LITERATURE REVIEW

Malignant Hyperthermia

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ABSTRACT
Malignant hyperthermia (MH) is a life-threatening clinical syndrome caused by hypermetabolism involving skeletal muscle. MH is very rare, but it is one of the causes of death in the operating room. MH is an autosomal dominant disease and can be triggered when exposed to certain anesthetic drugs. Genetic tests can help diagnose, but the gold standard is the caffeine halothane contracture test (CHCT). Initial symptoms are a decrease in pH and oxygen, as well as an increase in CO_2, lactate, potassium, and temperature. The increase in lactate reflects tissue hypoxia. Dantrolene is an antidote to MH, by reducing calcium loss from the sarcoplasmic reticulum in skeletal muscle and returning metabolism to normal conditions. Immediate detection and treatment can improve MH outcomes.

Keywords: anesthesia; autosomal dominant; dantrolene; hypermetabolism; malignant hyperthermia

INTRODUCTION

Malignant hyperthermia (MH) is a life-threatening clinical syndrome caused by hypermetabolism involving skeletal muscles. This condition is suspected to be triggered by volatile inhalation agents and muscle relaxants from the succinylcholine group. In humans suspected of having MH, the ryanodine receptor in skeletal muscles is abnormal, disrupting calcium regulation in the muscles. The abnormal ryanodine receptor, which regulates calcium release in the muscles, leads to calcium accumulation in the muscles. Consequently, a massive metabolic reaction occurs, resulting in increased carbon dioxide production, respiratory and metabolic acidosis, increased oxygen consumption, heat production, activation of the sympathetic nervous system, hyperkalemia, disseminated intravascular coagulation (DIC), and multi-organ dysfunction or failure.[1,2]

Anesthetic drugs do not always trigger MH. Individuals suspected of having MH may undergo anesthesia with MH-triggering agents without any issues. Genetic testing can assist in establishing a diagnosis; however, the gold standard remains the caffeine halothane contracture test (CHCT). Dantrolene serves as the antidote for MH by reducing calcium leakage from the sarcoplasmic reticulum in skeletal muscles and restoring metabolism to normal conditions. Prompt detection and management can improve the outcomes of MH.[1,3]

The reported incidence of MH in the United States ranges from 1 in 10,000 patients to 1 in 50,000 patients undergoing anesthesia, with a higher incidence in children. The North American Malignant Hyperthermia Registry reported, from 1987 to 2006, 8 cases involving cardiac arrest and 4 deaths, with the median age of patients experiencing cardiac arrest or death being 20 years.[2,3]

The incidence of MH in Indonesia is unknown due to the absence of a recording and reporting system. Various anecdotal case reports of suspected MH have been noted in Indonesia. Many of these cases were fatal, primarily due to the unavailability of dantrolene in the country.[3]

Given that MH is both extremely rare and life-threatening, all healthcare providers need to be trained in perioperative management to promptly identify and provide life-saving treatment for this condition.

Definition

Malignant hyperthermia (MH) is a hypermetabolic response to potent inhalation agents (such as halothane, sevoflurane, desflurane), depolarizing muscle relaxants like succinylcholine, and, rarely, in humans, to stress such as intense exercise and heat. The majority of patients with central core disease (CCD), a congenital myopathy characterized by muscle weakness, are susceptible to MH. Multi-minicore disease (MmCD) also predisposes individuals to MH episodes. The incidence of MH episodes during anesthesia ranges between 1:5,000 and 1:50,000–100,000 anesthetics. Genetically, MH is an autosomal dominant condition; the estimated prevalence of the genetic abnormality may reach one in 3,000 individuals (ranging from 1:3,000 to 1:8,500).[4]

The first occurrence of malignant hyperthermia (MH) was reported in 1960 when Denborough and Lovel described a cluster of intra-anesthetic clinical symptoms affecting a single family in Australia. Clinically, an increase in body temperature was identified as a characteristic marker.[2,3]

