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Malignant Hyperthermia in Liver Transplantation

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1. Introduction

Malignant hyperthermia (MH) is an inherited, pharmacogenetic disorder of the skeletal muscle, characterized by dangerous hypermetabolic state after anesthesia with succinylcholine and/or volatile halogenated anesthetic agents. MH may also be triggered in susceptible individuals by severe exercise in hot conditions, infections, neuroleptic drugs and overheating in infants[1-4].

MH produces rapid increase in body temperature (by as much as 1ºC in five minutes) and extreme acidosis. These are a result of acute loss of control of intracellular calcium levels and compensatory uncontrolled increases in skeletal muscle metabolism, which may progress to severe rhabdomyolysis. Critical worldwide attention to MH began in 1960 with the reports of Denborough and Lovell. They described MH in a young man who had a history of several deaths of relatives during anesthesia. He developed tachycardia, hot and sweaty skin, peripheral mottling and cyanosis during general anesthesia using halothane. After prompt symptomatic treatment, the episode was aborted[5-6]. The term malignant hyperthermia was first quoted by Wilson and colleagues in 1967[7]. In this same year, Dantrolene Sodium, a hydantoin derivative (1-[5-(4-nitrophenyl)-2-furanyl]methylene]imino]-2,4-imidazolidinedione), was first used because of its possible muscle-relaxing properties[8]. Shortly thereafter, dantrolene was shown to alleviate muscle spasticity effectively in animals[9] and humans[10]. Later, it was shown that dantrolene uncoupled the excitation-contraction process during skeletal muscle stimulation[11]. A few years later, an association between MH and porcine stress syndrome was proposed, providing an animal model for MH[12-13]. Because malignant hyperthermia was thought to result from continuous muscle contraction, perhaps through an abnormality in the excitation-contraction coupling mechanism, the compound was tested as a treatment for this condition[14].

In 1975, Harrison[15] described the efficacy of dantrolene in preventing and treating porcine halothane induced-MH. By 1979 the U.S. Food and Drug Administration (FDA) approved dantrolene for use in humans with MH[16]. The effectiveness of dantrolene in human MH was then confirmed in a multihospital evaluation of dantrolene used to treat anesthetic-induced episodes[17]. More than four decades after its discovery, dantrolene remains the primary basis for successful MH therapy[18].

In the late 1980s, Caffeine Halothane Contracture Test became the gold standard diagnostic test for MH and a variety of neuromuscular disorders associated with MH susceptibility. These disorders include central core disease, Duchenne muscular dystrophy, myotonia congenita, myotonic dystrophy, nonspecific myopathies, and King-Denborough syndrome[19].

During liver transplantation, some commonly employed anesthetic agents may trigger MH in susceptible patients. This occurrence, in such a complex scenario and with such delicate patients, can make anesthesia management even more challenging. Besides this, dantrolene is hepatotoxic, which can pose another injury risk to the graft[20].

2. General Information

2.1 Incidence and prevalence

In North America and Europe, the incidence of MH is currently estimated to be 1:15,000 anesthetics for children and adolescents and 1:50,000–1:150,000 anesthetics for adults[21-23]. The prevalence for this syndrome in the general population is unknown because of lack of universal reporting, but although it may be as common as one in 2000[24]. Malignant hyperthermia is more common in male patients[25]. The incidence and prevalence varies from country to country, based on differences in gene pools[26-30].

Although the incidence of reported episodes of MH has increased, the mortality rate from MH has declined. This may reflect a greater awareness of the syndrome, earlier diagnosis, and better therapy[31].

2.2 Risk factors

Apparently, MH can exist regardless of race or gender although predominance in males and adolescents has been suggested[25]. Family history of fatal general anesthesia complications associated with the use of volatile agents or depolarizing muscle relaxants should make the anesthesiologist aware about the increased risk for MH.

Patients with Duchenne muscular dystrophy, myotonia congenita, myotonic dystrophy, nonspecific myopathies, central core disease, King-Denborough, osteogenesis *imperfecta* and Schwartz-Jampel syndrome have an increased risk for MH syndrome[19]. Patients who develop masseter muscle rigidity (MMR) after administration of succinylcholine have an increased risk to develop MH in the next minutes, and 25% of these will show positive contracture tests to MH[32-33].

2.3 Pathophysiology

Malignant hyperthermia is an inherited pharmacogenetic disorder of skeletal muscle, characterized by an increased calcium release from the skeletal muscle sarcoplasmic reticulum. A mutation in the ryanodine receptor (RyR) may be the main causative factor in many patients and families with MH[34-35]. The ryanodine receptor type 1 (RYR1) gene encodes the human skeletal muscle calcium release channel. RYR1 gene is responsible for the release of sarcoplasmic reticulum stores of calcium. In about 50% of MH susceptible families, there is a mutation in RYR1[36]. The large variability among individuals may be explained by different genes causing MH in different families or by other predisposing factors being expressed differently in susceptible patients[36].

The vast majority of patients susceptible to MH are asymptomatic in the absence of anesthesia. In humans, the defect only appears to be expressed significantly in skeletal muscle, although receptors are present in cardiac muscle[37] and even in the liver[38]. Recently some authors suggested that RyR's play an active role in the Ca^{2+} signaling of hepatocytes, creating local Ca^{2+} microdomains that enhance the responsiveness of neighboring Inositol Trisphosphate Receptors through Ca^{2+}-positive feedback[38].

