analysis

Data was analysed using STATA version 11. Data was presented in tables. In terms of patients' demographic data, median values were used to represent age and body mass index and Wilcoxon signed rank sum test was used to compare the two groups. Sex, ASA status, smoking and operative procedures were presented as proportions and Pearson chi square test was used to compare the two groups.

Perioperative variables such as duration of surgery and anaesthesia, duration since last muscle relaxant was given were presented as means with standard deviations and two sample t-test used to compare the two groups. Outcome variables such as hypoxia, respiratory rate and indicators of upper airway obstruction such as tactile stimulation, airway maneuvers, snoring and re-intubation were presented as proportions and Pearson chi square test used to compare the two groups.

Logistic regression analysis using both univariate and multivariate analysis where applicable was used to test for association between hypoxia and

upper airway obstruction and study arm, operative procedure, duration of anaesthesia, duration since last muscle relaxant and BMI. These were presented as odds ratios with 95% confidence intervals.

P-value of less than 0.05 was considered as statistically significant.

Chapter 6: Ethical consideration

The study was approved by the Health Research Ethics Committee of the Aga Khan University, East Africa.

Patients were recruited after signing an informed consent, which clearly stated that it is a research study being conducted and that their information will be kept confidential.

They received health care as all other patients who came to theatre. They were not denied care if they declined to participate in the study. For those who did not understand English, instructions were explained in Swahili by the principal investigator.

An explanation on the study procedure was given to the patients both verbally and using a written form. It was made clear there shall be no direct benefit to the patients arising from participation in the study, but that the results could be used to change local practice in future. There were no added expenses to the patient.

The patients voluntarily signed the consent form and were recruited in the pre-anaesthesia clinic, day care unit or wards before coming to the operating theatres.

The patients were free to withdraw from the study at any stage and still be accorded standard care.

The study was registered by the Pan African Clinical Trials Registry registration number PACTR201501001021110.

Chapter 8: Results

Table 1 shows patient characteristics

	Clinical assessment group(N=84)	TOF group (N=84)	P-values
Sex, M,F	38(45%), 46(55%)	36(43%), 48(57%)	0.756
Age in yrs	37.5(29-47)	37(30-44)	0.819
BMI	25.5(22.4-27.3)	24.65(22.45-27.2)	0.938
ASA status			
I	57(68%)	61(73%)	0.500
II	27(32%)	23(27%)	0.500
Smoking, No/Yes	80(95%), 4(5%)	80(95%), 4(5%)	1.000
Operative procedures			
ENT	2(2%)	3(4%)	0.650
General	23(27%)	23(27%)	1.000
Gynecologic	21(25%)	30(36%)	0.131
Maxillofacial	1(1%)	5(6%)	0.096
Ophthalmologic	1(1%)	0(0%)	0.316
Orthopedics	19(23%)	15(18%)	0.442
Urologic	17(21%)	7(8%)	0.027
Plastic	0(0%)	1(1%)	0.316

Median and 25^{th}-75^{th} percentiles are given for age and BMI. Otherwise, numbers of patients (and % of patients) are given.

P-values for patients' data with median were calculated using Wilcoxon rank sum test while those with proportions were calculated using Pearson Chi-square test.

BMI-Body mass index, ASA- American Society of Anaesthesiology, ENT-Ear, Nose and Throat

After health research ethics committee approval, 178 patients were interviewed for inclusion in the study. 10 patients were excluded from the study; 5 declined to sign the consent form, 3 were asthmatic and 2 were ASA III. 168 fulfilled the inclusion criteria and were randomized into the study. No patient was excluded because of violation of study protocol after randomization. There was no statistical difference between the two groups in terms of patient demographic data. However, among operative procedures, there were many urologic procedures in the clinical assessment group (21% versus 8%, P-value 0.027) than TOF group as shown in table 1. This was purely by chance due to randomization.

Intraoperative variables such as duration of anaesthesia, duration of surgery and duration since last muscle relaxant were not different between the two groups as shown in table 2.

Table 2 shows Perioperative variables

	Clinical assessment group(N=84)	**TOF group (N=84)**	**95% Confidence intervals**	**P-values**
Anesthetic duration (mins)	130±71	134±70	-25.7 to 17.3	0.699
Surgical duration (mins)	114±66	119±67	-25.8 to 15.0	0.602
Duration since last muscle relaxant (mins)	53±16	53±15	-4.9 to 4.8	0.981

Patients with SPO2 values >94% in post anaesthesia care unit were more in the TOF group than clinical assessment group (85% versus 70% on arrival, P-value 0.016 and 94% versus 81% within 30minutes, P-value 0.010) as shown in table 3 and 4. Severe hypoxia was not statistically significant

between the two groups on arrival in PACU. However, while in PACU, mild hypoxia (90-93%) was more in the clinical assessment group than in the TOF group (12% versus 1%, P-value 0.005) as shown in table 4.

