Malignant Hyperthermia in a 2-Year-Old Following General Anesthesia: A Rare Case Report from Nepal

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ABSTRACT

Malignant hyperthermia (MH) is a pharmacogenetic disorder triggered by inhaled anesthetics or depolarizing muscle relaxants, leading to a catabolic state of skeletal muscle. Key clinical signs include tachycardia, hyperthermia, muscle rigidity, hypercapnia, acidosis, rhabdomyolysis, hyperkalemia, and renal failure. Without prompt and specific treatment, the mortality rate can reach 80%. However, early recognition and the administration of dantrolene sodium can reduce this rate to 5%. This article presents the case of a 2-year-old male patient admitted to the Intensive Care Unit with suspected MH following surgery for a crush injury to his left hand, which was performed under general anesthesia.

KEY WORDS

Dantrolene; Inhaled anesthetics; Isoflurane; Malignant Hyperthermia

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INTRODUCTION

Malignant hyperthermia (MH) is an inherited disorder of skeletal muscle characterized by an anesthesia-related hypermetabolic state. The pathophysiological mechanism relates to mutations in the RYR1, CACNA1S, and STAC3 genes responsible for regulating intracellular calcium homeostasis. [1] In susceptible individuals, a triggering stimulus causes hyperactivation of receptors, leading to uncontrolled calcium release from the endoplasmic reticulum (ER) of muscle cells. This results in elevated intracytoplasmic calcium, which activates enzymes that deplete ATP and increase oxygen consumption. Consequently, anaerobic metabolism is heightened, producing excessive heat and lactic acidosis.

The incidence of malignant hyperthermia during general anesthesia is estimated to range from 1 in 5,000 to 1 in 100,000 cases. [2] Key clinical features include tachycardia, hypercapnia, arrhythmias, muscle rigidity, cyanosis, metabolic and respiratory acidosis, lactic acidosis, hyperthermia, coagulopathy, and rhabdomyolysis.

Diagnosis is primarily clinical, with confirmation achieved through the halothane-caffeine contracture test (HCT) or genetic study of associated mutations; the gold standard remains the caffeine-halothane contracture test on a live muscle biopsy sample. However, clinical diagnostic criteria, laboratory findings, and genetic tests can provide supporting evidence. [3]

Without treatment, mortality from MH reaches approximately 80%. Still, with timely supportive measures and effective treatment, it drops to 5%. Treatment includes discontinuing halogenated agents, hyperventilation with 100% O_2, and administering dantrolene sodium, a muscle relaxant that inhibits calcium release from the ER by targeting RYR1. [4, 5] Dantrolene, the only clinically effective treatment for malignant hyperthermia, acts as a ryanodine receptor antagonist, reducing abnormal calcium release from the sarcoplasmic reticulum. Unfortunately, this drug is not available in Nepal, highlighting the challenges in managing MH when diagnostic and therapeutic resources are limited.

CASE DETAIL

A 2-year-old male was referred from a peripheral center after sustaining an accidental crush injury to his left hand in a mill machine. A 3x2x2 cm laceration was noted on the radial side of the volar aspect of the left hand, extending to the ulnar side. Additionally, near-total amputation of the left ring finger, with injuries to the radial artery, median nerve, and flexor carpi radialis (FCR), was found. The patient was planned for emergency surgery. Pre-anesthetic assessment revealed normal findings, and there was no family history of adverse anesthetic events. Initial systemic examination and laboratory investigations were unremarkable. Upon arrival, the patient had a respiratory rate of 28 breaths per minute, oxygen saturation of 100% on 5 L/min via facemask, a heart rate of 110 beats per minute, blood pressure of 90/50 mmHg, and a temperature of 99°F. An intravenous line was secured, and the patient was intubated with a size 4 endotracheal tube.