The exact mechanism by which different substances initiate a MH crisis has not been determined. It can be assumed, though, that a defect of intracellular Ca^{2+} homeostasis plays an important role. Susceptibility to MH is clearly based on an abnormal Ca^{2+} metabolism within the skeletal muscle, most probably caused by a defective Ca^{2+} release channel in the sarcoplasmic reticulum (SR), e.g. the ryanodine receptor which is the footplate protein seated between the dihydropyridine receptor and the sarcoplasmic reticulum[39-41]. The abnormal function of the ryanodine receptor of skeletal muscle in MH causes barely controlled concentration of calcium within the cell when it is not exposed to triggering agents[42,43]. The added loss of control of intracellular calcium on exposure to triggering agents or heat stress leads to marked metabolic stimulation within the cell to provide extra adenosine triphosphate to drive the calcium pumps that restore calcium to its reservoirs (e.g., sarcoplasmic reticulum, mitochondria, extracellular fluid)[44].

On a cellular level, magnesium acts as a physiological calcium inhibitor resulting in less-intense calcium liberation from the sarcoplasmic reticulum. In normal resting muscle, cytosolic Mg^{2+} exerts a potent inhibitory influence on the SR Ca^{2+} release channel (ryanodine receptor, RyR1). Impaired Mg^{2+}-regulation of RyR1 has been proposed as a causal factor in MH. The marked potentiation of SR Ca^{2+} release after a moderate reduction in cytosolic Mg^{2+} suggests that conditions which cause hypomagnesemia will increase the probability and possibly severity of an MH event. Conversely, maintenance of a normal or slightly increased cytosolic Mg^{2+} may reduce the probability of MH[45]. There is increasing evidence to suggest that defective Mg^{2+} regulation of RyR1 confers susceptibility to malignant hyperthermia. At the molecular level, interactions between critical RyR1 subdomains may explain the clustering of RyR1 mutations and associated effects on Mg^{2+} regulation[46].

MH is a syndrome caused by dysregulation of excitation-contraction (EC) coupling in skeletal muscle. The increased activity of pumps and exchangers trying to correct the increase in Ca^{2+} causes a need for ATP, which in turn produces heat. Thus, the end result is hyperthermia. The rigidity that is frequently seen during a fulminant MH episode is the result of the inability of the Ca^{2+} pumps and transporters to reduce the unbound myoplasmic Ca^{2+} below the contractile threshold[44,47]. Human malignant hyperthermia is a heterogeneous disorder, and the down-regulation of sodium channel subunit may be involved in the final common pathway through which mutations in any one of several proteins, including the ryanodine receptor, could render a person susceptible[48]. These changes would prolong the sodium current making the cell membrane depolarized for a longer time, increasing calcium release time period from the terminal cisternae. Patients expressing sodium channel abnormalities are at increased risk for muscle rigidity.

2.4 Triggering agents

All volatile anesthetics are triggers of malignant hyperthermia and must therefore be strictly avoided in malignant hyperthermia-susceptible patients. Furthermore, the depolarizing

muscle relaxant succinylcholine triggers the syndrome[49]. Isoflurane, desflurane and sevoflurane appear to be less potent triggers than halothane, but these agents can produce a more gradual or fast onset of MH[50-56]. The onset may be explosive if succinylcholine is used[57]. Local anesthetics, nondepolarizing muscle relaxants, barbiturates, benzodiazepines, droperidol, ketamine, nitrous oxide, opioids, and propofol are all safe drugs to administer in MH susceptible patients[49].

2.5 Clinical presentation

The commonest clinical presentation of MH is a hypermetabolic state in a genetically susceptible individual in response to certain anesthetic agents, notably succinylcholine or halogenated volatile anesthetics. One of the earliest clinical signs is MMR after succinylcholine. *In vitro* muscle testing in patients who have developed this sign alone reveals that 28–50% are susceptible to MH. In the full-blown syndrome there is a rapid and sustained rise in body temperature, without shivering, either in the operating theatre or in the recovery room, in the absence of any obvious cause such as infection or a hot and humid environment. Tachycardia, cyanosis, generalized muscle rigidity, and cardiac arrhythmias are common clinical signs. There may be heating and rapid exhaustion of the soda-lime canisters. Acidosis is an early finding and there may also be hyperkalemia, hyperphosphatemia, and hypocalcemia from muscle-cell breakdown. Rhabdomyolysis is an important feature of the syndrome and is best demonstrated by measuring serum CK, which usually peaks on the second or third day after the reaction. Tenderness and swelling of muscles may develop, especially in the thighs. Myoglobinemia and myoglobinuria are common and renal failure may result from the rhabdomyolysis. Another complication is disseminated intravascular coagulation[1].

In less obvious cases, MH may present with one or any combination of the above clinical signs. The first indication of MH may be an unexplained cardiac arrest or cardiac arrhythmia. A rise in end-tidal CO_2 is often the earliest indication of MH, and now that this is widely measured in clinical anesthesia MH may be picked up before the more florid signs develop. Previously apparently uncomplicated anesthesia with halothane and/or succinylcholine does not exclude the diagnosis of MH on a subsequent occasion. Factors such as the concentration of the anesthetic drugs used, the duration of the anesthesia, and the degree of MH susceptibility of the patient may explain why one anesthetic procedure is uneventful while another in the same patient is not[1].

When MH was first recognized as a complication of anesthesia the case-fatality rate was 70%. Today, with the use of a specific drug for MH and the introduction of an *in vitro* muscle-contracture test[59] to identify susceptibility to MH in individuals and their relatives, the case-fatality rate is only 5%[1].

