Current knowledge of malignant hyperthermia in a department of anaesthesiology

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Medicine in the branch of Anaesthesiology.

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Declaration

I, Farrah Josephine Rimmington declare that this research report is my own unaided work. It is being submitted for the Degree of Master of Medicine in the branch of Anaesthesiology at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.

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15 October 2020

Abstract

Background

Malignant hyperthermia (MH) is an inherited, pharmacogenetic disorder of skeletal muscle, which leads to a potentially fatal hypermetabolic state in response to certain triggering agents. These include most volatile anaesthetic agents and the depolarising muscle relaxant succinylcholine. These drugs are used daily in the Department of Anaesthesiology at the University of the Witwatersrand. The knowledge of MH in the department at Wits University is currently not known. Studies performed in other countries generally show inadequate knowledge of MH among theatre personnel.

Methods

A prospective, contextual, descriptive research design was used in this study. A knowledge-based questionnaire was completed by Wits anaesthetists. Permission to utilise a questionnaire obtained from a Dutch study was granted. This questionnaire was adapted for content and context with the help of South African MH expert Dr JC Brand.

Results

Percentages scored for the four subscales were: risk factors (58.3%), triggers (94.9%), diagnosis (75.2%) and treatment (42.4%). The overall mean (SD) score was 59.2% (12.6%). The mean (SD) score for juniors was 53.0% (13.4%) and for seniors 62.2% (11.1%). This difference was statistically significant (p=0.0001). Only 6 (4.4%) of participants achieved the pass mark of 80% or more, all of whom were seniors.

Conclusion

This study showed an inadequate level of knowledge of MH among anaesthetists in the department. These results are in keeping with those found in studies performed in other countries.

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Table of contents

Declaration ii

Abstract iii

Acknowledgements iv

Abbreviations ix

Statement xi

Section 1: Review of the literature 1

1.1 Introduction 1

1.2 History 1

1.3 Epidemiology 1

1.4 Porcine genetic model 2

1.5 Pathophysiology 3

1.6 Triggering of MH 4

1.7 Risk factors 6

1.8 Differential diagnosis of MH 7

1.9 Clinical presentation 8

1.9.1 Clinical signs 9

1.9.2 Larach grading scale 10

1.10 Laboratory diagnosis 13

1.11 Treatment 13

1.11.1 Prevention 16

1.11.2 Management of a Malignant Hyperthermia Crisis 16
1.11.3 EMHG Guidelines: Managing an MH Crisis 17
1.12 Studies assessing health care professionals' knowledge of MH 20
1.13 Summary 20
1.14 Permission to use guidelines 21
1.15 References 23
Section 2: Author's guidelines 26
Section 3: Draft article 33
Section 4: Proposal 47
4.1 Introduction 48
4.2 Problem statement 50
4.3 Aim and objectives 51
4.3.1 Aim 51
4.3.2 Objectives 51
4.4 Research assumptions 51
4.5 Demarcation of study field 52
4.6 Ethical considerations 52
4.7 Research methodology 53
4.7.1 Research design 53
4.7.2 Study population 53
4.7.3 Study sample 54

4.7.4 Inclusion and exclusion criteria 54
4.7.5 Data collection 54
4.7.6 Data analysis 55
4.8 Significance of the study 56
4.9 Validity and reliability of the study 56
4.10 Potential limitations 57
4.11 Project outline 58
4.11.1 Time frame 58
4.11.2 Budget 58
4.12 References 59
Section 5: Appendices 61
Appendix 1: Participants' information sheet 61
Appendix 2: Questionnaire 62
Appendix 3: Permission to use questionnaire 69
Section 6: Annexures 70
6.1 Ethics approval 70
6.2 Graduate studies approval 71
6.3 Turnitin Report 72
6.4 Turnitin Letter 74

List of tables

Literature Review

Table 1.1: Clinical Signs 9

Table 1.2: Clinical indicators for use in determining the MH raw score (27) 10

Table 1.3: Raw score range conversion to MH likelihood (27) 13

Table 1.4: EMGH Guidelines on managing MH crisis (26) 18

Draft Article

Of the 150 questionnaires handed out, 145 (96.7%) were returned. Of those returned, 9 questionnaires were completely blank and therefore excluded. The remaining 136 (91.0%) questionnaires were included and represents 65.4% of anaesthetists in the department.

The demographics of participants is shown in Table I. There were 44 (32.4%) junior and 92 (67,6%) senior participants.

Table I: Demographics of participants

Table II: Percentages scored per subsection

Table III: Percentage of participants who passed per subsection

Table IV: Correct answers per question.

Abbreviations

ACF	activated charcoal filter
Ach	acetylcholine
ATP	adenosine triphosphate
BMD	Becker muscular dystrophy
Ca^{2+}	calcium
CO_2	carbon dioxide
DHPR	dihydropyridine receptors
DMD	Duchenne muscular dystrophy
$ETCO_2$	end-tidal carbon dioxide
DNA	deoxyribonucleic acid
EMHG	European Malignant Hyperthermia Group
FR	Farrah Rimmington
IVCT	invitro contractility test
K^+	potassium
MH	malignant hyperthermia
MHN	malignant hyperthermia negative
MHS	malignant hyperthermia susceptibility
MHSc	malignant hyperthermia susceptible (caffeine)
MHSh	malignant hyperthermia susceptible (halothane)
MHShc	malignant hyperthermia susceptible (halothane and caffeine)

MAUS	Malignant Hyperthermia Association of the United States
NAMHG	North American Malignant Hyperthermia Group
O_2	oxygen
$PETCO_2$	partial end-tidal carbon dioxide
pH	potential of hydrogen
SR	sarcoplasmic reticulum
UK	United Kingdom
USA	United States of America
Wits	University of the Witwatersrand

Statement

The Research Report consist of a literature review, draft article, study proposal and appendices. The study proposal is included for background reference and is not for examination.

The formatting of this Research Report complies with the University of the Witwatersrand's Style Guide for Theses, Dissertations and Research Reports. The formatting of the draft article may differ from the rest of the Research Report in order to comply with the author guidelines of the South African Journal of Anaesthesia and Analgesia, the journal to which it is intended to be submitted.

Section 1: Review of the literature

1.1 Introduction

Malignant hyperthermia (MH) is defined by Rosenberg et al. (1) as

> a pharmacogenetic disorder of skeletal muscle, that manifests as a hypermetabolic response to potent volatile anaesthetic gases (such as halothane, isoflurane, sevoflurane, desflurane), the depolarising muscle relaxant succinylcholine, and rarely, in humans, to stressors such as vigorous exercise and heat.

MH will be explored from the literature. Initially the definition, history, epidemiology and porcine genetic model will be discussed. Following this a description of skeletal muscle contraction and the pathophysiology of this in MH will be explained. Finally, the triggers, risk factors, clinical presentation, differential diagnosis, diagnostic tests and treatment will also be included.

1.2 History

Louis Ombrédanne, in 1929, noted hyperthermia and pallor in some children post anaesthesia which was associated with a significant mortality rate (2). Initially this was called Ombrédanne's syndrome. It was only much later that the familial relationship associated with the condition was identified (2, 3).

Approximately thirty years later a pattern of inheritance was discovered. In 1960 a 21-year old university student was involved in a pedestrian vehicle accident while on campus, where he sustained a fracture of his lower limb (4). After presenting to the Royal Melbourne Hospital in Australia, the casualty staff noted that he was far more concerned about the need for a general anaesthetic than the fracture (4). He gave a significant family history of anaesthesia associated deaths involving ten of his relatives (2, 4). As ether was thought to be the culprit in the family members' deaths the anaesthetist, James Villiers used halothane instead (4). A few minutes into the anaesthesia the patient developed a tachycardia, decreasing blood pressure and was clinically pyrexial. Dr Villiers packed the patient in ice which he sourced from a nearby cardiac theatre. The surgery was quickly concluded, the

anaesthetic was stopped, symptomatic treatment was given, and the patient made a full recovery.

The following day Dr Villiers referred the patient to a colleague with an interest in clinical genetics, Dr R. Lovell (4). A complete clinical examination and routine biochemical tests were performed but all findings were unremarkable. Following review of the patient's family records however, Denborough and Lovell published this case report in, the Lancet in July 1960, and suggested a syndrome that was possibly inherited in an autosomal dominant fashion (5). Approximately a year later the same patient required another anaesthetic for removal of a stone in the ureter. After much consideration the anaesthetist opted for a spinal anaesthetic which was well tolerated. This was of great importance in this specific patient as he subsequently suffered from multiple episodes of kidney stones requiring spinal anaesthesia which was always well tolerated (4).

1.3 Epidemiology

The incidence of MH episodes is estimated to be between 1:10 000 to 1:250 000 anaesthetics (1). As MH is a subclinical myopathy, the true incidence of susceptibility remains unknown as most patients are asymptomatic with no phenotypic changes until exposure to a trigger or specific diagnostic testing (6). Of note is that even with exposure to a known trigger a MH-susceptible person may not develop a MH episode (7). Susceptible individuals have on average three anaesthetics before triggering a MH crisis (8). Larach et al. (9) noted that 50.7% of patients had two or more uneventful general anaesthetics prior to a MH episode. Two patients, one in the UK and the other in the USA, developed a MH reaction on their thirteenth and thirty-first exposure respectively, to general anaesthetic (10).

Due to the pattern of inheritance in MH, the estimated prevalence of the genetic abnormalities ranges from 1:3000 to 1:8500 (8). With improvement in understanding the pathophysiology, diagnosis, management and the use of dantrolene, the mortality rate for a MH crisis has decreased from 70 – 80% to approximately 5% (6, 11). Despite the decreased mortality rate the morbidity rate remains high. In a study by Larach et al. (9) a morbidity rate of 34.8% was found. Complications cited include changes in level of consciousness, cardiac, renal,

pulmonary and hepatic dysfunction as well as disseminated intravascular coagulopathy (6, 9). The potential for multi-organ dysfunction highlights the need for anaesthetists to be able to promptly diagnose and appropriately treat MH (6).

MH occurs globally in all ethnic groups (8) and races (6). There is a male predominance with reactions occurring more frequently in males than females (2:1) (1). The reason for this is unknown but theories suggest differences in ionic channels for muscle contraction, either due to the effect of sex hormones, or inherent differences among males and females (6).

Larach et al. (9) examined MH cases from 1987 – 2006 using data from the North American Malignant Hyperthermia Registry of the Malignant Hyperthermia Association of the United States (MHAUS). The authors found that young males accounted for 74.8% of MH episodes. Children under the age of 15 years old constitute 52.1% of all MH reactions (1). Although reactions have been suspected in the newborn, the earliest MH reaction confirmed by testing was in a six-month old while the oldest was in a 78-year old (8).