The estimated genetic prevalence is reported to be one in 2,000, while the incidence of clinical MH episodes varies regionally from one in 5,000 to one in 100,000. Unlike fulminant episodes, subclinical cases may occur more frequently but are difficult to diagnose due to their mild symptoms.[5]

Etiology and predisposing factors of malignant hyperthermia

Approximately 80% of MH cases are caused by the use of halogenated anesthetic agents and succinylcholine, either individually or in combination. Additionally, 50% of reported cases indicate a history of an MH episode triggered by suspected MH-inducing agents. Inhalation anesthetics like desflurane and sevoflurane are considered less potent MH triggers on their own, but this changes when combined with succinylcholine.[1,2,3]

The use of succinylcholine in humans demonstrates several responses, whether used alone or in combination. The first is muscle contracture, which may be accompanied by myotonic episodes or paralysis. The second is a change in muscle membrane permeability without contracture, leading to the release of creatine kinase and myoglobin. The third response is an increase in metabolism similar to that seen in MH, caused by muscle contractures and increased membrane permeability. The use of non-depolarizing muscle relaxants can prevent succinylcholine from triggering MH, and reversing non-depolarizing agents does not trigger MH either. Nitrous oxide (N_2O) is considered a weak MH trigger in humans.[1,2,3]

Epidemiological studies have reported cases of MH not triggered by anesthetic agents but rather by muscle activity during exercise. Intense muscle contractions can lead to rhabdomyolysis, which mimics the characteristics of MH.[2,6]

Table 1. Drugs known to trigger MH[10]

Halogenated General Anesthesia	Depolarizing Muscle Relaxants
Eter	
Siklopropan	
Halotan	
Enflurane	Suksinilkolin
Isoflurane	
Desflurane	
Sevoflurane	

Biomolecular research has revealed that the predisposition to MH is due to heterogeneous genetic abnormalities caused by mutations on one or more chromosomes. To date, the chromosomes identified as being associated with triggering MH are chromosomes 1, 3, 7, 17, and 19.[2,3,4]

Several musculoskeletal disorders are associated with a higher incidence of MH. These disorders include:[1,2] (1) definitively associated with MH: central core disease (CCD); (2) diseases highly likely to be associated with MH, characterized by systemic damage, include: duchenne muscular dystrophy, king-denborough syndrome, myopathy, becker muscular dystrophy, periodic paralysis, congenital myotonia, schwartz-jampel syndrome, fukuyama-type congenital muscular dystrophy, mitochondrial myopathy, sarcoplasmic reticulum adenosine triphosphate (ATP) deficiency.

Mechanism of malignant hyperthermia

MH is a myopathy characterized by an acute increase in intracellular calcium. Under normal conditions, the initiation of an action potential propagates through the muscle fiber membrane and the T-tubule system, causing a current flow through the sarcoplasmic reticulum cisternae, which then release calcium ions into the sarcoplasmic fluid. The dihydropyridine receptor on the T-tubule membrane functions to link the T-tubule membrane to the sarcoplasmic reticulum membrane. The interaction between the dihydropyridine receptor and ryanodine receptor 1 is thought to transmit signals through the triadic junction, leading to calcium release and enabling muscle contraction.

Intracellular calcium pumps rapidly transfer calcium back to the sarcoplasmic reticulum, and relaxation occurs when the concentration drops below the mechanical threshold. Both contraction and relaxation require adenosine triphosphate (ATP). Aerobic and anaerobic metabolism increases ATP supply to drive the calcium pumps, thereby maintaining calcium homeostasis through the sarcolemma, extracellular fluid, and ultimately the sarcoplasmic reticulum and mitochondria.[1,3,7]

During an MH episode, oxygen consumption and glycolytic metabolism increase dramatically. The increased oxygen consumption is followed by elevated blood lactate levels, leading to acid-base disturbances. Initial changes are observed in the venous system, including a decrease in pH and oxygen levels and an increase in CO_2, lactate, potassium, and temperature. The rise in lactate occurs before the decrease in venous oxygen levels, indicating the presence of tissue hypoxia.[3,7]