3. Sodium dantrolene

3.1 Pharmacokinetics

Flewellen et al showed that after an intravenous dose of dantrolene, therapeutic levels were rapidly achieved and remain stable for around 5.5h. Subsequently, the dantrolene blood level slowly declined following first order kinetics with a half-life elimination of 12h. The mean residual blood dantrolene concentration present 20h after the last dose was 1.7 $mcg.ml^{-1}$ and, after 50h, that level was 0.3 $mcg.ml^{-1}$ [60]. This same study evaluated neuromuscular effects of intravenous dantrolene in conscious patients and showed that

maximal depression of muscle twitch response (75% depression) and grip strength (42% depression) was accomplished after a cumulative dose of 2.4 $mg.kg^{-1}$ body weight. Twenty four hours after such regimen, dantrolene levels were still high enough to cause strength reduction and a subjective weakness complaint only disappeared 48h after the last dose. On the other hand, spontaneous respiratory parameters (peak expiratory flow rate, vital capacity, end-tidal carbon dioxide and respiratory rate) did not change significantly during dantrolene administration. In children, the pharmacokinetic profile is similar, with a half-life of approximately 10 h[61].

Metabolism of dantrolene is achieved microsomally in the liver via oxidative and reductive pathways. Oxidation results in hydroxylation of the hydantoin ring to 5-hydroxydantrolene (5HD), while reduction of the nitro group of dantrolene leads to the formation of aminodantrolene, which is then acetylated to the reduced acetylated derivative (RAD) of dantrolene[62].

5HD is a metabolite with muscle relaxant effects. Compared with dantrolene sodium, it has a longer half-life (15,5h vs. 6h), but its activity is lower and its plasma levels are only 30-50% of its parent drug[63]. As a result, in healthy patients, 5HD can only be considered to play a minor role on the skeletal muscle relaxant properties of dantrolene therapy. The other metabolites have no relaxant effect.

After an oral dose, 70% of dantrolene is absorbed. Twenty-five percent of the dose is excreted in urine, most of it as 5HD (79%) or RAD (17%); only 4% is excreted as unchanged drug[62]. Biliary excretion accounts for 45-50% of the oral dose administered[64]. Specific and detailed excretion studies after intravenous dantrolene are lacking.

3.2 Pharmacodynamics

Dantrolene is a unique muscle relaxant. Unlike neuromuscular blocking agents (site of action of which is at the nicotinic receptor of the neuromuscular junction) or the nonspecific relaxants (which modulate spinal cord synaptic reflexes), several studies have shown that dantrolene interferes with excitation-contraction coupling by reducing the concentration of myoplasmic calcium[65-69]. Consequently, muscle contraction is decreased without an effect on the action potential patterns of the neuromuscular junction[70].

However, the pathway by which dantrolene lowers myoplasmic Ca^{2+} is complex and still not fully understood. The ryanodine receptor of skeletal muscle (RyR1) has traditionally been thought to be the site of action of dantrolene[66], and recent studies have located the molecular target of dantrolene to the area comprising amino acid residues 590 through 609 of RyR1[71], strengthening that hypothesis. Some controversy was shed on that assumption when purified RYR1 was incorporated into an artificial planar lipid bilayer and no effect of dantrolene was detected in channel activity or pharmacology[72]. As a consequence, to date, we lack evidence of a direct action of dantrolene on purified RyR1 channels studied in lipid bilayers, even in the presence of calstabin 1, ATP, and activating concentrations of $Ca^{2}+$, suggesting that dantrolene's main action is to alter key protein-protein interactions[73].

3.3 Side effects

The two most frequently observed side-effects were muscle weakness in 22% and phlebitis in 10% of the patients.

Besides the intrinsic effect of dantrolene therapy, muscle weakness during MH may have a contribution of the muscle injury that is an integral part of the syndrome. Additionally, prolonged mechanical ventilation may, *per se*, exert deleterious effects on respiratory function. Although some authors objectively demonstrated strength reduction with clinically used doses of dantrolene[60], no studies of pulmonary function have been performed in patients after MH crises, dantrolene therapy and intensive care management. As a result, careful attention with respiratory function is essential in these patients, especially during weaning of mechanical ventilation or in patients with borderline respiratory function, like those neuromuscular disorders. The clinicians treating an MH episode should request repeated measurement of creatine kinase until it returns to normal levels[74].

Because of its high alkalinity (pH = 9.6) after reconstitution, dantrolene should be preferentially administered through a large bore peripheral or central venous access to avoid local inflammatory phlebitis at the infusion site. Moreover, the sites of infusion should be frequently inspected for signs of extravasation and tissue necrosis.

Besides these, the most commonly reported adverse effects can be grouped as of central (drowsiness, weakness, dizziness, malaise, fatigue, diplopia, dysarthria, seizures) and gastrointestinal (nausea, epigastric discomfort, diarrhea, constipation, abdominal pain) origin[70]. Gastrointesinal symptoms are more common with oral therapy[75]. Central nervous system symptoms may be worsened by sedatives and general anesthetics and it is not yet clear whether they are mediated by altered neuronal calcium homeostasis[76].

The side-effects were more commonly reported at the initiation of oral therapy and frequently disappeared with continued therapy and dose titration, although in 2.5% of patients they may be severe and persistent enough to warrant discontinuation of therapy[64].