INTRAOPERATIVE MANAGEMENT:

In the operating room, anesthesia was induced with intravenous propofol (2 mg/kg) for sedation, fentanyl (2 mcg/kg) for analgesia, and vecuronium (0.5 mg/kg) as a paralytic agent. Maintenance was achieved with isoflurane at 1.5 MAC. The patient was continuously monitored using an electrocardiogram (ECG), non-invasive blood pressure (NIBP), oxygen saturation (SpO_2), and end-tidal carbon dioxide ($EtCO_2$). Fifteen minutes into surgery, a sudden rise in $EtCO_2$ to 65 mmHg and an increase in heart rate up to 140 bpm were documented. The endotracheal tube placement was verified, and after confirming no issues with the breathing circuit, ventilation was assisted to maintain normal $EtCO_2$ levels. However, $EtCO_2$ continued to rise, reaching 90 mmHg, despite controlled ventilation and adequate muscle relaxation. An HME filter was removed to reduce dead space, and an arterial line was secured. The patient's body temperature escalated to 40.4°C, accompanied by tachycardia (heart rate = 170/min) and muscle rigidity in both upper and lower limbs. Active cooling measures were initiated, including intravenous ice-cold saline and irrigation through a Ryle's tube and bladder catheter. Ice packs, cold towels, and an ice-cooled drip were applied to facilitate conductive heat loss and control rising temperatures.

Ward/Value	Pre-Op	Intra-Op	Post-Op	6hrs Post-Op	12hrs Post-Op	24hrs Post-Op	48hrs Post-Op
TLC	11,410	N/A	9310	6230	6230	4330	N/A
Hemoglobin	10.6	12	10	12	12	9.7	N/A
Platelets	336,000	N/A	181,000	50,000	50,000	50,000	45,000
Temperature	37	40.8	N/A	39	39	41	40
Sodium (Na+)	142	144	139	N/A	N/A	146	156
Potassium (K+)	4.5	5.9	4.9	N/A	N/A	4.3	7
Urea	26	N/A	94	149	149	147	N/A
Creatinine	0.48	N/A	1.4	2.7	2.7	2.8	4.6
INR	1.02	N/A	N/A	2	2	2.6	3.5
PH	N/A	6.9	7.2	N/A	N/A	7.02	7.01
PaCo2	N/A	87	78	N/A	N/A	84	82
HCo3	N/A	15	18	N/A	N/A	17	14
Lactate	N/A	2.7	6.8	4	4	7	11

Table 1: Lab parameters values, TLC-total WBC Count, N/A-Not Available

FINDINGS AND MANAGEMENT

Arterial blood gas (ABG) analysis revealed severe metabolic acidosis, with a pH of 6.90, $PaCO_2$ of 80 mmHg, HCO_3 of 12 mmol/L, and elevated lactate levels of 8 mmol/L, indicating significant lactic acidosis. Subsequently, a bolus dose of 50 mEq of sodium bicarbonate was administered intravenously, followed by a maintenance dose of 10 mEq/hr to stabilize the acid-base balance. Urine appeared dark brown and remained low throughout the procedure despite adequate fluid resuscitation with crystalloids. The patient's heart rate escalated, blood pressure dropped to 40/26 mmHg, and sudden ventricular tachycardia followed by ventricular fibrillation occurred. Manual chest compressions were immediately initiated along with one episode of defibrillation using 260J, which resulted in the return of spontaneous circulation (ROSC). Noradrenaline infusion was initiated at 0.03–0.3 mcg/kg/min, titrated to maintain a mean arterial pressure of 65 mmHg. A central venous line (5 Fr) was inserted via the right internal jugular vein (IJV). A high suspicion of malignant hyperthermia (MH) was established. The total MH scoring was 48 with an MH rank of 5.

Clinical Finding (Maximum Score) 1	Manifestation 2	Score in Our Case
Respiratory acidosis (15)	End-tidal CO2 >55 mm Hg, PaCO2 >60 mm Hg	15
Cardiac involvement (3)	Unexplained sinus tachycardia, ventricular tachycardia, or ventricular fibrillation	3
Metabolic acidosis (10)	Base deficit >8 mEq/L, pH <7.25	10
Muscle rigidity (15)	Generalized rigidity, severe masseter muscle rigidity	0
Muscle breakdown (15)	Serum creatine kinase concentration >20,000/L units, cola-colored urine, excess myoglobin in urine or serum, plasma (K+) >6 mEq/L	10
Temperature increase (15)	Rapidly increasing temperature, T >38.8° C	10
Other	Rapid reversal of MH signs with dantrolene (score=5), elevated resting serum creatine kinase concentration (score=10)	0
Family history (15)	Consistent with autosomal dominant inheritance	0