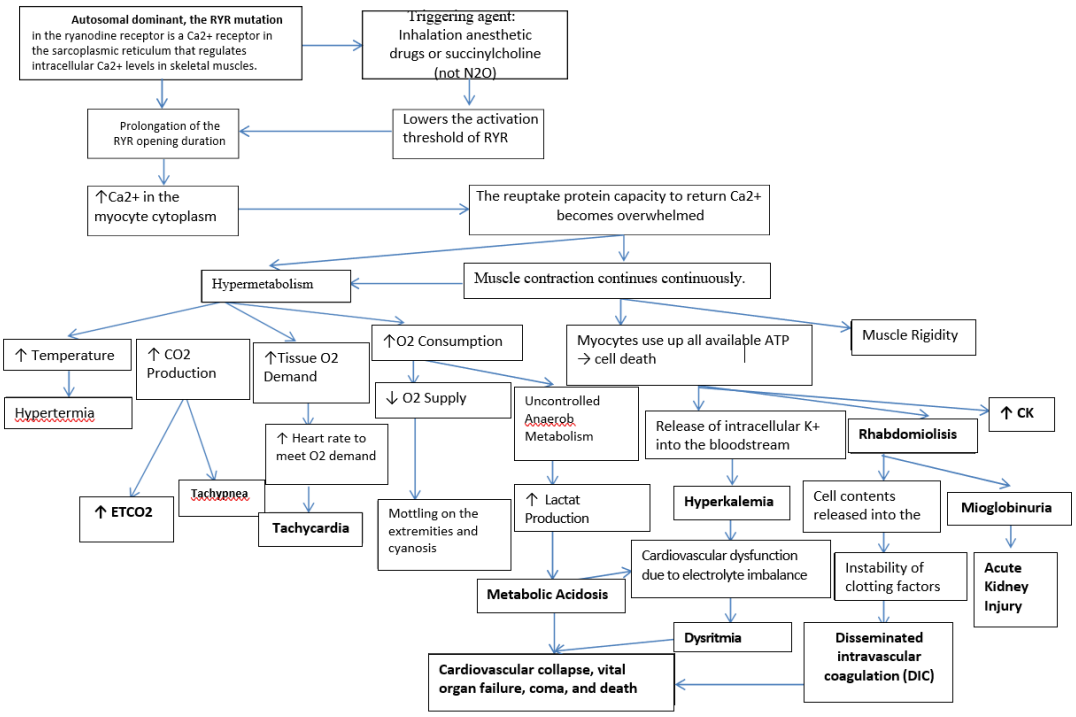

Figure 1. Pathophysiology of malignant hyperthermia[8]

Clinical presentation of malignant hyperthermia

The onset of MH can be acute and rapid, particularly during induction with inhalation anesthetics or the use of succinylcholine. In some cases, the onset may be delayed and only become apparent when the patient is in the recovery room. If clinical signs such as increased CO_2, muscle rigidity, tachycardia, and fever are present, MH should be suspected. However, the presence of only a single symptom cannot be definitively diagnosed as MH.[3,8]

Table 2 Signs of Malignant Hyperthermia (MH)

Early	Advance	After Crisis
1. Muscle rigidity	1. Hyperpyrexia (>43°C)	1. Muscle pain, edema
2. Tachycardia	2. Cyanosis	2. Central nervous system damage
3. Hypertension	3. Electrolyte disturbances, lactic acidosis	3. Kidney failure
4. Increased CO_2	4. Increased creatine kinase	4. Electrolyte imbalances
5. Lactic acidosis	5. Myoglobinuria	5. Disseminated intravascular coagulation (DIC), heart failure

Diagnosis and differential diagnosis of malignant hyperthermia

Diagnosing an MH episode can be quite challenging, especially if the onset is slow and the initial symptoms are nonspecific. If hypermetabolism and increased temperature occur, immediate treatment is necessary to prevent worsening of the condition. A rapid and accurate diagnosis is essential for achieving better outcomes.[1,3]

A definitive diagnosis of MH is established through in vitro physiological testing and chromosome analysis.