1.4 Porcine genetic model

MH is not unique to humans and can affect other species; including certain pig breeds, horses and dogs (8, 12). The porcine model has aided in the understanding of MH, especially in the development of muscle testing and specific drug treatment for MH (13). As a result, the mortality rate has decreased significantly (13). This model was developed because of reports of poor-quality meat due to increased skeletal muscle metabolism. It was noted that pigs that were intentionally inbred in order to produce certain characteristics, such as rapid growth and better muscling, suffered from porcine stress syndrome (3). This syndrome manifested as fever, rigidity and death in response to stresses such as fighting, coitus and preparation for slaughter. It was found that MH was induced on exposure to halothane and succinylcholine in the pigs with porcine stress syndrome (3). When pigs are compared to humans there are differences in the inheritance patterns of MH, but the clinical and laboratory findings are very similar (3). In 1975, the successful use of dantrolene to prevent and treat porcine MH was described by South African, Prof Harrison (3). It was noted during these

experiments on MH-susceptible pigs that dantrolene caused a rapid decline in muscle rigor and temperature rise, as well as termination of the acidosis characteristic of the syndrome. Following these findings dantrolene was tested in humans presenting with MH (14).

1.5 Pathophysiology

An imbalance in calcium (Ca^{2+}) homeostasis within the skeletal muscle cell ultimately results in a hypermetabolic state (6). A large percentage of body weight is made up of skeletal muscle hence the significant effects on whole body metabolism (2). The clinical signs result from this increased metabolism as oxygen consumption and therefore carbon dioxide production are accelerated (10). The biochemical reactions produce heat as many of them are exothermic in nature (3).

Consequently adenosine triphosphate (ATP) demand is increased (10). Depletion of energy in the form of ATP results in a reduced ability for active pumping of ions against their concentration gradients (15). This allows ions and molecules to move across membranes in the direction of their natural concentration gradients (15). Notably, ATP is not only required for contraction but for relaxation of skeletal muscle since relaxation is also an active process (3).

Importantly, MH-susceptible skeletal muscle is different from normal skeletal muscle, as a dysregulation of excitation-contraction (EC) coupling occurs on exposure to a trigger (10). This EC coupling is the process by which skeletal muscle converts a chemical signal into mechanical work in the form of muscle contraction (3). The normal physiology of the EC coupling process will be discussed prior to the pathology which occurs in MH.

The chemical signal in skeletal muscle is the neurotransmitter acetylcholine (Ach), which is released from the motor neuron terminal of the neuromuscular junction (3, 10). As a nerve impulse arrives at the neuromuscular junction, an action potential is generated at the motor endplate (10). Ach diffuses across the synaptic cleft to the postsynaptic membrane where it binds to nicotinic cholinergic receptors and causes depolarisation (3).

There is inward spread of depolarisation from the sarcolemma to the T-tubules of the myocyte. Within the T-tubule membrane an L-type voltage gated Ca^{2+} channel exists (2). Historically these Ca^{2+} channels were called dihydropyridine receptors (DHPRs), named after the drug, dihydropyridine, which can block these receptors (3). Once T-tubule depolarisation occurs, conformational changes within this Ca^{2+} channel complex occur (2, 3).

One of the DHPR subunits, the α_{1S}subunit, provides a physical link between the DHPRs in the T-tubules and the Ca^{2+} channels within the sarcoplasmic reticulum (SR) (3). This channel in the SR is called the skeletal isoform or ryanodine receptor 1 (RyR1) encoded by the RYR1 gene. There exists a highly organised arrangement of all α_{1S}-DHPRs into tetrads. Each one of these tetrads is situated near to a single RyR1 channel which consists of four identical subunits, each α_{1S}-DHPR overlies a single RyR1-subunit. The DHPR serves as a voltage sensor once depolarisation occurs and due to physical interaction with and then activation of RyR1, the release of Ca^{2+} from the SR is triggered (3). The Ca^{2+} binds to the troponin-tropomyosin complex which induces a conformational change in the thin filament or actin. This causes exposure of the myosin binding site on the actin filament which allows actin and myosin interaction and therefore muscle contraction to occur (6). For relaxation to occur the Ca^{2+} must be actively pumped back into the SR via a sarcoplasmic reticulum/endoplasmic reticulum Ca^{2+} ATPase pump (SERCA) (6).

In MH-susceptible muscle, certain triggers cause a dysregulation of EC coupling and accelerated release of Ca^{2+} from the SR (10). The cell's ability to sequester Ca^{2+} via the SERCA is overwhelmed and ATP levels decrease leading to impaired membrane integrity (10). The most common abnormalities in MH are mutations in RYR1 and CACNA1S genes which account for 40 – 80% and 1% of cases respectively (10). The RYR1 gene is located on chromosome 19q13.1 and at least 34 mutations identified are causal for MH (1). Molecular studies show that MH susceptibility is complicated by genetic heterogeneity with involvement of more than one gene (2). Other genes excluding the RYR1 where mutations have been identified in MH families is the gene coding for the α_1-subunit of the DHPR, or

the CACNA1 as well as STAC3 which is the most recently found gene associated with MH (16) .

Regardless of the mutation, the pathophysiology of MH is related to an uncontrolled release of Ca^{2+} from skeletal muscle SR (6, 8). Ultimately ATP stores will be depleted as the myocytes attempt to restore Ca^{2+} balance by increasing the uptake into the SR. The result is a compromise in muscle cell integrity leading to the leakage of cell contents out of the cell (8). Hence substances such as potassium and myoglobin will enter the circulation resulting in hyperkalaemia and potential renal failure respectively (7, 12). Eventually if left untreated multi-organ failure and death can result (7, 8).

1.6 Triggering of MH

Triggers can be divided into pharmacological and nonpharmacological or awake triggers.

All the volatile agents, excluding nitrous oxide and xenon, as well as the depolarising muscle relaxant, succinylcholine are pharmacological agents known to trigger MH (17). Volatile agents such as halothane, isoflurane and enflurane have been shown to have a more rapid onset and greater incidence compared to sevoflurane and desflurane (17).

The incidence with which individual volatile agents are implicated as the trigger will also be affected by the frequency of their clinical use. Previously in Japan it was sevoflurane, while currently in the United Kingdom, isoflurane is the most commonly blamed volatile agent (18). In contrast, non-depolarising muscle relaxants are considered safe in MH-susceptible patients (18).

In the porcine model it was found that stresses such as separation, fighting or coitus could trigger an MH episode in MH-susceptible pigs (3). In humans the concept of awake triggers has also been documented. Currently there is strong evidence that some MH-susceptible individuals are more likely to develop rhabdomyolysis following strenuous exercise than MH negative individuals (19). Further studies are required to define this relationship (19).

A report by Tobin et al. (20) provided evidence of this relationship. The case involved a 12-year old boy who subsequently died following exposure to heat and exercise in the form of a football game. The boy complained of muscle stiffness and weakness following a football game at high ambient temperatures. He was found to be pyrexial, sweating, acidotic and hyperkalaemic. Respiratory arrest occurred requiring endotracheal intubation which was impossible because of jaw rigidity. A few months prior to his death, he had a MH episode during general anaesthesia with sevoflurane, for reduction of a humerus fracture. He recovered from this initial episode without sequelae, following treatment with dantrolene . Posthumous DNA analysis revealed an altered RYR1 mutation causative for MH. Subsequently his father was found to have the same mutation (20).

1.7 Risk factors

MH is mostly inherited as an autosomal dominant trait (3). This translates into a 50% chance with each pregnancy that the offspring will inherit the disease (17). Once a genetically predisposed person is exposed to a triggering agent there is a risk of a MH crisis.

A diversity of coexisting conditions, enzymopathies and syndromes have been associated with MH susceptibility (MHS) by a clinical event or abnormal laboratory test with a higher incidence than one would expect with chance alone (21). For most conditions evidence is weak for a causal link with MHS (21). Patients with King-Denborough syndrome, however should be considered MH-susceptible and known triggers should be avoided (3, 21). Currently there is evidence that there are more than 20 RYR1 mutations associated with the coexistence of MH and Central Core Disease (CCD) and therefore patients with CCD should be considered MH-susceptible (6).

There is weak evidence of an association between osteogenesis imperfecta and MHS with only one convincing case report (21). Hyperthermia in osteogenesis imperfecta patients under general anaesthesia is a well-recognised event. This rise in temperature however, responds well to standard cooling measures and does not accompany other features of hypermetabolism (21). The association between MH and other myopathies is less clear and requires further investigation.

Recently the association between MH and strenuous exercise has been substantiated by case reports and studies. Wappler et al. (22) performed invitro contracture tests (IVCT) on 12 patients with exercise-induced rhabdomyolysis, 18 patients with anaesthesia-induced MH and 28 controls. Results showed that 10 of the 12 exercise-induced rhabdomyolysis patients were MH-susceptible while all of the control patients were MH negative (22).

A retrospective cohort study and systematic review was performed on literature published between 1995 – 2016 on genetic screening done on Canadian patients who presented with exertional rhabdomyolysis (23). The retrospective study on Canadian MHS patients with exertional rhabdomyolysis showed that ten out of seventeen patients carried mutations that were either known to be associated with MH or had the potential to be pathogenic variants (23). Results of the systematic review showed 39 different rare RYR1 variants. This included 13 MH-causative or associated mutations and five potentially associated CACNA1S variants in 78% of patients with exertional rhabdomyolysis (23).

1.8 Differential diagnosis of MH

There is no pathognomonic feature for MH (12). The collection of clinical features that occur in a MH crisis can resemble numerous medical conditions resulting in a variety of differential diagnoses. Iatrogenic causes such as excessive warming measures, inadequate depth of anaesthesia and insufficient ventilation can produce some of the features of MH (11). Endocrine pathology such as pheochromocytoma and thyrotoxicosis can cause diagnostic confusion (11). Multiple drugs including amphetamines, anticholinergics, monoamine oxidase inhibitors, cocaine and ecstasy should always be considered as potential differential diagnoses (12) .

Fever from any aetiology ranging from infection and sepsis to transfusion and allergic reactions can produce a similar clinical picture (11) . Anaphylactic reactions, serotonin syndrome and malignant neuroleptic syndrome are other conditions which may clinically mimic a MH crisis (10, 11). Anaesthesia induced rhabdomyolysis can resemble a MH crisis but is considered a separate entity and is associated with Duchenne muscular dystrophy (DMD) and Becker muscular

dystrophy (BMD) where a breakdown of skeletal muscle can occur on exposure to volatiles and succinylcholine (17). The aetiology is abnormal dystrophine gates in the sarcolemma and not an abnormal RYR1 gene (17). A potentially fatal hyperkalaemic cardiac arrest can occur if not treated rapidly (24). Gurnaney et al. (24) did not find an increased risk of MHS in patients with DMD or BMD.

In order to institute the appropriate treatment and reduce morbidity and mortality the correct diagnosis of MH must be made in a timely fashion.

1.9 Clinical presentation

There are multiple reasons for the heterogenous clinical presentation. Some of these reasons relate to differences in the individual such as age and genetic variability while others relate to the triggering agent such as potency, concentration and duration of exposure (6). This makes it difficult to clinically diagnose MH with absolute certainty.