Once the sarcoplasmic reticulum of heart muscle plays an essential role in the variable calcium release and uptake in excitation-contraction coupling, negative inotropic effects of dantrolene could be expected. The first studies to specifically address the effects of dantrolene on cardiovascular function evaluated healthy anesthetized dogs and showed no relevant effects on arterial pressure, central venous pressure, heart rate, coronary blood flow and cardiac output[77-78]. Later, other authors argumented that those results did not imply absence of effects on cardiovascular functions, since mechanisms of compensation may have had a role in maintaining the stability of the parameters investigated[79]. So, several authors began to study the effects of dantrolene in isolated animal cardiac muscle[79-81], but these investigations resulted in divergent results. The human studies that addressed this issue did not show any relevant effects of therapeutic doses of dantrolene on cardiovascular function [60], even in patients with poor cardiac function[82]. Whether this stability was due to complete absence of action of dantrolene on human myocardium or due to the action of compensating cardiovascular mechanisms is still a matter of debate.

Another relevant cardiovascular issue has recently emerged in a two-decade registry analysis of the complications associated with dantrolene administration[74]. The authors found that the risk of any complication with dantrolene therapy increases with larger doses of dantrolene and fluid administration; on the other hand, this same study showed that the associated use of furosemide decreased that risk. Besides this, considering only the subset of patients with serious underlying disease or complex surgery (like liver transplant), there was a greater incidence of complications and these patients commonly presented more than one type of complication.

The interpretation of these findings has to be undertaken in light of the administration peculiarities of dantrolene. Each vial with 20 mg of dantrolene contains 3 g of mannitol (to improve liposolubility) and has to be reconstituted with 60 mL of sterile water. Thus, the results of the registry analysis would suggest that the mannitol content of dantrolene formulations, when combined with fluid administration, would further aggravate the fluid shifts related to the pathophysiology of MH and major surgeries, justifying the occurrence of complications like pulmonary edema. On the other hand, the careful use of furosemide to maintain urinary output and regulate intravascular volume status decreased these complications and has long been suggested by many authors. In this registry analysis, two of the 386 enrolled patients (0.5%) presented a decrease in cardiac output, but the authors did not sufficiently describe these cases to determine if it may have been the result of direct negative inotropism of dantrolene or due to other possible causes, like fluid overload.

Liver transplantation is a very complex surgery and hepatorenal syndrome and cirrhotic cardiomyopathy are relatively common among liver transplant patients. Besides this, fluid management during liver transplantation, which is especially challenging because of massive bleeding and altered hemodynamics of cirrhotic patients, can become even more challenging with the occurrence of MH. As a result, dantrolene therapy may be especially prone to cardiovascular complications in this population. Because of these concerns, some authors suggest that documentation of cardiac filling pressures and cardiac output with continuous monitors such as echocardiography may improve management of critically ill subjects during MH treatment, although they were unable to demonstrate a reduction in dantrolene-associated complications with these measures. Furthermore, careful titration of the lowest effective dose regimen should always be sought.

Although rarely encountered, chronic oral dantrolene therapy has been linked to different grades of hepatic damage, including fatal hepatitis in 0.1-0.3% of patients[20,83]. As a result, it received a black box warning for hepatotoxicity in 1976, early after its release in 1974[84]. Despite these facts, a few authors suggest that other concomitant therapies may have had a role in that toxicity[75-76]. In addition, *in vivo* experiments in mice have not revealed any toxicity to hepatocytes[85-86]. In fact, recently, it was argued that dantrolene, due to its properties of restoring calcium homeostasis in scenarios of its disruption (like models of ischemia, hypoxia, seizure, trauma, anesthesia, and neurodegenerative diseases), may have cytoprotective effects in different tissue culture or animal models of diseases involving cytotoxicity induced by disruption of intracellular calcium homeostasis in pathogenesis[87].

Although the great majority of the studies agree that dantrolene may induce liver toxicity, the reports regarding intravenous short term dantrolene therapy are scarce, and most of the information is related to the oral long term dantrolene therapy in patients with spasticity disorders[20]. The only study that addressed the hepatic effects of intravenous dantrolene, found no significant differences in liver enzymes after its use, although it employed volunteers without any signs of MH[60]. In publications of oral therapy, some risk factors for dantrolene associated hepatitis have been identified like female sex, patients over the age of 35 years and greater accumulated doses[20,88].

Although larger doses were identified as a risk factor, there is no agreement about the reactions involved in dantrolene hepatotoxicity and, until now, it is not known if the mechanism is dose-related or attributable to hypersensitivity (idiosyncratic reaction after a few doses)[85,89-90]. As described in the pathophysiology section, ryanodine receptors were

recently discovered in hepatocytes[38]. Whether dantrolene causes liver toxicity through these receptors or during its metabolism is unclear.

Most of the patients with dantrolene hepatitis develop only mild and nonspecific symptoms (malaise, weakness, vomiting, fever, vomiting, jaundice)[90], although fatal acute hepatic failure has been described[93]. Laboratory exams show different degrees of alterations in liver enzymes (alkaline phosphatase, AST, ALT) and bilirubin levels[91]. Histological findings of liver biopsies did not show a homogenous pattern, and multiple different descriptions were published (Table 1)[20,88-90,92-95]. If signs of hepatic injury develop during MH therapy, the treatment is mainly supportive and dantrolene should be stopped soon after control of the crisis, as dantrolene hepatitis is usually reversible after its withdrawal.