Currently, the gold standard for diagnosing MH is the in vitro muscle contracture test (IVCT), also known as the caffeine-halothane contracture test (CHCT). This procedure requires a skeletal muscle biopsy from the suspected MH patient. The test itself is relatively straightforward. The biopsied muscle is exposed separately to halothane and caffeine. The resulting contractions are recorded and analyzed. However, 6–9% of cases may yield false-positive results.[3,9,10]

Table 3. Malignant hyperthermia raw score

Clinical Indicators	Raw Score
Generalized muscle rigidity	15
$ETCO_2$ >55 mmHg with controlled ventilation	15
Arterial $PaCO_2$ >65 mmHg	15
Abnormal increase in body temperature	10
Sinus tachycardia	3
Ventricular tachycardia/ventricular fibrillation	3
Arterial base excess more negative than -8 mEq/L	10
Arterial pH <7.25	10
Total score	81

Table 4. Malignant hyperthermia raw score interpretations

Raw score	Degrees of malignant hyperthermia	Description of probability
0	1	Almost impossible MH
3-9	2	Not MH
10-19	3	Unlikely MH
20-34	4	Likely MH
35-49	5	Highly probable MH
50+	6	Almost certain MH

When using inhalation anesthetics and depolarizing muscle relaxants, MH should be suspected if unexplained tachycardia, tachypnea, arrhythmias, skin mottling, cyanosis, increased temperature, muscle rigidity, sweating, and hemodynamic instability occur. If these symptoms arise, it will lead to increased metabolism, hyperkalemia, and acidosis.[6,8,10]

MANAGEMENT OF MALIGNANT HYPERTHERMIA

In most cases, the onset, diagnosis, and treatment of MH begin while the patient is in the operating room and continue in the post-anesthesia care unit (PACU) or intensive care unit (ICU). The first immediate step when encountering an acute MH case is to discontinue exposure to MH-triggering agents.[6] The following outlines the protocol for acute MH therapy: [6,8]

1. Discontinue all anesthetic agents and stop the surgical procedure. Initiate hyperventilation using 100% oxygen. Normal ventilation only removes CO_2 produced from normal metabolism, whereas in MH, there is increased aerobic metabolism and CO_2 production. Therefore, additional effort is required from the respiratory system to eliminate CO_2, which is achieved through hyperventilation.
2. Administer dantrolene repeatedly with an initial dose of 2 mg/kg body weight intravenously every 5 minutes until the total dose reaches 10 mg/kg body weight. The maximum reported dose used is up to 29 mg/kg body weight.
3. Administer bicarbonate at 2–4 mEq/kg body weight to correct metabolic acidosis, as lactate production from skeletal muscles can persist. Once ionized, lactate may move to the extracellular space, exacerbating the existing acidosis.
4. Take measures to address hyperthermia by infusing cold saline (15 mL/kg body weight). Perform gastric, bladder, and rectal lavage, apply ice packs, use cooling blankets, and monitor body temperature to prevent hypothermia. Cooling efforts should be stopped once the temperature drops below 38°C to avoid hypothermia.
5. Monitor urine output to prevent acute kidney failure or acute tubular necrosis while addressing myoglobinuria. Maintain urine output at >2 mL/kg body weight/hour, and monitor fluid balance using central venous pressure (CVP).
6. Administer inotropic agents and antiarrhythmics as needed.
7. Treat severe hyperkalemia with 25–50 grams of IV dextrose and 10–20 units of regular IV insulin (adult dosage). Life-threatening hyperkalemia can be treated with calcium (2.5 mg/kg body weight $CaCl_2$). Consider invasive monitoring with arterial blood pressure and central venous pressure, urinary catheters, and nasogastric tubes.