1.9.1 Clinical signs

The clinical features of MH are usually grouped as early or late according to timing of onset in the reaction (18). These time periods demonstrate a temporal relationship and are not quantified due to the variability that exists among patients (18). The most common and often the earliest sign in the mechanically ventilated patient, is inappropriately increased carbon dioxide (CO_2) production (6). This will manifest as an elevated end-tidal CO_2 despite increased minute ventilation (1) and if the patient is breathing spontaneously then tachypnoea will be noted (10) . Larach et al. (9) examined the presentation of 255 cases of MH and reported the first or only MH clinical sign noted was hypercarbia (38.0%), sinus tachycardia (31.0%) or masseter spasm (20.8%) (9). Historically a severe, rapidly developing hyperthermia was the hallmark feature when MH was initially described in 1960. Currently studies have found increasing body temperature to be a relatively late sign (6).

The European Malignant Hyperthermia Group (EMHG) guidelines on recognising a MH crisis are summarised in Table 1.1 (25).

Table 1.1: Clinical Signs

Early signs	Later signs
• Metabolic ○ Inappropriately elevated CO_2 production (raised end-tidal CO_2 on capnography, tachypnoea if breathing spontaneously). ○ Increased O_2 consumption. ○ Mixed metabolic and respiratory acidosis. ○ Profuse sweating. ○ Mottling of skin. • Cardiovascular ○ Inappropriate tachycardia. ○ Cardiac arrhythmias (especially ectopic ventricular beats and ventricular bigeminy). ○ Unstable arterial pressure. • Muscle ○ Masseter spasm if succinylcholine has been used. ○ Generalised muscle rigidity.	• Hyperkalaemia. • Rapid increase in core body temperature. • Grossly elevated blood creatine phosphokinase levels. • Grossly elevated blood myoglobin levels. • Dark-coloured urine due to myoglobinuria. • Severe cardiac arrhythmias and cardiac arrest. • Disseminated intravascular coagulation.

1.9.2 Larach grading scale

The non-specific nature of an MH episode is evidenced by the extensive differential diagnosis list. There is no specific clinical or biochemical finding for MH. In order to overcome this problem a clinical grading scale to predict MH susceptibility was developed in 1994 by Larach et al. (26) using an international panel of eleven MH experts. This scale does not require specialised diagnostic testing and it relies on the anaesthetist's judgement to decide if certain clinical signs are appropriate for the condition, anaesthetic technique and type of surgery.

This grading scale can be utilised in two important scenarios. Firstly, to qualitatively estimate the likelihood that an adverse anaesthetic event is clinical MH and secondly to determine an individual's qualitative likelihood of MH susceptibility in the presence of a positive family history with or without a personal adverse anaesthetic event (26).

The experts that developed the MH clinical grading scale created scoring rules in order to address multiple issues (26). A double-counting rule was created in order not to overestimate likelihood of MH. If more than one indicator represents a single process, then only the indicator with the highest score must be counted. This is because several of the indicators are manifestations of the same physiologic process (26). The experts also felt that due to the pattern of inheritance, additional points for family history are added to the raw score to determine an individual's MH susceptibility. Ranks for MH events and MH susceptibility were made separate in order to allow determination of likelihood in individuals who never personally experienced an adverse anaesthetic event (26).

Table 1.2: Clinical indicators for use in determining the MH raw score (27)

Process	Indicator	Points
I: Rigidity	Generalized muscular rigidity (in absence of shivering due to hypothermia, or during or immediately following emergence from inhalational general anaesthesia) Masseter spasm shortly following succinylcholine administration	15 15
II: Muscle Breakdown	Elevated creatine kinase >20 000 IU after anaesthetic that included succinylcholine Elevated creatine kinase >10 000 IU after anaesthetic without succinylcholine Cola coloured urine in perioperative period Myoglobin in urine >60µg/L Myoglobin in serum >170 µg/L Blood/plasma/serum K^+ > 6mEq/L (in absence of renal failure)	15 15 10 5 5 3
III: Respiratory Acidosis	$PETCO_2$ >55mmHg with appropriately controlled ventilation Arterial $PaCO_2$ > 60mmHg with appropriately controlled ventilation $PETCO_2$ >60 mmHg with spontaneous ventilation Arterial $PaCO_2$ > 66mmHg with spontaneous ventilation Inappropriate hypercarbia (in anaesthesiologist's judgement) Inappropriate tachypnoea	15 15 15 15 15 10
IV: Temperature Increase	Inappropriately rapid increase in temperature (in anaesthesiologist's judgement) Inappropriately increased temperature >38.8◦C in the perioperative period (in anaesthesiologist's judgement)	15 10
V: Cardiac Involvement	Inappropriate sinus tachycardia Ventricular tachycardia or ventricular fibrillation	3 3
VI: Family History (used to determine MH susceptibility only) **Other indicators that are not part of a single process ǂ**	Positive MH family history in relative of first degree* Positive family history in relative not of first degree* Arterial base excess more negative than -8 mEq/L Arterial pH <7.25 Rapid reversal of MH signs of metabolic and/or respiratory acidosis with iv dantrolene Positive MH family history together with another indicator from the patient's own anaesthetic experience other than elevated resting serum creatine kinase* Resting elevated serum creatine kinase* (in patient with a family history of MH)	15 5 10 10 5 10 10

* These indicators should be used only for determining MH susceptibility

ǂ These should be added without regard to double counting

The grading scale consists of six processes, as shown in table 2, each with multiple indicators that have a point value assigned to each individual indicator. The qualitative likelihood that an adverse anaesthetic event is MH is determined by the addition of points assigned to certain clinical and biochemical findings. These points are added to obtain a raw score. The raw score is then translated into a MH rank that determines the risk of likelihood ranging from 1 (almost never) to 6 (almost certain) (26).

Table 1.3: Raw score range conversion to MH likelihood (27)

Raw Score Range	MH Rank	Description of Likelihood
0	1	Almost never
3 – 9	2	Unlikely
10 – 19	3	Somewhat less than likely
20 – 34	4	Somewhat greater than likely
35 – 49	5	Very likely
50+	6	Almost certain

1.10 Laboratory diagnosis

The two currently approved methods of diagnosis for MH susceptibility include a muscle contracture test and molecular genetic testing (11). The muscle contracture test is usually performed only once a suspected MH event has occurred in an individual or in a family member, as most MH-susceptible patients appear normal and are asymptomatic until exposure to a trigger (6).

The gold standard for diagnosis of MH is a muscle contracture test (6, 8, 27). This involves a surgical muscle biopsy and exposure of live muscle specimens to certain concentrations of caffeine and halothane. If the contracture forces exceed defined thresholds, then a diagnosis of MH susceptibility is made (6). Two forms of this test have been developed; one by the EMHG called the invitro contracture test

(IVCT) and the other by the North American Malignant Hyperthermia Group (NAMHG) called the caffeine-halothane contracture test (6, 8). Similarities between the two protocols do exist (8). Some of these similarities include criteria for muscle sampling, biopsy to extraction testing time and muscle viability assessments (6). Some of the differences will be considered further. The NAMHG protocol allows any muscle site to be used for biopsy in contrast to the EMHG protocol which specifies the quadriceps muscle, either the vastus medialis or vastus lateralis as the biopsy site (6). The two protocols differ in the concentration and mode of halothane application. While NAMHG protocol uses a single concentration of halothane (3%), the EMHG uses incremental exposure to halothane (0.5, 1, 2 %) (6).

As South Africa follows the EMHG guidelines for IVCT these will be discussed in more detail. There are requirements for the muscle specimen dimensions which include; 20 – 25 mm in length between ties, a thickness of 2 – 3 mm and a weight of 100 – 200mg (16). A time limit of five hours from biopsy to completion of testing exists and hence it is advised that the biopsy is performed at a MH centre (16). The muscle specimen must be obtained using a regional or trigger-free general anaesthetic technique and transported to the laboratory in a specific solution. Local anaesthetic infiltration into the biopsy site should not be performed as this may impair the viability of the specimen (16).

The EMHG (2015) laboratory diagnostic classification includes the following (19):

- MHS_{hc}: Malignant hyperthermia susceptible (halothane and caffeine) a caffeine threshold at a caffeine concentration of 2 mmol/L or less in at least one caffeine test, and a halothane threshold concentration at 0.44 mmol/L or less in at least one halothane test.

- MHS_{h}: Malignant hyperthermia susceptible (halothane): a halothane threshold concentration at 0.44 mmol/L or less in at least one halothane test and a caffeine threshold at a caffeine concentration of 3 mmol/L or more in all caffeine tests.

- MHS_c: Malignant hyperthermia susceptible (caffeine) a caffeine threshold at a caffeine concentration of 2.0 mmol/L or less and a halothane threshold concentration above 0.44 mmol/L in all halothane tests.

- MHN: Malignant hyperthermia negative: a caffeine threshold at a caffeine concentration of 3.0 mmol/L or more in all caffeine tests and a halothane threshold concentration above 0.44 mmol/L in all halothane tests.

Previously when using the EMHG protocol, a third diagnosis could be made of MHE or equivocal when only either the halothane or caffeine test was positive. This has subsequently been replaced by the above classification of MHS_{hc}, MHS_h, MHS_c and patients not susceptible indicated by MH negative (MHN) (16).

The EMHG protocol has a sensitivity of 99% and a specificity of 93.6% while the NAMHG protocol has 97 – 98% sensitivity and 78 – 80% specificity (6). Therefore in comparison, the EMHG protocol possibly has a reduced chance of false positive and false negative results compared to the NAMHG protocol (6) .

An important role of MH diagnostics is to be cautious in making a MHN diagnosis as a false negative will have potentially catastrophic sequelae (16). If the IVCT was performed in an EMHG-accredited laboratory, then the MHN diagnosis carries a high degree of reliability (16). MHN patients cannot pass on MH susceptibility to their offspring, but it is possible that the children could be susceptible via inheritance from the other untested parent or via a spontaneous mutation (16).

A positive diagnosis has implications for the family members who will now require testing (17). Patient counselling, referral for diagnosis and family follow-up will be required and is the responsibility of the anaesthetic consultant (10). The patient will be instructed to wear a medic-alert bracelet in order to make health care professionals aware in the event of an accident or emergency (17, 27).

In October 2017, South Africa opened an IVCT laboratory at Midstream Mediclinic, headed by Dr JC Brand (27). It is equipped with all the necessary equipment for reliable diagnosis. Currently this is the only MH diagnostic laboratory in Africa.

Once a muscle contracture test is positive then genetic testing can be performed using DNA analysis from a blood sample (17). Gene sequencing can initially be

performed looking for known causative mutations. If no known causative mutation is found, then further sequencing can be performed. Only when a causative mutation is found then other family members can be tested for the same mutation (16). However, absence of a causative mutation does not exclude the possibility of MH susceptibility. This is due to the complex genetics of MH. Half of MH-susceptible patients do not carry the pathological variants in the known MH associated genes causing MH genetic testing to have a relatively low sensitivity (16). This means that if the causative mutation is found then the person is classified as MH-susceptible but if not found then MH susceptibility cannot be excluded. Consequently, a muscle contracture test would be required to definitively exclude MH susceptibility. Of significance is patients of African origin as causative mutations are population specific. These patients are more likely to be negative for mutations found in Caucasians (16). African DNA mapping still requires further research (27).