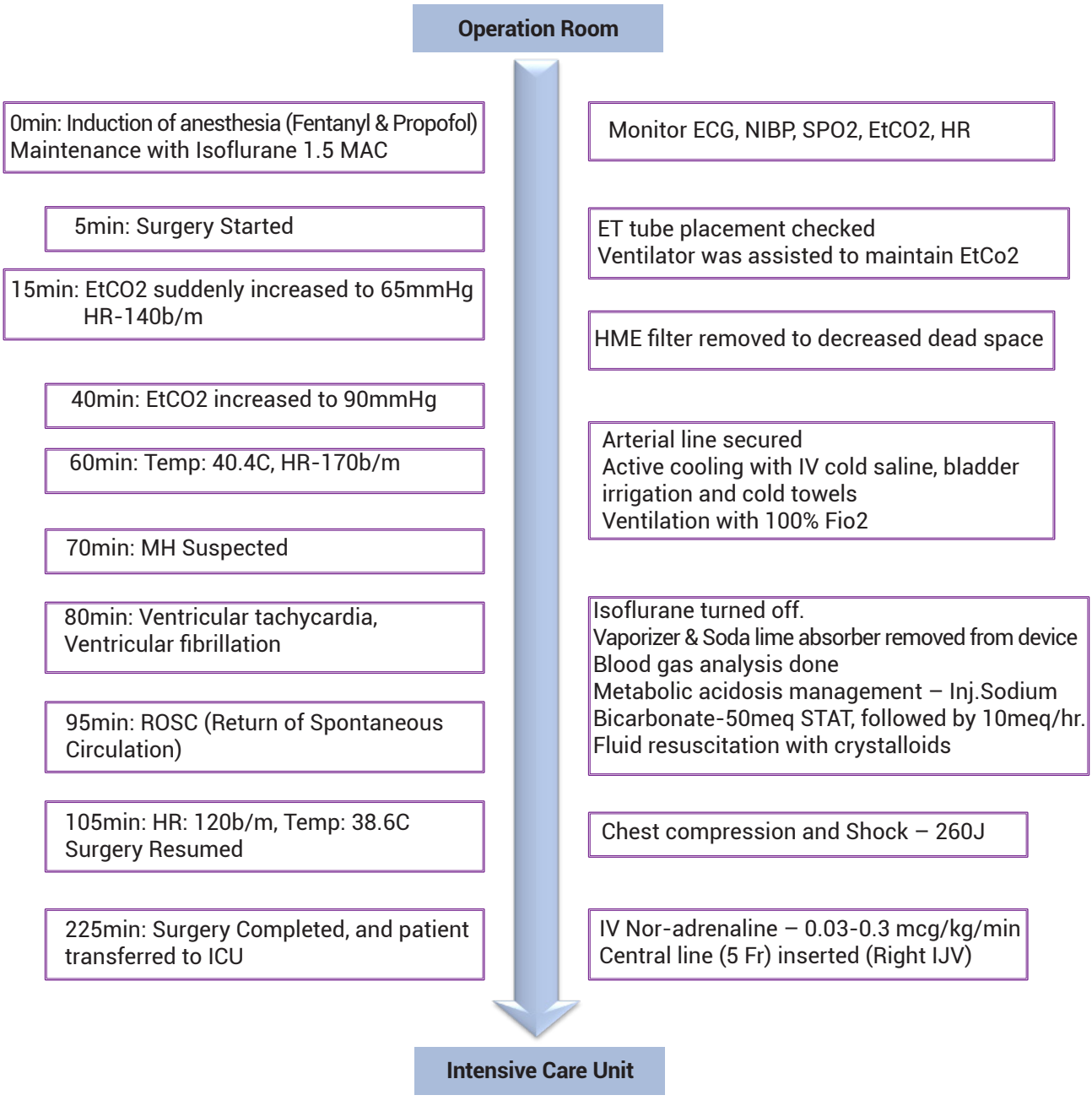
Table 2: Criteria Used in the Clinical Grading Scale For MH, adapted from Larach et al.[6] and Rosenberg et al.[2].