In the post-acute phase, perform the following:

a. Observe the patient in the ICU for at least 24 hours.
b. Administer dantrolene at 1 mg/kg body weight every 6 hours IV for 24–48 hours after the episode, followed by oral dantrolene at 1 mg/kg body weight every 6 hours for 24 hours.
c. Monitor arterial blood gas (ABG), potassium, calcium, urine and serum myoglobin, coagulation factors, and body temperature until they return to normal (e.g., every 6 hours). In the initial management of MH, there are 4 steps abbreviated as COLD, namely cancel anesthesia (stopping the anesthesia), oxygen (administering

100% oxygen), liquids (administering cold fluids of 0.9% NaCl intravenously, irrigation and ice compresses), and dysrhythmias (management of dysrhythmias).[11]

The administration of dantrolene requires precise dosing and clear targets. To make it easier to remember, there are four key points for the use of dantrolene summarized with the acronym DRUG, which stands for:[11]

D: Dantrolene 2.5 mg/kgBW (dantrolene 2.5 mg/kg body weight)
R: Repeat dantrolene at 1 mg/kgBW (repeat dantrolene dose at 1 mg/kg body weight)
U: Until temperature reaches 38°C (until body temperature reaches 38°C)
G: Group supplies: bag of H_2O, 60 cc syringe, stopcocks, infusion pins, etc. (supplies needed for administering dantrolene).

In supportive management and monitoring required for the treatment of MH, there are several key points summarized with the acronym MHAUS, including:

M: Monitoring elektrolit
H: Hyperkalemia, treated with insulin and dextrose
A: Acidosis, treated with sodium bicarbonate
U: Urine, monitored by hourly urine output
S: Significant other

Some cases may only require treatment with a single dose of dantrolene, which is a postsynaptic muscle relaxant. However, repeated doses should be administered if there are signs of recurrence (increased rigidity, acidosis, elevated temperature, hypercarbia). Subsequent doses should be 1 mg/kg every six hours, although fulminant cases may require continuous infusion to maintain stability. Since 80% of recurrences occur within 16 hours after initial MH treatment, it seems reasonable to suggest that if a patient receiving dantrolene remains metabolically stable for 24 hours following initial therapy, dantrolene can be discontinued.[12,13]

Dantrolene

Dantrolene is a hydantoin derivative and a sodium salt of complex imidazoline that is poorly soluble in water but highly lipid-soluble, allowing it to cross cell membranes. Dantrolene is a specific drug for restoring metabolic abnormalities in MH. Its rapid reduction of metabolism normalizes potassium and catecholamine levels, as well as blood pressure, heart rate, and sympathetic activity.[6,8,14]

It is packaged as a powder containing 20 mg of dantrolene, 3 grams of mannitol, and sodium hydroxide, resulting in a pH of 9.5. The powder is dissolved by adding 60 mL of sterile water, producing a 0.33 mg/mL solution that is clear yellow to orange-yellow in color. Heating the solution in hot water or placing it in an autoclave for a few minutes helps dissolve it quickly. Seven to twelve vials are required for therapy at a dose of 2.5 mg/kg body weight in adults.[3,6,8]

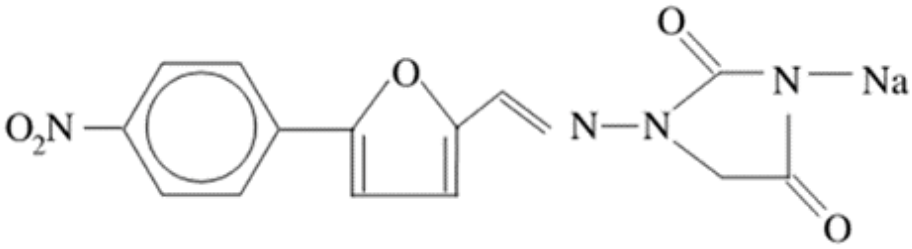

Figure 2. Chemical structure of dantrolene

Pharmacokinetics of dantrolene

After oral administration, 70% of the dantrolene dose is absorbed. Its plasma concentration varies, with peak levels reached within 6 hours. Plasma concentrations remain stable within the therapeutic range for 5 hours after administration. The elimination half-life of dantrolene is estimated to be around 12 hours. In children, the pharmacokinetic profile of dantrolene is similar to that in adults, with a half-life of 10 hours.