In the two available reports of the use of dantrolene sodium during liver transplantation, there were alterations in postoperative laboratory exams, but the liver graft recovered uneventfully[56,96]. Actually, although dantrolene may pose an additive threat in the large set of perioperative injuries to the graft, abnormal symptoms and laboratory exams may be masked in the routine postoperative course of hepatic transplantation. Besides this, biopsies may not be of great help because histological patterns of dantrolene hepatitis do not greatly differ from those usually observed postoperatively in liver grafts. Consequently, prevention of dantrolene-induced hepatic injury is crucial. So, if malignant hyperthermia happens during liver transplantation, it seems prudent to, besides supportive treatment, use the lowest effective dose of dantrolene for the shortest time possible.

Less commonly reported effects are acne-like rash, pruritus, urticaria, fever, hypersensitivity pleural effusion with pericarditis.

4. Malignant hyperthermia in liver transplantation

4.1 Preoperative evaluation and investigation of susceptibility

Preoperative evaluation is crucial for all liver transplant candidates and, although involvement of multiple specialties like surgery, gastroenterology, cardiology, nephrology and endocrinology may be beneficial, it does not dispense with a judicious assessment by an anesthesiologist. Before planning anesthesia in a patient with known or suspected susceptibility to malignant hyperthermia, complete information about previous anesthetic procedures including complications or adverse events and other medical reports is needed[97]. Such evaluation is best accomplished and documented with the use of systematic formularies, where all collected data are registered and the anesthetic technique is individualized according to the risk factors for MH. The survey should include questions regarding muscular disorders, complications, deaths, unexplained high fever or dark-colored urine after surgery. Symptoms like fever, cramps, muscular fatigue and weakness may suggest muscular disorders and susceptibility, but are overly common among candidates for liver transplantation and are of limited value.

All common premedications like opioids, benzodiazepines, barbiturates, anticholinergics, and antihistamines are safe, but phenothiazines should not be administered. There is no need for preoperative use of dantrolene, but it must be immediately available in the operating room.

It must be emphasized that uneventful previous anesthetics (even more than once) with MH-triggering agents do not preclude the occurrence of MH in future exposures[56,98].

Some factors may have a role in attenuating MH crisis: pre-exposure hypothermia[99], differential trigger potency for MH[100] and variable genetic penetrance[101]. One of the described cases of MH during liver transplantation occurred in a patient who had previous uneventful general anesthetic[31].

4.2 Factors influencing the choice of anesthetic agents for liver transplantation and alternatives

The choice of anesthetic agents for liver transplant surgery takes into account three key factors: maintenance of hemodynamic stability, lack of hepatic toxicity and pharmacokinetic profile[102].

Circulation of cirrhotic patients is hyperdynamic, showing low systemic vascular resistance and high cardiac output[103-104]. The use of betablockers for the prevention of variceal bleeding may render these patients bradycardic and hypotensive on arrival at the operating room. Besides this, large volume paracentesis, manipulation of major vessels, presence of surgical retractors, high propensity to massive bleeding and the reperfusion syndrome may all, *per se*, result in profound intraoperative hemodynamic changes. To further aggravate the scenario, it is widely known that most drugs used in anesthesia have negative effects on the cardiovascular system. As a result, judicious choice of anesthetic agents may help alleviate the tendency toward hemodynamic instability – the following choices are considered reasonable[105].

- Hypnotic agents for anesthetic induction: propofol in low doses (1.0 – 1.5 $mg.kg^{-1}$)[106]; etomidate (0.2 – 0.3 $mg.kg^{-1}$). Hypnotics are not triggers of MH.
- Analgesic agents: fentanyl, sufentanil and remifentanil in continuous infusion are recommended; doses should be lower than usual, as the hepatic clearance is reduced. If remifentanil is used, postoperative hyperalgesia may be a concern[107] and pain control regimens should receive special attention. Opioids are not triggers of MH.
- Neuromuscular blocking agents: rapid sequence induction is recommended, since these patients commonly present with ascites[108] and gastroparesis[109]. Succinylcholine is a common choice in these cases, although it should be avoided in patients susceptible to MH. Rocuronium is a safe alternative, although its effects may be prolonged because of its hepatic metabolism; furthermore, postoperatively, in case of graft dysfunction, extubation may be delayed[110]. For the maintenance of neuromuscular block, intermittent bolus or continuous infusion of intermediate-acting drugs independent of hepatic metabolism (atracurium or cisatracurium) are a good choice and should be guided by neuromuscular monitoring.
- For maintenance of anesthesia during liver transplantation, halogenated inhalational agents (except halothane) or propofol in continuous infusion can be used. It has been shown that anesthetic requirements during liver transplantation are inversely proportional to the degree of hepatic dysfunction[111], so careful titration of anesthetic doses with monitors like BIS© can minimize the negative cardiovascular effects of these drugs[112]. Isoflurane seems to be the most adequate halogenated agent, because it has few hemodynamic effects, lacks hepatotoxicity and protects hepatocytes from graft reperfusion injury[113-114]. On the other hand, isoflurane may be stronger trigger of MH than sevoflurane[100].
- In such a way, in MH susceptible patients, succinylcholine and halogenated inhalational anesthetics must be avoided and dantrolene must be available in the operating room.

Local anesthetics, nondepolarizing muscle relaxants, barbiturates, benzodiazepines, droperidol, ketamine, nitrous oxide, opioids, propofol and vasoactive drugs are all safe drugs to administer to these patients[115].