1.11 Treatment

1.11.1 Prevention

The pre-operative assessment plays a vital role in identifying individuals who are at risk for MH. This will be accomplished by obtaining a thorough history from the patient. If it becomes apparent that the individual or a family member has had a previous adverse anaesthetic event that is suspicious for MH, then they can be referred for a formal diagnostic work-up.

This is a lengthy procedure and if the surgery is an emergency or if the individual is known to be MH-susceptible then a trigger-free anaesthetic should be administered (17). Dantrolene prophylaxis is no longer recommended but sufficient amounts should be readily available in the theatre complex should the need for its use arise (17). Volatile agents and succinylcholine must be avoided. Regional anaesthesia is considered a safe option.

The anaesthetic machine needs to be prepared adequately for MH-susceptible individuals. This involves disconnection and removal of the vaporiser, change of soda lime and new circuit tubing (17). Each anaesthesia machine manufacturer and generation has varying procedures and decontamination times for cleansing

the machine of any remaining volatile . This can usually be found in the manual. However, as a general guide if there is uncertainty, it is advised to flush the machine for 70 minutes at 10 l/min and to maintain flows of 10 l/min for the duration of the procedure (17).

Alternatively, activated charcoal filters (ACF) can be used to expedite the machine preparation for MH-susceptible patients (28). Regardless of the machine make or model, ACFs can clean the machine in 90 seconds (16). A single ACF can be placed on the inspiratory limb of the circuit but it is recommended that ACFs are used as a pair with one on the inspiratory limb and one on the expiratory limb. This is to avoid the accidental placement on the expiratory limb only which could have catastrophic results (16).

1.11.2 Management of a Malignant Hyperthermia Crisis

Early recognition and prompt treatment of an MH episode are required to improve the prognosis (6, 29). This means that anaesthetists need to be familiar with the varied clinical presentation and the emergency treatment of a MH crisis.

Once a MH episode is suspected all trigger agents must be urgently withdrawn (10). In most cases this will involve turning off the volatile agent and disconnecting the vaporiser. Following this the patient should be hyperventilated with 100% oxygen at high flow. If the surgery cannot be immediately terminated, then total intravenous anaesthesia can be used in the interim (29). If muscle relaxation is required, then a non-depolarising agent can be safely used. The depolarising muscle relaxant, succinylcholine, the must be avoided. Communication is always vital during any emergency and the rest of the theatre team should be informed, and additional experienced help sought.

The only specific drug to manage MH is dantrolene (6, 30). This drug is a hydantoin derivative and is classified as a skeletal muscle relaxant (17). It blocks Ca^{2+} release from the sarcoplasmic reticulum of the myocyte (30). The exact mechanism of how it blocks Ca^{2+} is not completely understood (17, 30). Dantrolene is a lipophilic orange coloured powder that is poorly soluble in water. Each intravenous vial contains 20mg of lyophilised dantrolene sodium added to 3g of mannitol to improve water solubility. The content of each vial has to be

thoroughly dissolved in 60ml of sterile water and must be clear and without visible particles prior to administration (17, 30). The initial recommended dose varies between articles and textbooks, but the range is between 2 – 2.5 mg/kg intravenously (iv) and then repeated every five minutes up to a total dose of 10 mg/kg or until clinical signs subside (17, 29). Following control of an acute MH crisis, a maintenance regimen of dantrolene sodium must be continued for the next 24 hours in order to prevent recurrence of symptoms (17). Recrudescence which occurs in approximately 20% of patients can occur for hours after initial resolution of symptoms (29). Maintenance can be given every 4 – 6 hours (dantrolene 1 mg/kg) or as an infusion (10 mg/kg/24hrs) (17). Some of the side effects of dantrolene include muscle weakness, respiratory failure, nausea, vomiting, diarrhoea and phlebitis (30). Ryanodex is a more concentrated and soluble formulation of dantrolene sodium however it is not yet available in South Africa (17).

During an acute MH crisis, routine anaesthetic monitoring including core temperature measurement, must be continued. Invasive lines such as an arterial line and central venous catheter should be placed as well as a urinary catheter. Table 4 provides invaluable information.

1.11.3 EMHG Guidelines: Managing an MH Crisis

Table 1.4: EMGH Guidelines on managing MH crisis (26)

Treatment	
Immediately	• Stop all trigger agents. • Hyperventilate (use a minute volume 2 – 3 times normal) with 100% O_2 high flow. • Declare an emergency and call for help. • Change to non-trigger anaesthesia. • Disconnect the vaporizer, do not waste time changing the circuit/anaesthetic machine. • Inform the surgeon and ask for termination/postponement of surgery.
Dantrolene	• Give dantrolene 2 mg/kg via an intravenous line (ampoules of 20 mg are mixed with 60 ml sterile water).

Treatment	
	• Obtain dantrolene from other sources, for example, pharmacy/nearby hospitals. At least 36 — 50 ampoules may be needed for an adult patient. • Dantrolene infusions should be repeated until the cardiac and respiratory systems stabilize. • The maximum dose (10 mg/kg) may need to be exceeded.
Monitoring	• Continue routine anaesthetic monitoring (pulse oximetry, electrocardiogram, non-invasive blood pressure, $ETCO_2$). • Measure core temperature. • Establish good intravenous lines with wide-bore cannulas. • Consider inserting an arterial line, central venous line and a urinary catheter. • Obtain samples for measurement of K^+, creatine kinase, arterial blood gases, myoglobin and glucose. • Check renal and hepatic function and coagulation. • Check for signs of compartment syndrome. • Monitor the patient for a minimum of 24 hour (intensive care/high dependency unit or in a recovery unit).
Symptomatic treatment	
Treat hyperthermia	• 2000 – 3000 ml of chilled (4°C) 0.9% saline intravenously. • Surface cooling: wet, cold sheets, fans and ice packs placed in the axillae and groin. • Other cooling devices if available. • Stop cooling once temperature <38.5°C
Treat hyperkalaemia	• Dextrose: 50%, 50 ml with 50 IU insulin (adult dose). • Calcium chloride: 0.1 mmol/kg intravenously. • Dialysis may be required.
Treat acidosis	• Hyperventilate to normocapnoea. • Give sodium bicarbonate intravenously if pH < 7.2.
Treat arrhythmias	• Amiodarone: 300 mg for an adult (3 mg/kg intravenously). • Beta-blockers (e.g. propranolol/metoprolol/esmolol) if tachycardia persists.

Treatment	
Maintain urinary output >2 ml/ kg / h	• Furosemide 0.5 – 1 mg/ kg. • Mannitol 1 g/ kg. • Fluids: crystalloids (e.g. lactated Ringer's solution or 0.9% saline) intravenously.
Consult your local Malignant Hyperthermia Investigation Unit about the case	

1.12 Studies assessing health care professionals' knowledge of MH

A study aimed at measuring the level of information among Brazilian anaesthesiologists regarding MH was performed in 2003 (31). Over 6000 members of the Brazilian Society of Anaesthesiology were mailed a questionnaire consisting of 20 questions on MH diagnosis, prevention and treatment. Approximately ten percent of the questionnaires were returned. Over 90% of correct answers about clinical diagnosis and treatment were obtained however, almost 50% of anaesthesiologists gave incorrect answers about pharmacology of dantrolene and indications for muscle biopsy (31).

In 2013, a study was performed to determine the knowledge of nursing professionals in a surgical centre in São Paulo (32). The evaluation instrument used consisted of 10 theoretical questions with five possible answers for each question and only one of these alternatives was correct. Regarding definition, triggering and professionals involved, the nurses got 80% of the answers correct. However, in the category of diagnosis and treatment, the scores were 14.3% and 47.2% respectively. The results revealed the nursing team had insufficient knowledge of MH (32). A follow-up study was then performed after an educational intervention. This was in the form of a 20-minute lecture with a PowerPoint presentation. Following this, participants were invited to take part in a simulation of a MH crisis (33). One week after the educational intervention the questionnaire was re-administered. Effectiveness of the intervention was demonstrated by a statistically significant improvement in knowledge (33).

A survey was performed among Dutch anaesthesia personnel to assess level of knowledge of MH in 2014 (34). This consisted of an online survey which entailed

12 questions. The first three questions determined the responder's profession, hospital of employment and if the participant had encountered MH in their clinical practice. The remaining nine questions assessed knowledge on incidence, triggers, symptoms, prevention, early recognition and treatment. Approximately half the responders did have previous experience with MH in practice and this group had a significantly higher knowledge score. Anaesthesiologists and registrars had better knowledge than trainee nurse anaesthetists. Unfortunately, even the highest average knowledge score was lacking with 4.68 scored out of a maximum of 12 (34).

1.13 Summary

It is clear from the studies mentioned that there is a lack of knowledge among health care professionals regarding MH. There are possibly multiple reasons for this including the rarity of the condition. What is shown in the literature is the importance of early diagnosis and urgent management. The life-threatening nature of a MH crisis warrants an in-depth understanding of the condition.

A discussion of MH has been presented in the literature review. Importantly, although MH is uncommon, it can be fatal if not recognised early and treated promptly. The diagnosis of MH has implications for the patient and their family members. Currently, South Africa has the only MH diagnostic laboratory in Africa. This will enable the practise of preventative medicine and ultimately improve patient outcome.

1.14 Permission to use guidelines

From: Thierry Girard <thierry.girard@unibas.ch>
Date: 10 November 2016 at 15:54:13 SAST
To: "farrahgermanus@gmail.com" <farrahgermanus@gmail.com>
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Thank you for your message. As these guidelines have been published you are fine to use them as long as you do reference them properly.

Best regards
Thierry Girard

On 10 November 2016 at 14:06:21, no-reply@emhg.org (no-reply@emhg.org) wrote:

> NAME: Dr Farrah Rimmington
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> I am currently specialising in Anaesthesiology at Wits university, South Africa. May I please have permission to use the EMHG guidelines on recognising and managing a malignant hyperthermia crises in my research project. I will of course reference the guidelines.

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The following are sample references:

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Section 3: Draft article

Current knowledge of malignant hyperthermia in a department of anaesthesiology

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Key words: malignant hyperthermia triggers crisis knowledge

Abstract

Background

Malignant hyperthermia (MH) is an inherited, pharmacogenetic disorder of skeletal muscle, which leads to a potentially fatal hypermetabolic state in response to certain triggering agents. These include most volatile anaesthetic agents and the depolarising muscle relaxant succinylcholine. These drugs are used daily in the Department of Anaesthesiology at the University of the Witwatersrand (Wits). The knowledge of MH in the department at Wits University is currently not known. Studies performed in other countries generally show inadequate knowledge of MH among theatre personnel.

Methods

A prospective, contextual, descriptive research design was used in this study. A knowledge-based questionnaire was completed by Wits anaesthetists. Permission to utilise a questionnaire obtained from a Dutch study was granted.This questionnaire was adapted for content and context with the help of South African MH expert Dr JC Brand.