Dantrolene is metabolized in the liver microsomes into 5-hydroxy dantrolene, a metabolite that acts as a skeletal muscle relaxant. Reduction of the nitrogen bond on the benzene ring forms aminodantrolene, which is further metabolized into acetylated dantrolene derivatives. Dantrolene and its metabolites are eliminated through urine and bile.[11,15]

Pharmacodynamics of dantrolene

The mechanism of action of dantrolene is specifically targeted at skeletal muscle by reducing the calcium released from the sarcoplasmic reticulum without affecting its reuptake. Dantrolene does not cause paralysis; at maximum doses, it may induce muscle weakness, but it still allows for adequate deep breathing and coughing. An initial dose of 2–2.5 mg/kg body weight can be repeated every 5 minutes up to a total of 10 mg/kg body weight, followed by repeated doses of 1 mg/kg body weight every 6 hours for 24–48 hours. Dantrolene does not have serious effects when administered for less than three weeks.[6,8,15]

Dantrolene can restore hypermetabolism during an MH episode by reducing muscle rigidity and returning muscle function to normal. Serum potassium levels decrease as potassium is driven back into the cells, allowing cardiac function to normalize. Once cellular metabolism is restored and respiration returns to normal, acid-base disturbances will also normalize.[6,14,16]

ANESTHESIA MANAGEMENT FOR SUSPECTED MALIGNANT HYPERTHERMIA PATIENTS

Anesthesia for patients suspected of having malignant hyperthermia (MH) should still follow the anesthesia triad, using anesthetic agents such as nitrous oxide, barbiturates, etomidate, propofol, opioids, benzodiazepines, and non-depolarizing muscle relaxants. MH-triggering anesthetic agents, such as volatile agents and succinylcholine, must be strictly avoided, even if dantrolene has been prepared to manage MH. Prophylactic use of dantrolene is not routinely performed but may be administered if desired, at a dose of 2.5 mg/kg body weight intravenously 15–30 minutes before surgery and anesthesia. Side effects of this premedication may include nausea, vomiting, injection site pain, and, in rare cases, postoperative respiratory insufficiency.[6,8]

The choice of regional anesthesia techniques is also a safer alternative. However, it should be noted that local anesthetics of the amide group have the potential to induce and exacerbate contractures, which may lead to an increased release of calcium ions. Intravenous lidocaine, first used in 1970 for acute MH therapy, showed promising results.[4]

The anesthesia machine must be purged of volatile agents by flushing non-volatile gas into the anesthesia circuit at a rate of 10 units for five minutes. Alternatively, the breathing circuit can be replaced, and a new CO_2 absorber used. Flushing the anesthesia machine, ventilator, and breathing circuit with O_2 at 10 liters per minute for one hour ensures that the inspired gas no longer contains substances that could trigger MH. Strict monitoring of $ETCO_2$ and temperature is essential in this process.[1,6,8]

SUMMARY

Malignant hyperthermia (MH) is extremely rare but is one of the causes of mortality in the operating room. MH is an autosomal dominant condition that can be triggered by exposure to certain anesthetic drugs.

Hypermetabolism occurs in susceptible individuals due to increased intracellular calcium levels. The patient's muscles become rigid, and excessive heat is generated, leading to a dangerous rise in body temperature.

With prompt and appropriate diagnosis and treatment, morbidity and mortality rates can be reduced. Dantrolene is the primary drug of choice for managing MH, and its rapid administration can restore hypermetabolism, thereby preventing death.

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