In terms of upper airway obstruction in the PACU, 45% of patients in the clinical assessment group compared to 14% in the TOF group required an intervention such as jaw thrust/chin lift, oropharngeal airway (P-value <0.0001). 21% versus 2% required tactile stimulation to maintain their airway (P-value <0.0001). 31% versus 12% were snoring in PACU (P-value 0.003). This was statistically significant as shown in table 5. There was no difference in respiratory rate between the two groups. No patient required re-intubation in PACU.

Table 3 shows SPO2 values on arrival in post anaesthesia care unit

	Clinical assessment group(N=84)	**TOF group (N=84)**	**P-values**
No. with SPO2 >94%	59(70%)	72(85%)	0.016
No. with SPO2 90-93%	9(11%)	4(5%)	0.149
No. with SPO2 <90%	16(19%)	8(10%)	0.078

Table 4 shows SPO2 values for first 30 minutes in the post anaesthesia care unit

	Clinical assessment group(N=84)	TOF group (N=84)	P-values
No. with SPO2 >94%	68(81%)	79(94%)	0.010
No. with SPO2 90-93%	10(12%)	1(1%)	0.005
No. with SPO2 <90%	6(7%)	4(5%)	0.373

Table 5 shows airway variables in the post anaesthesia care unit

	Clinical assessment group(N=84)	TOF group (N=84)	P-value
No. requiring airway maneuver, Yes/No	38(45%),46(55%)	12(14%), 72(86%)	<0.0001
Tactile stimulation, Yes/No	18(21%), 66(79%)	2(2%), 82(98%)	<0.0001
Snoring, Yes/No	26(31%),58(69%)	10(12%),74(88%)	0.003
Respiratory rate	16±2	17±3	0.089
Re-intubation, Yes/No	0(0%), 84(100%)	0(0%), 84(100%)	0.36

Table 6 shows logistic regression analysis for respiratory events in PACU

	Unadjusted odds ratio (95% confidence interval)	P-value	Adjusted odds ratio (95% confidence interval)	P-value
	Mild hypoxia (90-93%)			
Study arm	0.09(0.01- 0.71)	0.023	0.11(0.14-0.93)	0.043
Operative procedure	1.90(1.25 -2.86)	0.002	1.80(1.18-2.74)	0.006
Anesthetic duration	1.00(1.01-1.01)	0.281		
Duration since last muscle relaxant	1.01(0.97-1.05)	0.548		
BMI	1.29(0.68-2.43)	0.441		
	Tactile stimulation			
Study arm	0.09(0.02-0.40)	0.002		
Operative procedure	1.16(0.92-1.47)	0.205		
Anesthetic duration	1.00(1.00-1.01)	0.305		
Duration since last muscle relaxant	1.00(0.97-1.03)	0.797		
BMI	1.54(0.92-2.55)	0.098		
	Airway maneuver			
Study arm	0.20(0.10-0.43)	<0.001		
Operative procedure	1.15(0.97-1.36)	0.107		
Anesthetic duration	1.00(1.00-1.01)	0.403		
Duration since last muscle relaxant	1.00(0.97-1.01)	0.420		
BMI	1.33(0.94-1.86)	0.104		
	Snoring			
Study arm	0.30(0.13-0.68)	0.004		
Operative procedure	1.03(0.86-1.25)	0.717		
Anesthetic duration	1.00(1.00-1.01)	0.466		
Duration since last muscle relaxant	1.00(0.98-1.02)	0.918		
BMI	1.36(0.92-1.99)	0.119		

-Smoking was not analysed due to the very small numbers per group (4 each). Adjusted odds ratios were not calculated for tactile stimulation, airway manoeuvre and snoring because the other variables were not statistically significant.

Chapter 9: Discussion

The time between extubation and recovery of TOF ratios ≥0.9 represents a particularly vulnerable period for adverse respiratory events(27). Several factors may be associated with residual paresis in PACU. These include duration of anaesthesia and surgery, type of muscle relaxant used and use of reversal agent for NMBA at end of anaesthesia. In this study, anaesthetic technique was standardised and neostigmine was given as reversal agent. Cisatracurium was used in both groups and duration of anaesthesia and surgery was not statistically significant.

There were many patients with SPO2>94% in the TOF group compared to clinical assessment group on arrival in PACU and during the first 30minutes. Logistic regression analysis showed a patient was less likely to develop mild hypoxia if in the TOF group compared to clinical assessment group (adjusted OR 0.11 P-value 0.043). However, incidence of severe hypoxia (SPO2<90%) was not statistically significant between the two groups (P-value 0.373). This study therefore concurs with a study by Murphy et al which showed that use of acceleromyographic TOF ratio intra-operatively reduces adverse respiratory events during early recovery from anaesthesia(5).