4.3 Suspected cases and confounding factors during liver transplantation

MH syndrome exhibits a wide range of symptoms including tachycardia, progressive elevation of the exhaled CO_2, arrhythmias, hyperthermia, profuse sweating, fever up to 40^0C, cyanosis, poor skin perfusion and blood pressure instability[31]. The only physical sign typical of MH is muscular rigidity, although it may be hard to detect due to the limited access for physical evaluation. MMR may be observed upon anesthetic induction and is predictive of the syndrome[32-33].

However, tachycardia, arrhythmias, poor skin perfusion, blood pressure instability and other subtle manifestations of the initial phase of HM are commonly observed during liver transplantation, as it involves large volume paracentesis, manipulation of major vessels, massive bleeding and reperfusion syndrome[116]. Inadequate anesthetic depth and pyrogenic reaction can mimic some of those symptoms.

Most of liver transplant patients are maintained normothermic with the aid of forced warm air mattresses. After the reperfusion, the graft begins to produce heat by its exothermic metabolic reactions and the addition of this new source of heat may lead to hyperthermia. However this temperature rise only begins lately in the course of the surgery, usually is minimized by turning off the mattresses and rarely exceeds 39ºC. Another potential source of confusion in the diagnosis of MH is the use of defective equipment for patient heating (leading to overheating and sweating) or poorly calibrated temperature monitors.

Some situations can induce severe intraoperative Systemic Inflammatory Response Syndrome (SIRS) during liver transplantation, like bacteremia/sepsis, acute rejection and graft non-function. Although SIRS may show up with hyperthermia[117], other MH symptoms like severe hypercapnia are not usually present in these cases.

Hypercapnia may have several causes during liver transplantation, like intrinsic pulmonary diseases, accumulation of lung secretions in the airway, lung compression by retractors, inappropriate mechanical ventilation, exhaustion of soda lime and faulty carbon dioxide monitoring. However, after checking and solving all these issues, the maintenance of a progressive rise on end-tidal carbon dioxide becomes a strong indicator of malignant hyperthermia.

To make diagnosis even problematic, most early laboratory manifestations of malignant hyperthermia, such as respiratory and lactic acidosis and hyperkalemia, are also commonly observed in anesthesia for liver transplantation. The reasons for respiratory acidosis were described above. Lactic acidosis frequently results from the combination of tissue hypoperfusion and decreased hepatic clearance of lactate during the anhepatic phase. Hyperkalemia during liver transplantation may have several reasons, like poor baseline renal function, large and rapid transfusion of red cells and high-potassium content of preservation solutions. Nonetheless, mixed venous oxygen saturation (SvO_2) may have a lower value when MH is suspected. Due to severe increase in cellular oxygen consumption,

the SvO_2 of patients with MH is usually low. Such low values are not usually seen in liver transplantation, since cirrhotic patients generally have systemic shunts and a hyperdynamic circulation, yielding high values of SvO_2[118].

4.4 Intraoperative differential diagnosis

Several disorders share similarities with MH and may be confused with the syndrome. Neuroleptic malignant syndrome is characterized by hyperthermia, acidosis, hyperkalemia and myoglobinuria following use of a wide variety of neuroleptics, especially haloperidol. Patients taking mono-amino-oxidase inhibitors who receive meperidine may present with hyperthermia, acidosis and an increase in creatine kinase concentration, what may become fatal. Other conditions that may resemble the MH situation include – but are not limited to – : iatrogenic overheating, thyroid storm in thyrotoxicosis, hypothalamic lesions, heat illness, pheochromocytoma, and intrathecal injection of high osmolar contrast agents, cocaine or ecstasy overdose, hypoxic encephalopathy and sudden cardiac arrest in a patient with occult myopathy[119]. None of these disorders, however, is frequent in liver transplant patients.

4.5 Investigation of suspected cases

Investigation of susceptibility should begin upon clinical suspicion during preoperative evaluation.

Creatine kinase (CPK) dosage during rest has been suggested as a component of a clinical grading scale to predict malignant hyperthermia susceptibility for patients with positive family history; increased resting values could suggest myopathy and MH susceptibility[120]. The use of this test is not recommended for the general population as it would yield an unacceptably high rate of false positive results. Cirrhotic patients habitually have reduced muscle mass and decreased exercise-tolerance, thus high CPK results in patients with positive family history are suggestive.

Caffeine-Halothane Contracture Test (CHCT) is considered the gold standard for the diagnosis of MH. This test, which uses a small piece of live muscle from biopsy, assesses the muscular contractility in response to increasing concentrations of halothane and caffeine exposure. It has a 97% sensitivity and 78% specificity[121]. Even in typical cases, CHCT is beneficial to guide the necessity of investigation of relatives. MH is inherited in an autosomal dominant pattern, meaning that if one of the parents has the disease, the risk of his or her passing it down to sons or daughters is 50 per cent[122]. Muscle biopsy for CHCT should be avoided in patients whose weight is less than 20 kg, patients under chronic dantrolene or calcium channel blocker therapy and in the first three months after a MH crisis, because muscle lesion may still be present[123]. A muscle sample is removed from the *vastus lateralis* or *medialis* or *rectus abdominis*. As the tests have to be finished up to five hours after its collection, patients have to be transported to specialized MH centers. The procedure is performed under general or regional anesthesia, obviously avoiding potentially trigerring agents and keeping dantrolene immediately available[123]. CHCT is indicated in patients preoperatively deemed at risk for MH, postoperatively in patients with a typical MH crisis during liver transplantation and the relatives of the patients with a positive CHCT.

4.6 Management and treatment of MH during anesthesia for liver transplantation

4.6.1 Intraoperatively

Protocols for MH treatment prioritize four mainstays: immediate discontinuation of trigger agents, administration of antidote (sodium dantrolene), life support measures and prevention of complications[124-125].