Results

Percentages scored for the four subscales were: risk factors (58.3%), triggers (94.9%), diagnosis (75.2%) and treatment (42.4%). The overall mean (SD) score was 59.2% (12.6%). The mean (SD) score for juniors was 53.0% (13.4%) and for seniors 62.2% (11.1%). This difference was statistically significant (p=0.0001). Only 6 (4.4%) of participants achieved the pass mark of 80% or more, all of whom were seniors.

Conclusion

This study showed an inadequate level of knowledge of MH among anaesthetists in the department. These results are in keeping with those found in studies performed in other countries.

Introduction

During an emergency in theatre the anaesthetist's knowledge and clinical acumen become paramount. The patient's outcome will be influenced by what the anaesthetist does or fails to do. A malignant hyperthermia (MH) crisis will create such an emergency. MH is a pharmacogenetic disorder of skeletal muscle which results in a hypermetabolic state in response to certain triggering agents (1, 2). With the exception of nitrous oxide and xenon, all the volatile agents as well as the depolarising muscle relaxant succinylcholine, are considered triggers (1).

The pathophysiological changes are a result of uncontrolled calcium release in the myocyte (2, 3). Eventually adenosine triphosphate will be depleted, and this will lead to a compromise in cell membrane integrity (2). Substances such as potassium and myoglobin will leak out and be detected in the circulation (4, 5). Ultimately there is an abnormality in the excitation-contraction coupling on a molecular level (6). Most commonly a mutation in the ryanodine receptor is implicated (2). MH susceptibility is complicated by genetic heterogeneity and incomplete penetrance (3). This means a previous uneventful anaesthetic cannot exclude MH susceptibility (3). The diagnosis is further complicated as it is a subclinical myopathy and individuals are asymptomatic in daily life (7).

MH is not specific to humans and has been known to occur in pigs, dogs and horses (4, 8). The porcine genetic model has added significant value to the understanding and treatment of MH (9). It was discovered that pigs that were inbred in order to enhance growth and muscling suffered from porcine stress syndrome. When exposed to MH triggering agents, MH could be induced in these pigs. Dantrolene was initially used to treat porcine MH prior to its use in humans (10). South African, Professor Harrison, discovered the benefits of dantrolene during experiments on MH-susceptible swine (11).

MH occurs globally in all races (3) and ethnic groups (8) with a male preponderance. The male: female ratio is 2:1 (8). As MH is inherited mostly in an autosomal dominant fashion the prevalence varies from 1:3000 – 1:8500 (2). Therefore, implications exist for the patient's family members too. Due to the introduction of dantrolene and better intra-operative monitoring techniques the

mortality rate of an acute MH crisis has decreased significantly from 70 – 80% to approximately 5% (12). However despite the reduction in mortality, Larach et al. (13) found a significant morbidity rate of 34.8%.

Once an individual has had a potential MH crisis or if there is a positive family history then testing can be performed. The gold standard for diagnosis is a muscle contracture test (8, 14). Due to the cost and invasiveness of the test it is not recommended for screening of the general population (3). There is no pathognomonic sign or symptom of MH and the clinical picture can be variable (4). The differential diagnoses are extensive and some examples include: iatrogenic causes such as overheating, infection and sepsis, endocrine abnormalities and drug induced causes (4, 12).

The clinical features are usually grouped as early or late (15). The most common and often the earliest sign is inappropriately elevated carbon dioxide (CO_2) production which manifests as a raised end-tidal CO_2 (3). Historically the hallmark feature of MH was a rapidly rising core temperature hence the name of the condition. However, it is generally accepted that an elevation in temperature is now considered a late sign (3).

Larach et al. (16) developed a clinical grading scale to overcome the difficulty in diagnosis of an MH episode and in determining susceptibility to MH. This scale provides a means of estimating the likelihood of MH without the use of specialised diagnostic tests.

During a MH crisis emergency treatment must be implemented promptly (15). The prognosis depends on how quickly MH is suspected and how rapidly appropriate treatment is started (15). The European Malignant Hyperthermia Group has developed guidelines for the management of a suspected MH crisis (17). Initially it is vital to stop all trigger agents, hyperventilate the patient with 100% oxygen and call for help. Dantrolene is the only specific drug used for the treatment of MH (3, 18). An initial bolus dose of 2.5 mg/kg is given, however dantrolene must be continued for 24 hours to prevent recurrence of symptoms (1). During the acute MH episode routine anaesthetic monitoring, including core temperature measurement must be continued. The placement of invasive lines such as an

arterial line and central line should be considered. Simultaneously treatment of the acidosis, hyperkalaemia, arrhythmias and hyperthermia must be implemented (17). Once recovered, the patient and family require referral for MH testing (14).

Despite the infrequency of this condition it is important for anaesthetists to have a good knowledge of MH because of the high morbidity and mortality if misdiagnosed. The aim of this study is to describe the current knowledge of anaesthetists regarding MH in the Department of Anaesthesiology at the University of the Witwatersrand (Wits).

Methods

Approval to conduct the study was obtained from the Wits Human Research Ethics (Medical) Committee and other relevant authorities. A prospective, contextual, descriptive research design will be followed in this study. The study population will consist of anaesthetists working in the Department of Anaesthesiology at Wits. A convenience sampling method will be used, and the sample size will be determined by the response rate. A minimum of 60% (125) of anaesthetists in the department will be considered an acceptable sample size (19, 20). Exclusion criteria include interns and anaesthetists who decline participation. In this study, a junior anaesthetist refers to medical officers and registrars with three years or less of training, while a senior anaesthetist refers to medical officers and registrars with more than three years of training and consultants.

Following a literature review, a questionnaire by Wolvetang et al. (21) was deemed appropriate for the study. Consent to use and adapt the questionnaire was obtained from the corresponding author. The questionnaire was adapted for content and context. The adapted questionnaire was reviewed by the Director of the Malignant Hyperthermia Centre of South Africa and the necessary corrections were incorporated, thereby ensuring content and face validity. The questions are multiple choice with a single best answer format. The questionnaire consists of two sections namely a demographic and a knowledge section. The knowledge section consists of 16 questions regarding: triggers, risk factors, diagnosis and management. MH is an immediate life-threatening condition that equates to a

resuscitation situation. In this study 80% will be regarded as adequate knowledge, in keeping with other resuscitation guidelines.

Data will be collected at multiple departmental academic meetings. The study will be explained, the anaesthetists will be invited to take part and those who agree will receive an information letter and a questionnaire. One author (FR), will be present during completion of the questionnaires to assist with any queries and to prevent data contamination. Each anaesthetist who receives a questionnaire, regardless of whether it is filled in or not, will be requested to fold the questionnaire in half and place it into a sealed box.

Data will be captured onto a Microsoft Excel spreadsheet and analysed using descriptive and inferential statistics. The program Stata® version 13.1 will be used with the assistance of a biostatistician. Categorical variables will be described using frequencies and percentages. Numerical variables will be described using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. The comparison will be made using an independent t-test if the data is normally distributed, otherwise a Mann-Whitney test. A p-value of <0.05 will be considered statistically significant.

Results

Sample realisation

Of the 150 questionnaires handed out, 145 (96.7%) were returned. Of those returned, 9 questionnaires were completely blank and therefore excluded. The remaining 136 (91.0%) questionnaires were included and represents 65.4% of anaesthetists in the department.

The demographics of participants is shown in Table I. There were 44 (32.4%) junior and 92 (67,6%) senior participants.

Table I: Demographics of participants

Demographic	Number	Percentage
Professional designation:		
Medical officers	19	14.0
Registrar (1 – 3 years)	40	29.4
Registrars (>3 years)	27	19.9
Career Medical Officer	4	2.9
Consultants	46	33.8
Years of anaesthetic experience:		
< 1 year	9	6.6
1 – 3 years	35	25.7
4 – 6 years	49	36.0
7 – 10 years	24	17.6
> 10 years	19	13.8

The overall mean (SD) score achieved for the questionnaire was 59.2% (12.6%). The mean (SD) score for junior participants was 53.0% (13.4%) and for senior participants 62.2% (11.1%). This difference was statistically significant (p=0.0001).

The percentages (SD) scored per subsection of the questionnaire and among junior participants and senior participants is shown in Table II.

Table II: Percentages scored per subsection

Subscales	All participants mean % (SD)	Junior participants mean % (SD)	Senior participants mean % (SD)
Overall score	59.2 (12.6)	53.0 (13.4)	62.2 (11.1)
Risk Factors	58.3 (30.9)	43.2 (29.8)	58.3 (30.2)
Triggers	94.9 (17.5)	89.8 (25.2)	97.3 (11.3)
Diagnosis	75.2 (22.0)	66.5 (23.8)	79.4 (19.7)
Treatment	42.4 (17.6)	39.0 (16.8)	44.1 (17.7)

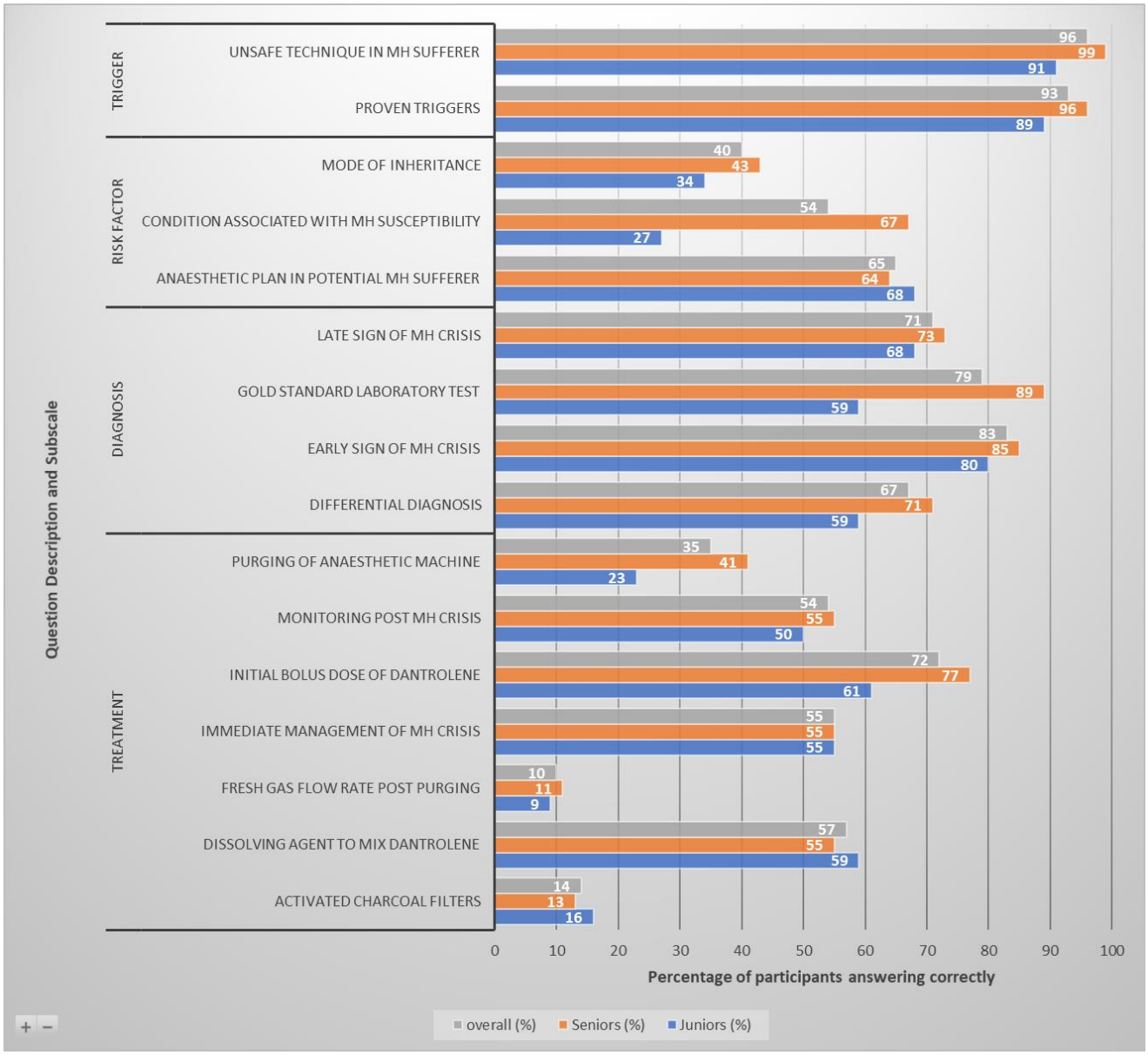
The number and percent of overall participants as well as junior participants and senior participants who passed the questionnaire with ≥ 80% overall and per subscale is shown in Table III.