Raw Score Range	MH Rank	Description of Likelihood of MH
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

Table 3: MH Clinical Grading Scale Score Interpretation, adapted from Larach et al.[6] and Rosenberg et al.[2].

Based on the clinical suspicion and MH score, the offending agent, isoflurane, was immediately discontinued. The vaporizer and soda lime absorber were removed, and the closed circuit system was changed. Anesthesia was maintained with propofol infusion for the remainder of the case. However, dantrolene could not be administered due to its unavailability in our center, necessitating continued cooling maneuvers and supportive measures. Subsequently, the patient's heart rate and temperature began to decrease. The surgery was resumed, involving exploration, debridement, transection and ligation of the radial artery, followed by K-wire fixation. The total surgery duration was 3.5 hours. Post-operatively, the patient was transferred to the Intensive Care Unit (ICU) for further management, during which sedation (propofol and fentanyl) and paralysis (vecuronium) were maintained under controlled mechanical ventilation.

Figure 1: Flowchart of Timeline of patient from Operating Room to ICU



POST-OPERATIVE COURSE

In the ICU, the patient was closely monitored with periodic ABG analysis, renal function tests (RFT), and creatine phosphokinase (CPK) levels checked every eight hours. Urine output was targeted to maintain at 2-2.5 mL/kg/hour to support renal function. Broad-spectrum antibiotics (meropenem and flucloxacillin) were initiated. Additionally, vitamin K, dexamethasone, and paracetamol were administered for supportive care. The patient received two pints of fresh frozen plasma (FFP) and three pints of platelet-rich plasma (PRP) to manage coagulopathy. Several critical parameters demonstrated improvement in the ICU. Metabolic acidosis began to resolve, with pH levels improving to 7.2, reductions in PaCO to 50 mmHg, and an improvement in the base deficit. Urine output normalized to 2 mL/kg/hour, and urine color improved from dark brown to clear, indicating recovery from myoglobinuria. Respiratory acidosis improved with optimized ventilatory settings while hyperkalemia was effectively corrected. Cardiac arrhythmias, including ventricular tachycardia (VT) and ventricular fibrillation (VF), were managed successfully, stabilizing the patient's cardiac rhythm.

Despite these improvements, challenges persisted. Hypotension remained refractory, requiring high-dose inotropic support. The fever persisted and worsened despite aggressive cooling interventions. Additionally, muscle rigidity continued, indicating ongoing pathological muscle activity that could not be fully managed in the absence of dantrolene.

Outcome:

On the second day, the patient developed disseminated intravascular coagulation (DIC), evidenced by a prolonged INR of 3.5, low fibrinogen levels, and elevated D-dimer, accompanied by acute renal shutdown with anuria and rising creatinine levels (4.6 mg/dL), along with refractory hypotension despite escalating doses of inotropes. The patient exhibited a further decline in platelet count (45,000/µL), persistent metabolic acidosis (pH 7.01, base deficit -20), and worsening hyperkalemia (7 mEq/L). Despite intensive management and resuscitative efforts, patient landed into cardiac arrest. Tragically, the patient could not be revived.

Discussion

Malignant hyperthermia (MH) is a potentially fatal genetic disorder characterized by excessive muscle metabolism triggered by inhaled anesthetics. [7] This pharmacogenetic alteration manifests as a hypermetabolic response after exposure to volatile anesthetics and muscle relaxants such as succinylcholine. [8] Our case involved exposure to the inhaled anesthetic agent isoflurane, which likely triggered the hypermetabolic state.

While MH usually occurs in genetically predisposed individuals, there are often no phenotypic abnormalities before anesthesia, making diagnosis challenging without prior exposure or specific testing. In this case, the patient had no known family history of MH, nor had any genetic testing been performed. [9]

The incidence of MH ranges from 1/50,000 to 1/250,000 in adults and 1/15,000 in children, with variations in males and females. [10, 11] The incidence in Nepal is undocumented, making this case potentially the first reported incidence in the country.