In the acute phase of MH the following steps are recommended:

1. **Immediate discontinuation of triggering agents:** some MH crisis may be attenuated or aborted with discontinuation of triggering agents. When MH or MMR is identified soon after induction, postponement of the surgery is commonly recommended[119]. In liver transplant surgery, however, the decision to postpone the procedure is very tough. The anesthesiologist is faced with a patient who has a delicate clinical status that may be worsened either by a MH crisis or by returning to the waiting list. All the medical team should be involved in this sentence.
2. **Call for help:** initiation of measures to treat MH, including the laborious process of dantrolene dilution, may be troublesome for one only anesthesiologist. Consequently the presence of another health professional (preferably an anesthesiologist) may be of valuable help.
3. **Adjust ventilation:** increase minute ventilation to lower $EtCO_2$ and use 100% oxygen. There is no need to change the breathing circuit or the soda lime canister[126].
4. **Administer the antidote:** Dantrolene is the drug of choice in treatment of malignant hyperthermia[127]. The contents of each bottle should be diluted in 60 mL of sterile water rather than solutions such as 5 percent dextrose in water or bicarbonate because the extra molecules in solution lead to a salting-out effect with greater difficulty in dissolving dantrolene. If it does not dissolve immediately, producing a clear yellow to yellow-orange color, it should be heated under tap water or autoclaved for a few minutes[128]. In a dire emergency, it should be administered through a blood filter without concern for crystals. Dantrolene should be preferentially administered through a large bore peripheral or central venous access to avoid local inflammatory phlebitis at the infusion site.

   General dosing regimens recommend an initial bolus of 2.5 $mg.kg^{-1}$, which can be repeated every 5 minutes until normalization of the hypermetabolic state and the disappearance of all MH symptoms. After this initial control, a continuous intravenous dantrolene infusion at 10 $mg.kg^{-1}.day^{-1}$ should be given for at least 24 h after initial successful therapy[76].

   Although this is the classical regimen, it may be excessive and deleterious in liver transplantation patients. In this scenario, although the diseased liver is removed and a new liver graft is transplanted, the transplanted liver unavoidably sustains warm, cold, and reperfusion injuries during graft procurement and transplantation[129]. Dantrolene sodium is considered hepatotoxic and the hepatic effects of dantrolene on such liver allografts are unknown. As a result, it seems prudent to use the lowest effective dose for the shortest time possible.

   There are two published case reports of MH in liver transplantation, with identical clinical presentation and successful treatment with lower than usual dantrolene doses[56,96]. One of the reports used a 1 $mg.kg^{-1}$ dose intraoperatively, followed by 1 $mg.kg^{-1}$ every eight hours for 36 hours; the authors observed signs of hepatic

dysfunction 9 days after the transplant, which was attributed to dantrolene and had spontaneous resolution[56]. In the other report, the same intraoperative dose was used (1 mg.kg^{-1}) and no maintenance dose was used; in this case, no signs of liver graft dysfunction were observed[96].

Therefore, to minimize the risks of graft toxicity by dantrolene, it seems prudent to adopt intraoperative doses of 1 mg.kg^{-1}, which may be repeated every 30 minutes until control of symptoms. Next, the patient should be closely observed for MH recrudescences; if these occur, a regimen of 1 mg.kg^{-1} every eight hours for 36 hours should be instituted.

5. **Begin active cooling measures:** hypothermic blanket under and over the patient (if possible); cold isotonic saline for intravenous infusion and for gastric, vesical, peritoneal or rectal irrigation, as appropriate; ice packs to groin, axilla, and neck. To avoid hypothermia, cooling measures should be stopped when temperature decreases to 38ºC[130].
6. **Treatment of metabolic acidosis:** drugs like sodium bicarbonate or THAM are usually required to keep pH within the acceptable range[132].
7. **Treatment of hyperkalemia:** pH should be raised with the aid of hyperventilation and/or sodium bicarbonate or THAM. Glucose-insulin infusions may be helpful. In the past, authors contraindicated the use of Calcium Chloride during MH because they feared worsening of the crisis[131], on the other hand, today, it seems reasonable to use it to antagonize hyperkalemia-induced electrocardiographic changes[132].
8. **Treatment of cardiac arrhythmias:** the control of hyperkalemia and acidosis usually alleviates this problem. When they persist, the treatment should be guided according to internationally accepted protocols, like Advanced Cardiac Life Support©. Calcium blockers should not be used along with dantrolene, since hyperkalemia (sometimes culminating in cardiovascular collapse) has been described in animals with such a drug combination[132].
9. **Optimize urine output:** an output greater than 2 mL.kg^{-1} should be instituted with the use of fluids and diuretics, like furosemide and mannitol. Such measure prevents the development of renal injury secondary to rhabdomyolysis and helps the control of hyperkalemia[124].
10. **Follow blood gases, electrolytes, creatine kinase, coagulation profile and urine myoglobin.**
11. **Call for specialized center:** several countries have toll-free phone numbers for MH centers. As MH is a rare disorder, few anesthesiologists are fully used to its treatment when it happens. With such call, one may receive valuable instructions.