In the same study, Murphy et al demonstrated 0% incidence of severe hypoxia in PACU when using acceleromyography intraoperatively for monitoring neuromuscular function(5). However, in this study the incidence of severe hypoxia was 5% in the TOF group. This could be attributed to other factors such as residual sedation from opioids and isoflurane given intraoperatively. Murphy et al used Bispectral index monitoring in their study but depth of anaesthesia monitoring was not done in this study. In addition, acceleromyographic TOF ratio was used to guide the anaesthesiologists in the Murphy study on when to top up the muscle relaxant. This tends to

reduce the cummulative dose of muscle relaxant given intraoperatively as compared to topping up every 30-45minutes as was done in this study.

The incidence of upper airway obstruction as demonstrated by requirement of an airway maneuver, tactile stimulation and snoring was less in the TOF group compared to the clinical assessment group. Logistic regression analysis revealed patients in the TOF group were less likely to require tactile stimulation, an airway maneuver or snored while in PACU. In the Murphy study, 0% of patients required an airway maneuver or tactile stimulation in PACU to maintain the normal SPO2. However, in this study 14% and 2% of patients in the TOF group required airway maneuver and tactile stimulation respectively. This could again be attributed to residual sedation. In addition, TOF ratios were done in awake patients in the Murphy study and these could explain their findings.

With all the possible confounders adjusted for, it appears that acceleromyographic TOF ratio >0.9 before tracheal extubation reduced incidence of hypoxia and upper airway obstruction in PACU but did not completely eliminate them. This is clinically significant given that a single episode of hypoxia or upper airway obstruction can be catastrophic if not addressed immediately. This should however be combined with objective monitors of depth of anaesthesia to completely eliminate critical respiratory events in PACU.

Limitations of this study included lack of objective measure of recovery from general anaesthesia, variation in the type of operative procedures done and a low nurse to patient ratio in the PACU. This was because at the Aga Khan University hospital Nairobi, objective measurement of depth of anaesthesia is not routinely done and this study aimed to mimick normal clinical practice which is a reflection of anaesthesia practice in Kenya. The nurse patient ratio in our PACU was 1 to 2 against a WHO recommendation of 1 to 1 ratio and

these could have influenced the high incidences of hypoxia and upper airway obstruction observed due to late interventions.

Recommendations based on this study include:

1) A repeat study in patients undergoing same surgical procedure.

2) A follow-up of the patients who develop critical respiratory events in PACU to find out long term effects.

In conclusion, this study has demonstrated a lower incidence of critical respiratory events and mild hypoxia in post anaesthesia care unit with the use of neuromuscular monitoring using TOF ratio ≥0.9 to assess neuromuscular function before endotracheal extubation compared with the use of clinical assessment methods and and this should be the standard of care in our operating theatres.

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APPENDIX 1

Data collection tool

Age.....

Sex Male Female

Height.....

Weight.....

BMI.....

ASA status.....

Type of surgery.....

Opioids given intraoperatively.....

Time since last muscle relaxant given in minutes.....

Duration of surgery in minutes.....

Duration of Anaesthesia in minutes.....

History of smoking in pack years.....

Stridor Yes No

Snoring Yes No

Laryngospasms Yes No

Chin lift/ Jaw thrust Yes No

Oropharyngeal /Nasopharyngeal airway Yes No

Tactile stimulation Yes No

Re-intubation Yes No

Time (mins)	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30
SPO_2																
RR																

Appendix II EXPLANATION FORM

A randomized control trial comparing train of four ratio ≥0.9 to clinical assessment of return of neuromuscular function before endotracheal extubation on critical respiratory events in adult patients undergoing elective surgery at the Aga Khan University hospital Nairobi.

Name of principal investigator: Dr Adembesa Isaac

Name of the institution: Aga Khan University Hospital, Nairobi

Introduction

I am a medical doctor training for a postgraduate degree in Anaesthesiology at the Aga Khan University Hospital, Nairobi.

I am conducting a study to compare return of normal muscle function during general anaesthesia using a machine to a clinician assessment before removal of a breathing tube on respiratory events such as low oxygen in blood and obstruction of airway in the recovery room in adult patients undergoing elective surgery.

Train of four is a pattern of stimulating a nerve in order to find out whether a patient has recovered from muscle relaxation after undergoing general anaesthesia. A ratio of ≥0.9 before removing a breathing tube indicates at least 90% recovery of muscle and therefore it is thought it will reduce chances of respiratory complications. Routinely, we use clinical methods to

determine recovery of muscles but studies have demonstrated they are unreliable.