MH can present with non-specific symptoms of a hypermetabolic reaction, which can be fatal without prompt treatment with dantrolene sodium. Common initial symptoms include hypercarbia (30.7%), masseter spasm (24.8%), and sinus tachycardia (21.1%). [12] An unexplained increase in ETCO is often uncontrollable via ventilatory adjustments, present in 90% of cases. [13] Our patient demonstrated hypercarbia, as evidenced by elevated EtCO levels that persisted despite mechanical ventilation adjustments.

In susceptible individuals, the triggering stimulus causes hyperactivation of receptors leading to uncontrolled calcium release from the ER of muscle cells, resulting in increased intracytoplasmic calcium and enzymatic activation that raises anaerobic metabolism, heat production, and lactic acidosis. Our patient exhibited these pathophysiological changes, including hypercarbia, hyperthermia, metabolic acidosis, and signs of rhabdomyolysis consistent with uncontrolled calcium release.

Diagnosis should be confirmed using the Clinical Grading Scale (CSG) for MH developed by Larach. [6] A score above 50 classifies the episode as almost certainly malignant hyperthermia. In this case, the total MH score was 48, corresponding to an MH rank of 5, classifying the episode as "very likely" malignant hyperthermia. Immediate cessation of stimulants is critical, while anesthesia should continue with alternative drugs as needed.

Administration of stimulants should be stopped immediately, and anesthesia should be continued with other drugs, such as opioids, intravenous hypnotics, and non-depolarizing relaxants (Cisatracurium) if needed.

Diagnosing MH postoperatively is particularly challenging, typically based on clinical signs observed during the crisis, later confirmed through muscle biopsy test. [14] In Nepal, HCT testing is not available, and this patient had no family history of malignant hyperthermia that would support genetic susceptibility.

Dantrolene, a muscle relaxant, targets the RYR1 receptor to reduce intracellular calcium availability, alleviating excessive skeletal muscle contractions. The recommended initial intravenous bolus is 2.5 mg/kg, with repeat dosing every

3–5 minutes until symptom control is achieved, followed by a maintenance dose of 1 mg/kg every 6 hours. Dantrolene has been shown to reduce mortality to less than 10%. [15] However, in this case, it was unavailable at our center, and neither the in vitro contracture test nor dantrolene is currently available in Nepal. Limited use, high cost, and storage requirements hinder its accessibility. Although it can be imported under license, it was not accessible at our hospital. The patient was managed symptomatically with active cooling, hemodynamic support, and treatments addressing hyperthermia, hyperkalemia, acidosis, renal failure, and arrhythmias.

Symptoms such as tachycardia and fever must be differentiated from conditions such as sepsis, febrile nonhemolytic transfusion reactions, or postsurgical pain. Blood cultures and inflammatory markers did not indicate infection, ruling out bacteremia. There was no history of recent blood transfusion, excluding febrile nonhemolytic transfusion reactions, and the nature of the symptoms did not align with typical postsurgical pain patterns. Other differential diagnoses, such as muscle diseases, thyroid toxicity, pheochromocytoma, and substance withdrawal or overdose, were excluded based on a thorough preoperative evaluation, which included normal thyroid function tests, an absence of clinical features indicative of endocrine disorders, and no history of substance abuse.

Without confirmation via the caffeine-halothane contracture test, the diagnosis of malignant hyperthermia in this patient remains uncertain. This case emphasizes the need for enhanced diagnostic accuracy and awareness of MH, particularly in contexts with uncertain health insurance coverage, where a serious condition could significantly impact the patient's health record.

Conclusion

Effective management of malignant hyperthermia depends on the anesthesiology team's ability to rapidly recognize the condition, alongside timely access to an adequate supply of dantrolene and the skills to administer it correctly. Due to the rarity of MH, many anesthesiologists may never encounter a case during their careers, underscoring the importance of continuous education, simulation training, and preparedness to manage this life-threatening emergency.

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