Table III: Percentage of participants who passed per subsection

Subscale	Passed		
	All participants n (%)	Junior participants n (%)	Senior participants n (%)
Overall	6 (4.4)	0 (0)	6 (6.5)
Risk factors	26 (19.1)	4 (9.1)	22 (24.0)
Triggers	124 (91,2)	37 (84.1)	87 (94.6)
Diagnosis	45 (33.1)	9 (20.5)	36 (39.1)
Treatment	2 (1.5)	0 (0)	2 (2.2)

The correct answers per question overall and among junior participants and senior participants is shown in Table IV.

Table IV: Correct answers per question.



Discussion

Due to the potentially fatal nature of a MH crisis, rapid diagnosis and management is crucial for the patient's survival. This translates into a great responsibility placed on anaesthetists, as their knowledge and clinical acumen will ultimately determine the patient's outcome. Lack of this knowledge can equate to a fatal result. The anaesthetist can set in motion a sequence of deadly events as most cases occur in response to drugs given by the anaesthetist during a surgical procedure, and as

As MH is considered a rare condition there may be a lack of knowledge and clinical practice in treating it.

Participants in this study scored a mark of 59.2% for the questionnaire and only 4.4% of participants passed the entire questionnaire, all of whom were seniors. This is similar to the overall mark of 59.0% obtained by nurses in a study by Sousa and da Cunha (22) from a surgical centre in São Paulo. In a study by Wolvetang et al. (21) of Dutch anaesthesia personnel which included anaesthesiologists, residents, nurse anaesthetists and trainee nurse anaesthetists the overall mark obtained was 29.0%.

The senior participants in this study achieved an average of 62.2% and junior participants achieved 53.0%. In contrast Wolvetang et al. (21) showed an overall score for anaesthesiologists of 39.0% and for residents 35.0%. Both studies showed seniors to score higher than juniors which could be expected in view of greater experience and the teaching roles of senior participants.

Notably, Sousa et al. (23) performed a follow-up study after an educational intervention, which included a Microsoft PowerPoint presentation and a simulation scenario on MH. Questionnaires were administered in the pre-intervention phase and reapplied one week after the educational intervention. Results post-intervention demonstrated a statistically significant improvement in knowledge ($p< 0.00$) (23). Despite this improvement, decay of knowledge over time is likely to occur. The short duration of one week between the educational intervention and the reapplication of the questionnaire may not allow for an accurate presentation of long-term knowledge retention.

In this study 91.2% of participants passed the questions relating to triggers of MH. Of the Brazilian anaesthesiologists (24) 82.7% and 83.6% correctly answered the two questions relating to triggers while, 77.3% of the Dutch anaesthesiologists and 85% of the residents identified basic triggering medication correctly (21). Sousa and da Cunha (22) showed 64.6% of nurses knew the triggering agents.

The high marks achieved by Wits participants in the triggers' subscale may be accounted for by the recommended pharmacology textbook which has a section dedicated to MH that was written by South African MH expert, Dr JC Brand.

Regarding risk factors of MH, only 19.1% of participants in this study correctly identified all the risk factors. Brazilian anaesthesiologists in a study by Simões et al. (24) showed that 47.1% correctly identified King-Denborough myopathy as a risk factor while 54% of the Wits participants were aware of this. Notably the questions from these two studies were not identical but similar.

A score of 75.2% was achieved by participants in this study for the diagnosis subscale of MH. More than 80% of Wits participants knew the early signs of a MH crisis. Of the Brazilian nurses 30.2% of participants correctly identified the early clinical manifestations of MH (22). The Dutch study found that 68.2% of anaesthesiologists and 65.0% of residents correctly identified tachycardia as an early sign (21). Of the Brazilian anaesthesiologists 78.2% correctly identified early manifestations of MH (24). Late signs of a MH crisis were known by over 70% of Wits participants, 40.9% of Dutch anaesthesiologists and 50.0% of Dutch residents (21).

Participants in this study scored 42.4% overall for questions relating to the treatment subscale of MH. The dose of dantrolene was asked in all the studies except the nursing study. The correct dose was known by over 70% of the Wits participants and more than 90% of the Brazilian anaesthesiologists (24). Wolvetang et al. (21) found that more residents (55.0%) than anaesthesiologists (45.5%) were aware of the correct dose of dantrolene.

The reason for good knowledge among the Brazilian doctors regarding diagnosis and treatment of MH could be accounted for by multiple reasons. Since the early 1990s there was an effort to spread information about MH in Brazil (24). The development of malignant hyperthermia diagnostic centres at the universities of Rio de Janeiro and São Paulo as well as the creation of a 24-hour, MH hotline service in Brazil in 1991 was likely to assist in improvement of knowledge.

The low marks scored in the treatment subscale by participants in this study may be accounted for by the lack of clinical experience due to the rarity of MH. Wolvetang et al. (21) noted that participants who had previous experience with MH scored significantly higher than those without this experience.

The results of this study must be read against the background of certain

limitations. Since the study was carried out contextually in the Department of Anaesthesiology at Wits, the results may not be generalisable to other anaesthetic departments.

This study did not assess if prior experience to a MH episode lead to an improvement in knowledge which could be viewed as a limitation.

There is a risk of data contamination in this study as the questionnaire was used at different academic meetings over time. This would influence the study results as it allows participants to read about MH in preparation of completing the questionnaire. However, as no participants subsequently performed better it is assumed that data contamination did not occur. Convenience sampling was used to collect the data, and this may not adequately reflect the knowledge of the department but only the knowledge of those present who chose to complete the questionnaire. It is recommended that an ongoing educational initiative be implemented in the form of a program that targets health care professionals in the theatre environment, including nurses in the recovery room.

Conclusion

Without continued education and improvement in knowledge, MH will remain as life- threatening as it was many years ago.

Due to the rarity of this condition, clinical exposure will be limited and decay of knowledge over time must be taken into account. It is therefore prudent to provide educational interventions regularly. Information dissemination can be in the form of lectures, presentations, in-service training, workshops and simulation scenarios. South African doctors must be made aware of the accessibility of information in the form of the MH hotline service (+27 83 285 4486) and the Malignant Hyperthermia Centre of South Africa (MHCSA) (mh-info@lantic.net).

Conflict of interest

The author declares that I had no financial or personal relationships which may have inappropriately influenced me in writing this paper.

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Section 4: Proposal

Current knowledge of malignant hyperthermia in a department of anaesthesiology

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4.1 Introduction

During an emergency in theatre the anaesthetist's knowledge and clinical acumen become paramount. The patient's outcome will be influenced by what the anaesthetist does or fails to do. A malignant hyperthermia (MH) crisis will create such an emergency. MH is a pharmacogenetic disorder of skeletal muscle which results in a hypermetabolic state in response to certain triggering agents (1-3). With the exception of nitrous oxide and xenon, all of the volatile agents as well as the depolarising muscle relaxant succinylcholine, are considered triggers (1).

The pathophysiological changes are a result of uncontrolled calcium release in the myocyte (2, 3). Eventually adenosine triphosphate will be depleted, and this will lead to a compromise in cell membrane integrity. Substances such as potassium and myoglobin will leak out and be detected in the circulation (2). Ultimately there is an abnormality in the excitation-contraction coupling at a molecular level (4, 5). Most commonly a mutation in the ryanodine receptor is implicated (4). MH susceptibility is complicated by genetic heterogeneity and incomplete penetrance (4). This means a previous uneventful anaesthetic cannot exclude MH susceptibility. The diagnosis is further complicated as it is a subclinical myopathy and individuals are asymptomatic in daily life (6).

MH is not specific to humans and has been known to occur in pigs, dogs and horses (2, 7). The porcine genetic model has added significant value to the understanding and treatment of MH (7). It was discovered that pigs that were inbred in order to enhance growth and muscling suffered from porcine stress syndrome. When exposed to MH triggering agents, MH could be induced in these pigs. Dantrolene was initially used to treat porcine MH prior to its use in humans (7).

MH occurs globally in all races and ethnic groups with a male preponderance (8). The male: female ratio is 2:1 (1). As MH is inherited mostly in an autosomal dominant fashion the prevalence varies from 1:3000 – 1:8500 (2). Therefore, implications exist for the patient's family members too. Due to the introduction of dantrolene and better intra-operative monitoring techniques the mortality rate of an acute MH crisis has decreased significantly from 70 – 80% to approximately 5%

(9). However despite the reduction in mortality, Larach et al. (8) found a significant morbidity rate of 34.8%.

Once an individual has had a potential MH crisis or if there is a positive family history then testing can be performed. The gold standard for diagnosis is a muscle contracture test (9, 10). Due to the cost and invasiveness of the test it is not recommended for screening of the general population (3). A surgical muscle biopsy is performed and then the live muscle specimen is exposed to caffeine and halothane. If the contracture forces exceed certain thresholds then a diagnosis of MH susceptibility is made (9). There is no pathognomonic sign or symptom of MH and the clinical picture can be variable. The differential diagnoses are extensive (2) and some examples include: iatrogenic causes such as overheating, infection and sepsis, endocrine abnormalities and drug induced causes (11-13).

The clinical features are usually grouped as early or late (14). The most common and often the earliest sign is inappropriately elevated carbon dioxide (CO_2) production which manifests as a raised end-tidal CO_2 (9). Larach et al. (8) examined the presentation of 255 cases of MH and reported the first or only MH clinical sign noted was hypercarbia (38.0%), sinus tachycardia (31.0%) or masseter spasm (20.8%) (8). Historically the hallmark feature of MH was a rapidly rising core temperature hence the name of the condition. However it is generally accepted that an elevation in temperature is now considered a late sign (11).