Kindly ask me for any clarification if you do not understand any statement or word in this form.

Purpose of the research

This research aims to determine if the use a machine that monitors muscle relaxation to clinical assessment of return of normal muscle before a breathing tube is removed will reduce critical respiratory events such as low oxygen in blood or airway obstruction during recovery from general anaesthesia.

Type of research intervention

For this research you will receive standard treatment at AKUH, N. Our medical staffs are dedicated to patient care and comprises of a multi-disciplinary team with internationally recognized expertise in different fields. Our theatres are modern and have state of the art equipment capable of handling a wide range of both elective and emergency procedures. For your surgical procedure, we will use the standard medication for the general anaesthesia and pain management, and either a machine monitoring muscle relaxation or clinical assessment before a breathing tube is removed. Before being recruited in this research you will be asked a series of questions to ensure that you will not suffer any serious effects of nerve stimulation by the machine.

Participant selection

You are being asked to participate as part of a group of patients who will need general anaesthesia involving use of muscle relaxants.

Procedures

If you agree to participate, we shall be performing general anaesthesia using muscle relaxants in the routine standard way and using the standard equipment. The only difference will be the addition of either a machine for monitoring muscle relaxation or clinical assessment of muscle recovery.

Risks and discomforts

You are not expected to have any additional risks by participating in this study. Nerve stimulation by the machine causes discomfort in the nerve being stimulated but the current we are going to use has not been shown to cause harm. The stimulation will be done when you are still under anaesthesia and therefore you will not feel or remember the discomfort. In the unlikely event of an injury related to this test, then adequate medical care and follow-up will be provided for you without any added cost. Should you develop any pain or discomfort during the procedure we will use painkillers to control pain.

Benefits

It is believed that collecting and studying this information will lead to important knowledge about routine monitoring of muscle relaxation using objective instruments and therefore reducing any potential respiratory problems during recovery.

Compensation

You will receive no compensation for participating in this study. In case commercial products such as new monitors are developed as a result of this study, you will not receive monetary or other benefit from the development of such products.

Confidentiality

Any information you provide during the study will be kept strictly confidential. Your full name will not appear on any study document and only staff participating in this study will have access to the information you provide.

Right to refuse or withdraw

Your participation in this research is entirely voluntary. You are free to choose whether or not you wish to participate. Your decision whether or not to participate will not affect your current or future relations with Aga Khan university Hospital Nairobi. You will suffer neither penalties nor loss of any benefit should you decide not to participate. If for any reason, you are not eligible for the study, or decide not to participate, you will receive normal care and standard treatment and medications. You are also free to withdraw from the study at any time should you wish to do so, for any reason.

Your co-operation is appreciated. Should you have any questions feel free to communicate with me concerning the study on the following address,

Dr Adembesa Isaac

Tel number 0720949430

P.O Box 30270-00100

Aga Khan University Hospital, Nairobi, Kenya

Appendix III: CONSENT FORM

I……..hereby consent to participate in this study, having been fully informed of the nature of the study by Dr Adembesa.

Date……. Signature……..

I..... (Spouse/Guardian) hereby give consent for.....to participate in this study, having been fully informed of the nature of the study by Dr Adembesa.

Date……. Signature……..

I, Dr Adembesa confirm that I have fully explained to my patient what this research involves and hereby undersign.

Date……Signature…….

Appendix IV FOMU YA IDHINI

Fomu hii itatiwa sahihi na mgonjwa anayetayarishwa kufanyiwa upasuaji usio wa dharura kwenye chumba cha upasuaji, kabla ya kushirikishwa kwenye utafiti huu.
Ikiwa kwa sababu moja au nyingine hataweza kutia sahihi, basi mtu wa ukoo wake wa kwanza anayetambuliwa na hospitali hii anaweza kutia sahihi kwa niaba yake.

Mimi.....nakubali kwa hiari yangu kushiriki kwenye utafiti huu baada ya kuelezwa kwa kina kuhusu utafiti huu na daktari Adembesa.
Tarehe .....sahihi (mgonjwa).....

Ama

Mimi.....natoa idhini kwa niaba ya..... (Jina la mgonjwa) ili ashiriki kwenye utafiti huu baada ya kuelezwa kwa kina kuhusu utafiti huu na daktari Adembesa.

Tarehe.....sahihi (mtu wa ukoo).....

Mimi daktari Adembesa nimehakikisha ya kwamba nimemuelezea mgonjwa pamoja na mtu wa ukoo wake kuhusu utafiti huu kwa kina.

Tarehe……. Sahihi…….