4.6.2 Postoperatively

1. **Observation and monitoring:** as much as 25% of patients with MH will present a recrudescence of the syndrome several hours after its initial control[133]. As a result, authors recommend observation in Intensive Care Units for 24-72 hours postoperatively[32]. Samples for blood gases, electrolytes, creatine kinase, coagulation profile and blood and urine myoglobin should be collected every 6-12 hours[76,131]. Habitually, immediate postoperative tests show evidence of hepatic injury (increased liver enzymes) and coagulopathy. Such profile mainly results of the ischemic injury to the graft and is self-limited when the graft begins to work. When MH occurs during liver transplantation, it is not clear if dantrolene can make these abnormalities more

severe nor if it can contribute to graft dysfunction. Irrespective of these uncertainties, the postoperative management is similar: graft function should be closely followed, dantrolene doses should be minimized to control symptoms and supportive treatment should be instituted. Liver biopsy has a limited value in this scenario, since the histopathological patterns of dantrolene hepatotoxicity are comparable to the ones usually observed in liver transplantation and the treatment choice does not change. If severe graft dysfunction ensues despite minimal use of dantrolene, retransplantation should be considered.

2. **Postoperative dantrolene therapy:** in liver transplant patients, after initial control of MH, dantrolene should be reserved for recrudescences (to minimize liver toxicity). The dosage regimen is recommended 1 $mg.kg^{-1}$ every eight hours for 36 hours.
3. **Mechanical ventilation weaning:** one of the most reported side-effects of dantrolene is muscle weakness, which may persist up to 24-48h after the last dose. Although some authors objectively demonstrated strength reduction with clinically used doses of dantrolene[60], no studies of pulmonary function have been performed in patients after MH crises, dantrolene therapy and intensive care management. As a result, careful attention with respiratory function is essential in these patients, especially during weaning of mechanical ventilation or in patients with borderline respiratory function, like those neuromuscular disorders.
4. **Refer patient and family to MH Testing Center for contracture or DNA testing[134-135].**

4.7 Perioperative management of liver transplantation candidates susceptible to malignant hyperthermia

Patients at risk for MH may be identified based on data collected on preoperative evaluation, like clinical symptoms, presence of muscular disease and personal and family history of previous anesthetics (see preoperative evaluation section). CHCT is indicated in patients preoperatively deemed at risk for MH, postoperatively in patients with a typical MH crisis during liver transplantation and the relatives of the patients with a positive CHCT. Anesthesia for liver transplantation in patients with some risk factors for MH must be free of succinylcholine and halogenated inhalational agents. Additionally, dantrolene must be immediately available in the operating room. Besides this, some precautions have to be taken with the anesthesia machine. Avoidance of succinylcholine is an easy to deal issue. However, avoidance of vapor anesthetics is more challenging because anesthesia machines retain anesthetic vapors long after discontinuation. Instructions for clearing residual anesthetic gases include removal or disabling of vaporizers, flushing the machine with a fresh gas flow rate more than 10 $L.min^{-1}$ using the ventilator for at least 20 min, and replacement of the fresh gas outlet hose, carbon dioxide absorbent, and anesthesia circuit. The goal is to decrease the residual anesthetic vapor concentration within the breathing circuit. These precautions represent the standard of care for the management of MH-susceptible patients. These instructions for purging anesthetic gases were derived from studies designed to optimize gas clearance in older generation machines. Modern anesthesia workstations are more complex and contain more gas absorbing materials. The current guidelines are inadequate to prepare newer generation workstations, which require more time for purging anesthetic gases, autoclaving or replacement of parts, and modifications to the gas delivery system. As a result, institutions must develop protocols that individualize their own new generation anesthesia machines[136].

5. Conclusion

Malignant hyperthermia is an inherited pharmacogenetic disorder of the skeletal muscle. It can be triggered by any halogenated inhalational agent or by succinylcholine. A mutation on the Ryanodine Receptor (RyR) may be the main causative factor, resulting in a defect of intracellular Ca^{2+} homeostasis. Besides muscle tissue, RyR's are present in hepatocytes. Dantrolene is the only available treatment for MH and is a unique muscle relaxant that interferes with excitation-contraction coupling by reducing the concentration of myoplasmic calcium. This drug seems to be hepatotoxic, although the exact mechanism is unclear. Preoperative evaluation of liver transplant candidates by anesthesiologist is critical to identify patients at risk or susceptible to MH. There is a significant overlap between the MH clinical manifestations and the usual physiological behavior during liver transplantation, and early clinical diagnosis is a challenge. Sustained and progressive increases in $EtCO_2$, despite checking and solving other possible causes, should raise suspicion of MH. Treatment should be aimed towards discontinuing triggering agents, administering the antidote and instituting supportive measures. Due to its possible hepatotoxicity, dantrolene should be used in doses lower than usual and for shorter periods of time.

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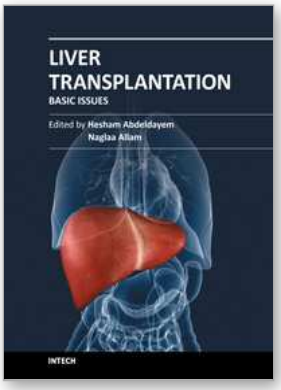

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This book covers a wide spectrum of topics including history of liver transplantation, ischemia-reperfusion injury, immunology of liver transplantation, viral hepatitis and liver transplantation, other indications for liver transplantation, prognostic factors and perioperative period. The authors of the chapters are experts in their respective fields. They are proponents covering different aspects of liver transplantation and come from many centers across the world. The interdisciplinary approach and the authority of the contributors resulted in a valuable reference to anyone interested in developing a global view in liver transplantation including medical students, residents, fellows, nurses, and practicing physicians and surgeons as well as researchers in the field of liver transplantation.

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