Larach et al. (15) developed a clinical grading scale to overcome the difficulty in diagnosis of an MH episode and in determining susceptibility to MH. This scale provides a means of estimating the likelihood of MH without the use of specialised diagnostic tests (9).

During a MH crisis, emergency treatment must be implemented promptly (16). The prognosis depends on how quickly MH is suspected and how rapidly appropriate treatment is started (10). The European Malignant Hyperthermia Group has developed guidelines for the management of a suspected MH crisis (11). Initially it is vital to stop all trigger agents, hyperventilate the patient with 100% oxygen and call for help. Dantrolene is the only agent currently available in South Africa for the specific treatment of MH (17). An initial bolus dose of 2.5 mg/kg is given, however

dantrolene must be continued for 24 hours to prevent recurrence of symptoms (11). During the acute MH episode routine anaesthetic monitoring, including core temperature measurement must be continued. The placement of invasive lines such as an arterial line and central line should be considered. Simultaneously treatment of the acidosis, hyperkalaemia, arrhythmias and hyperthermia must also be implemented (2, 11). Once recovered, the patient and family require referral for MH testing (2, 11).

Due to the infrequent nature of MH there is limited exposure of anaesthetists to the condition. It is possible that a gap in knowledge exists because of this lack of experience. Wolvetang et al. (18) performed a survey to assess knowledge on MH and found the results to be disappointing. A similar study was conducted to assess knowledge of nursing professionals in a surgical centre in São Paulo. This study also revealed insufficient knowledge about MH (19).

4.2 Problem statement

MH is a pharmacogenetic disorder of skeletal muscle that leads to a hypermetabolic state (9). It has the potential to be life-threatening if not recognised early and treated promptly. The mortality rate has decreased over time from 70 – 80% down to 5% due to the use of dantrolene but the morbidity rate according to a recent study is 34.8% (8).

Despite the infrequency of this condition it is important for anaesthetists to have a good knowledge of MH because of the high morbidity and mortality if misdiagnosed. The agents responsible for triggering an MH crisis include most of the volatile anaesthetic drugs and the muscle relaxant, succinylcholine. These drugs are used on a daily basis in the Department of Anaesthesiology at the University of the Witwatersrand (Wits). The knowledge of MH in the department at Wits University is currently not known.

4.3 Aim and objectives

4.3.1 Aim

The aim of this study is to describe the current knowledge of anaesthetists regarding MH in the Department of Anaesthesiology at Wits.

4.3.2 Objectives

The primary objectives of this study are to:

- describe the current knowledge of MH among anaesthetists regarding triggers and risk factors; and
- describe the current knowledge of MH among anaesthetists regarding diagnosis and treatment.

The secondary objective of this study is to compare the current knowledge of MH between junior and senior anaesthetists.

4.4 Research assumptions

The following definitions will be used in this study.

Anaesthetist: is a qualified doctor working in the Department of Anaesthesiology including medical officers, registrars and consultants.

Medical officer: is a qualified doctor practising in the Department of Anaesthesiology under specialist supervision. Medical officers with more than 10 years of anaesthetic experience are career medical officers and are regarded as consultants.

Registrar: is a qualified doctor who is registered with the Health Professionals Council of South Africa as a trainee anaesthetist.

Anaesthesiologist: an anaesthetist who has completed the required South African Colleges of Medicine examinations, or equivalent, and all other criteria to become a specialist in anaesthesiology.

Consultant: an anaesthesiologist or career medical officer.

Junior anaesthetist: in this study refers to medical officers and registrars with three years or less of training.

Senior anaesthetist: in this study refers to medical officers and registrars with more than three years of training and consultants.

Adequate knowledge: MH is an immediate life-threatening condition that equates to a resuscitation situation. In this study 80% will be regarded as adequate knowledge, this is in keeping with other resuscitation guidelines.

4.5 Demarcation of study field

The study will be conducted in the Department of Anaesthesiology, affiliated to the Faculty of Health Sciences at Wits. The staff complement of the department is 74 consultants, 112 registrars and 22 medical officers. The following hospitals are affiliated to the department:

- Charlotte Maxeke Johannesburg Academic Hospital, a 1200-bed central hospital
- Chris Hani Baragwanath Academic Hospital, a 2880-bed central hospital
- Helen Joseph Hospital, a 500-bed tertiary hospital
- Rahima Moosa Mother and Child Hospital, a 338-bed regional hospital
- Wits Donald Gordon Medical Centre, a 190-bed public/private hospital.

4.6 Ethical considerations

Approval to conduct the study will be obtained from the Human Research Ethics Committee (Medical) and the Graduates Studies Committee at Wits.

The researcher will explain the study and invite anaesthetists to participate, those who are interested will receive an information letter (Appendix 1) and a self-administered questionnaire (Appendix 2). Consent is implied on completion and return of the questionnaire. Every effort will be taken to ensure confidentiality and

anonymity. Questionnaires will be numbered for data collection purposes only and will not require identifying information. Completed questionnaires will be folded in half and placed into a sealed box. Confidentiality will be ensured as only the researcher and supervisors will have access to the raw data.

If the results of the study demonstrate that anaesthetists have inadequate knowledge of MH, the researcher will report this to the Head of the Department of Anaesthesiology. Further, a workshop for the department facilitated by the Director of the South African Malignant Hyperthermia Centre will be organised.

The raw data will be stored for six years after the completion of the study in a locked cupboard. The study will be conducted in accordance with the Declaration of Helsinki (20) and the South African Guidelines for Good Clinical Practice (21).

4.7 Research methodology

4.7.1 Research design

A prospective, contextual, descriptive research design will be followed in this study.

A prospective design measures variables that will occur during the course of the study (22). The questionnaire will be completed by the participants at the time the study takes place.

According to Burns and Grove (23) a descriptive design is one that is used to identify a phenomenon of interest, identify variables within the phenomenon, develop conceptual definitions of variables, and describe variables. The level of knowledge will be the phenomenon of interest in this study.

A contextual study is one which refers to a specific group or population (24). In this study it refers to the group of doctors working in the Department of Anaesthesiology at Wits.

4.7.2 Study population

The study population will consist of anaesthetists working in the Department of Anaesthesiology at Wits.

4.7.3 Study sample

Sample size

The sample size will be determined by the response rate. A minimum of 60% (125) of anaesthetists in the department will be considered an acceptable sample size (25, 26).

Sampling method

In this study a convenience sampling method will be used. This is a non-probability sampling technique and is also known as “availability sampling” (22). It involves the selection of the most readily available subjects or objects for a study because “they happen to be in the right place at the right time” (22). In this study anaesthetists present at departmental academic meetings will be invited to take part in the study.

4.7.4 Inclusion and exclusion criteria

The inclusion criterion in this study is all anaesthetists present at departmental academic meetings at the time of data collection.

Exclusion criteria include interns and anaesthetists who decline participation.

4.7.5 Data collection

Questionnaire development

Following a review of the literature, a questionnaire by Wolvetang et al. (18) was deemed appropriate for the study. Consent to use and adapt the questionnaire was obtained from the corresponding author (Appendix 3). The questionnaire was adapted by the researcher for content and context. The adapted questionnaire was reviewed by the Director of the South African Malignant Hyperthermia Centre and the necessary corrections were incorporated, thereby ensuring content and face validity. The questions are multiple choice with a single best answer format.

The questionnaire (Appendix 2) consists of two sections namely a demographic and a knowledge section. The demographic section requests the following information:

- professional designation
- years of experience in anaesthesia.

The knowledge section consists of 16 questions regarding:

- triggers
- risk factors
- diagnosis
- management.

Data collection

Data will be collected at multiple departmental academic meetings. This will include combined as well as individual hospital's academic meetings in order to increase the opportunity for all anaesthetists in the department to participate. The researcher will approach the chairperson at the meetings for permission to address the anaesthetists. The study will be explained, and the anaesthetists will be invited to take part and those who agree will receive an information letter (Appendix 1) and a questionnaire (Appendix 2). The researcher will be present during completion of the questionnaires to assist with any queries and to prevent data contamination. Each anaesthetist who receives a questionnaire, regardless of whether it is filled in or not, will be requested to fold the questionnaire in half and place it into a sealed box. This will ensure that the researcher is appropriately blinded regarding participation.

4.7.6 Data analysis

Data will be captured onto a Microsoft Excel spreadsheet and analysed using descriptive and inferential statistics. The program Stata® 1.3 (Statsoft, USA) will be used. Categorical variables will be described using frequencies and

percentages. Numerical variables will be described using means and standard deviations or medians and interquartile ranges depending on the distribution of the data. The comparison will be made using an independent t-test if the data is normally distributed, otherwise a Mann-Whitney test. A p-value of <0.05 will be considered statistically significant.

4.8 Significance of the study

MH is a rare but potentially fatal condition. The outcome of a MH crisis is improved with prompt diagnosis and treatment (2). Failure to recognise and hence implement correct treatment can result in the death of a patient. Larach et al (8) showed that even if a patient survived a MH crisis, the morbidity was still high (34.8%).

Studies worldwide have demonstrated that anaesthetic staff lack knowledge on MH (18, 19). The results from this study will describe the anaesthetists' knowledge regarding MH. If the results reveal that anaesthetists have inadequate knowledge, a workshop facilitated by the Director of the South African Malignant Hyperthermia Centre will be organised to improve their knowledge, and therefore ensure that patients with MH receive quality care.

4.9 Validity and reliability of the study

According to Botma et al (27) validity of a study refers "to the degree to which a measurement represents a true value" and reliability "represents the consistency of the measure achieved." The validity and reliability of this study will be ensured by the following measures:

- the use of an appropriate study design
- the use of a previously published questionnaire that was adapted for content and context with the assistance of a MH expert
- the researcher will be present during completion of the questionnaire to assist with queries and to prevent data contamination
- quality checks will be performed when data is entered on the spreadsheet

- the statistical analysis will be done in consultation with a biostatistician.

4.10 Potential limitations

This study will be carried out contextually in the Department of Anaesthesiology. Therefore, the results may not be generalisable to other anaesthetic departments. It does however provide useful information regarding knowledge of a serious condition in the Department of Anaesthesiology at Wits.

Convenience sampling will be used to collect the data in this study. This may not adequately reflect the knowledge of the department but only the knowledge of those present at the time of data collection, who choose to complete the questionnaire.

Sample size will be determined by the number of anaesthetists attending departmental academic meetings and their willingness to complete the questionnaire. The sample size may be too small to adequately power the comparison being made in the secondary objective.

4.11 Project outline

4.11.1 Time frame

Activity	Oct 2016	Nov 2016	Jan 2017	Mar 2017	Apr 2017	May 2017	Jul 2017	Aug 2017	Sep 2017
Proposal preparation									
Literature review									
Proposal submission									
Ethics approval									
Postgraduate approval									
Data collection									
Data analysis									
Draft article									
Submission									

4.11.2 Budget

Item	Price per page	Number of pages	Copies	Total
Proposal	1	15	10	R 150
Ethics	1	10	25	R 250
Post graduate form	1	2	6	R 12
Complete report	1	100	4	R 400
Grand total				**R 812**

The Wits Department of Anaesthesiology will incur the costs of paper and printing.

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Section 5: Appendices

Appendix 1: Participants' information sheet

Dear Colleague,

Hello, my name is Farrah Rimmington and I am currently a registrar in anaesthesiology, studying for my Master of Medicine degree at the University of the Witwatersrand. I would like to invite you to participate in my study: The current level of knowledge of malignant hyperthermia in the department of anaesthesiology.

Should you agree to participate in this study, you will be asked to complete a self-administered questionnaire. No personal incentive will be provided for completion of the questionnaire but hopefully this study will contribute to improved awareness and clinical management of this condition. Participation is voluntary, and consent is implied on completion of the questionnaire. It should take approximately 15 minutes to complete the questionnaire and you are required to complete it on your own without sharing information with colleagues. Please note that the questions will be in multiple choice single best answer format. If you choose not to participate there will be no negative personal consequences. All information will be confidential and anonymous. No identifying information will be required to complete the questionnaire. All questionnaires, completed or not, will be folded in half and then placed into a sealed box. Numbering of questionnaires is purely for data collection purposes. Only my supervisors and I will have access to the raw data. If knowledge is found to be lacking, then a lecture or workshop will be organised by the researcher.

This study has been approved by the Human Research Ethics (Medical) Committee and the Graduates Studies Committee at Wits University. Should you have any queries you are welcome to contact me on 079 873 1498 or the chairman of the Ethics Committee on 011 717 1234.Thank you for your time.

Sincerely,

Farrah Rimmington

Appendix 2: Questionnaire

Section 1: Demographic questions

Please tick the appropriate box.

Professional designation	Medical Officer	
	Registrar (1 – 3 years)	
	Registrar (>3 years)	
	Career Medical Officer	
	Consultant	
Years of experience in anaesthesia	<1 year	
	1 – 3 years	
	4 – 6 years	
	7 – 10 years	
	11 – 20 years	
	>20 years	

Section 2: Knowledge questions

Please tick the appropriate box.

Single best answer multiple choice questions.

A six-year-old child presents for an emergency operation. The child's biological mother explains to you that she herself had a definite malignant hyperthermia (MH) crisis as a child. Taking into consideration mode of inheritance only and excluding variability of penetrance and expressivity, what is the chance of this child having a MH crisis on exposure to a trigger?

A	0%	
B	25%	
C	50%	
D	75%	
E	100%	

During an acute MH episode, the signs and symptoms displayed may be difficult to differentiate from other emergencies. A condition that you will, most likely, **not** consider in the differential diagnosis is:

A	Thyroid storm	
B	Neuroleptic Malignant Syndrome	
C	Acute myocardial infarction	
D	Pheochromocytoma	
E	Bair Hugger on maximum	

A patient with a history of a previous MH crisis presents for an emergency appendectomy. Which one of the following is a proven trigger and the most likely culprit to trigger a crisis in this patient?

A	Rocuronium	
B	Sevoflurane	
C	Thiopentone	
D	Nitrous Oxide	
E	Ketamine	

A patient develops signs and symptoms intra- operatively suspicious of a MH crisis. He was treated appropriately and subsequently discharged a week later. The gold standard laboratory test you would send him for to confirm MH susceptibility is:

A	Serum creatine kinase	
B	In-vitro contracture test	
C	Serial urine myoglobin	
D	Serum potassium levels	
E	Mutation screening	

A most likely **early** sign of developing malignant hyperthermia is:

A	Hyperthermia	
B	Hypercapnoea	
C	Hypoxia	
D	Hypertension	
E	Dysrhythmias	

Following an undiagnosed MH crisis, the patient demises three hours later in the intensive care unit (ICU). The most likely cause of death is:

A	Renal failure due to myoglobinuria	
B	Hypoxia due to pulmonary oedema	
C	Disseminated intravascular coagulopathy	
D	Dysrhythmias due to hyperkalaemia	
E	Brain oedema due to hypercapnia	

A 25-year-old ASA1 male patient presents for an open reduction and internal fixation of his humerus fracture following a fall from height. A few minutes after induction he appears to have a MH crisis. During the immediate management, the action that is most likely **not** necessary is:

A	Changing to a TIVA technique	
B	Closing the vapouriser	
C	Hyperventilating with 100% O2	
D	Calling for available assistance	
E	Changing the anaesthetic machine	

In keeping with the above scenario (Question 9), you decide to give the patient dantrolene as it's the only currently available drug in South Africa used for definitive treatment of a MH crisis. The initial bolus dose of this drug is:

A	1 – 1.5 mg/kg	
B	2 – 2.5 mg/kg	
C	3 – 3.5 mg/kg	
D	5 – 5.5 mg/kg	
E	10 – 10.5 mg/kg	

Dantrolene requires mixing as it is manufactured in a powder form. The dissolving agent to be used is:

A	Ringers lactate	
B	Normal saline 0.9%	
C	Sterile water	
D	5% dextrose water	
E	Sodium bicarbonate 8.4%	

The patient is transferred to ICU following the initial MH episode in theatre. It is recommended that the patient is monitored in a high dependency area for recurrence of symptoms for at least:

A	6 hrs	
B	12 hrs	
C	24 hrs	
D	36 hrs	
E	48 hrs	

A 24-year-old proven MH susceptible patient is booked for an emergency caesarean section for foetal distress. An **unsafe** anaesthetic technique is a:

A	Spinal using heavy bupivacaine and fentanyl	
B	TIVA with succinylcholine	
C	Epidural using bupivacaine	
D	TIVA with rocuronium	
E	Spinal block with bilateral TAP blocks	

A condition that is associated with MH susceptibility is:

A	Myotonic dystrophy	
B	Osteogenesis imperfecta	
C	King-Denborough myopathy	
D	Pierre Robin syndrome	
E	Duchenne muscular dystrophy	

A known MH susceptible patient requires surgery. The anaesthetic machine must be purged of anaesthetic vapour. Manufacturers have specific instructions on the duration of flushing for different machines. As a rule of thumb, when there is uncertainty on how to flush a specific anaesthetic machine, one should use high fresh gas flows of 10 litres/min for:

A	10 mins	
B	30 mins	
C	45 mins	
D	60 mins	
E	70 mins	

In keeping with the above scenario (Question 15), the anaesthetic machine has been flushed and the surgical procedure is underway. The advised management of the fresh gas flow (FGF) rate is that:

A	Immediately FGF can be reduced to <2 l/min	
B	After 10 mins FGF can be reduced to <2 l/min	
C	After 30 mins FGF can be reduced to <2 l/min	
D	After 60 mins FGF can be reduced to <2 l/min	
E	FGF must be kept at 10 l/min for entire procedure	

The following statements are regarding activated charcoal filters (ACF). The one false statement regarding ACF is that they:

A	Should be placed on the inspiratory limb of the circuit	
B	Should be placed after changing to a new circuit and fresh soda lime	
C	Need to be exchanged hourly in order to be effective	
D	Can be placed only once machine is flushed for 90 seconds	
E	Reduce the time required to prepare an anaesthetic machine for MH susceptible patients	

A nine-month-old boy presents for insertion of grommets on an elective list. During the history-taking the mom tells you that her biological brother (the boy's uncle) nearly died following a MH crisis during a tonsillectomy. The mother had an uneventful general anaesthetic previously for an appendectomy. The most appropriate anaesthetic plan is:

A	Inhalational induction and maintenance with sevoflurane, iv line, hold the mask	
B	Total intravenous anaesthesia using propofol and alfentanil	
C	Cancel the case and send the family for MH susceptibility testing	
D	Use ketamine sedation only	
E	Treat the child prophylactically with dantrolene	

Appendix 3: Permission to use questionnaire

Farrah Germanus <farrahgermanus@gmail.com>
Nov 15 (8 days ago)
to T.Wolvetang

Good Afternoon Mr Wolvetang,

My name is Dr Farrah Rimmington. I am currently specialising in Anaesthesiology at Wits University, South Africa. I am doing a research study on the level of knowledge of anaesthetists in my department regarding malignant hyperthermia. I thoroughly enjoyed reading about the survey you performed on the same topic. I am contacting you to kindly ask permission to use the questions which you used in your online questionnaire. My plan is to contextualise it to my department by adding some questions with the help of South African malignant hyperthermia expert, Dr J. Brand. If you grant me permission may I please have some information on your scoring system?

Your help would be greatly appreciated.

Yours Sincerely

Dr. Farrah Rimmington

T. Wolvetang
Nov 16 (7 days ago)
to me

Good morning Dr Farrah Rimmington,

Thank you very much for your email and interest in the MH-questionnaire. I looked up the questionnaire and the full article I wrote last year which fortunately contains all information about the scoring system, as I don't remember it exactly. If you like we can collaborate on this research study to create a better MH- questionnaire, as the one I used might be updated / adjusted to achieve a clearer picture on the knowledge level. Would you be interested in this full article?

Kind regards,

Timothy Wolvetang

Section 6: Annexures

6.1 Ethics approval

R14/49 Dr Farrah Rimmington et al

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170110

NAME: (Principal Investigator)	Dr Farrah Rimmington et al
DEPARTMENT:	Anaesthesiology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Knowledge of Malignant Hyperthermia in a Department of Anaesthesiology
DATE CONSIDERED:	27/01/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Juan Scribante
APPROVED BY:	Professor P. Cleaton-Jones Chairperson, HREC (Medical)
DATE OF APPROVAL:	17/07/2017

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 Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised 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 to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review January and will therefore be due in the month of January each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

6.2 Graduate studies approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Private Bag 3 Wits, 2050
Fax: 027117172119
Tel: 02711 7172076

Reference: Mrs Sandra Benn
E-mail: sandra.benn@wits.ac.za

12 June 2017
Person No: 9804798G
PAG

Dr FJ Rimmington
PO Box 238
Bergbron
1712
South Africa

Dear Dr Rimmington

Master of Medicine: Approval of Title

We have pleasure in advising that your proposal entitled *Current knowledge of malignant hyperthermia in a Department of Anaesthesiology* 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

Mrs Sandra Benn
Faculty Registrar
Faculty of Health Sciences

6.3 Turnitin Report

9804798g:Turnitin_2019-01-23.docx

by Farrah Rimmington

Submission date: 24-Jan-2019 09:44PM (UTC+0200)
Submission ID: 1068085985
File name: ts_609cebf4-71d9-483b-9640-8302937b64a7_Turnitin_2019-01-23.docx (428.57K)
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6.4 Turnitin Letter

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG | FACULTY OF HEALTH SCIENCES

24th January, 2019

The Chairperson
Graduate Studies Committee
Faculty of Health Sciences
University of the Witwatersrand

Dear Madam,

Re: M Med: **Current knowledge of malignant hyperthermia in a department of anaesthesiology**

Dr Farrah Rimmington, student number: 9804798G, has submitted her research report to Turnitin which revealed a similarity index of 15%. These similarities appear not to be plagiarism but mainly the use of common terminology and phrases specific to the topic of the research.

Yours sincerely,

Juan Scribante
Supervisor

1