

Case Report

Full recovery without complications by early intervention for malignant hyperthermia that occurred during general anesthesia: A case series of two infants with facial anomaly

ABSTRACT

Introduction: Malignant hyperthermia (MH) is a rare and life-threatening condition characterized by muscle rigidity, hypermetabolism, and other symptoms triggered by certain anesthetic agents. It is linked to abnormal calcium release in skeletal muscles, often associated with genetic susceptibility or musculoskeletal disorders like scoliosis. Early recognition of MH symptoms, including muscle rigidity, tachycardia, and acidosis, is crucial for prompt intervention. Here, we report two infants of successful recovery following early MH intervention during general anesthesia.

Case report 1: A 26-month-old male with cleft hard palate, prematurity history, and chromosomal anomaly underwent palatoplasty. Anesthesia was induced with thiopental, fentanyl, and rocuronium, followed by sevoflurane/remifentanyl maintenance. During surgery, heart rate increased suddenly with hypercapnia. Hyperthermia of 39.5°C, suggestive of MH, arose. Sevoflurane was discontinued, cooling measures were initiated, and dantrolene was administered 2 hours later. Temperature normalized, ventilation improved, and extubation succeeded. Creatine phosphokinase (CPK) level was briefly elevated to 1062 IU/L but returned to normal. Despite being suspected of having MH, the patient was discharged without any complications after one day of intensive care unit (ICU) care.

Case report 2: A 5-month-old female with cleft lip underwent cleft lip repair surgery. She had underlying congenital heart diseases. During anesthesia, sudden hypercapnia and hyperthermia indicated potential MH. Sevoflurane was discontinued, ketamine, and fentanyl were used to maintain anesthesia. Dantrolene was administered after 80 min, cooling the patient and stabilizing hypercapnia. Surgery ended 110 min after the sudden hyperthermia. In the ICU, metabolic acidosis was managed with sodium bicarbonate. Postoperative muscle enzyme, such as CPK, levels slightly rose, then normalized. Stable recovery led to discharge after 8 days without complications.

Conclusion: In both cases, MH occurred in infants with facial anomalies and early interventions, such as dantrolene administration, for suspected MH was done. Early suspicion, supported by diagnostic tools like MH Clinical Grading Scale, is vital.

Keywords: Malignant hyperthermia, infant, genetic defect, dantrolene

1. INTRODUCTION

Malignant hyperthermia (MH) is a rare, life-threatening hypermetabolic state with muscle rigidity, hyperthermia, hypercapnia, hypoxemia, tachycardia, acidosis, hyperkalemia followed by using MH triggering agents. These clinical features are related to uncontrolled calcium release from sarcoplasmic reticulum in skeletal muscle cells leading to activation of muscle contractile elements and hypermetabolism [1,2]. Volatile anesthetics and/or the depolarizing muscle relaxant, succinylcholine may act as a triggering agent during general anesthesia.

A family history, if present, particularly in a first-degree relative, is a strong indicator of MH susceptibility [3]. MH susceptible individuals are often associated with underlying musculoskeletal disorders/signs such as scoliosis and central core disease, multi-minicore disease, King-Denborough syndrome, etc.[4,5]. Nevertheless, since all MH patients does not exhibit such comorbidity, anesthesiologists should consider the possibility of MH when presenting early signs of MH such as generalized muscular rigidity, tachycardia, hypercapnia, hypoxia, combined metabolic-respiratory acidosis after using the triggering agent, and early intervention for MH treatment should be provided if needed[4].

We notice the importance of early recognition and treatment of MH patients by reporting the following two cases of complete recovery without complications by early intervention for MH that occurred during general anesthesia.

2. CASE REPORT 1

A 26-month-old male with cleft hard palate decided to undergo elective palatoplasty. The patient, of Asian descent, was 75cm tall and weighed 8.5kg, exhibiting delayed growth for approximately fifteen months.

He was born as a premature infant at 31 weeks and 5 days gestation due to maternal preeclampsia, weighing 1.5kg at birth. At 1 min after birth, his APGAR score was 6, and at 2 min and 30 sec after birth, his arterial oxygen saturation by pulse oximetry (SpO₂) was 49%, leading to the application of positive end expiratory pressure (PEEP). At 5 min after birth, his APGAR score improved to 8, and SpO₂ was maintained above 90%. He received treatment in the neonatal intensive care unit (ICU), but did not experience respiratory distress and had smooth feeding, leading to the discharge from the hospital at 3 months of age.

He has underlying conditions of patent foramen ovale and shows an inversion of the 9th chromosome, inv(9), based on chromosome study. The occurrence of inv(9), a relatively common heteromorphism, is thought to be common in the general population, with an estimated prevalence of 1-3% of chromosomes [6]. While it is mostly considered a normal variant, less than 10% have been reported to be associated with infertility or accompanying physical abnormalities such as polydactyly, club foot, microtia, deafness, asymmetric face, intrauterine growth restriction, cardiomyopathy, and cleft palate.

Additionally, at birth, ventricle dilation and increased periventricular echogenicity were observed on ultrasound. However, no abnormal findings were noted on a brain ultrasound performed at 2 months of age. About these conditions, the consultation by a pediatric cardiologist, pulmonologist and neurologist was done for preoperative evaluation. Perioperative cardiovascular, pulmonary, and neurologic risk was low considering his condition.

He was born with a cleft lip and cleft palate. At the age of 5 months, he underwent cheiloplasty for the cleft lip, and he was scheduled to undergo palatoplasty for the cleft

palate. He had experienced two uneventful anesthesia before this palatoplasty. One was performed for the cheiloplasty, which was done at our hospital using thiopental sodium, rocuronium, sevoflurane and fentanyl. The other one was performed for the stitch out, which was done at our hospital, also using thiopental sodium, rocuronium sevoflurane and fentanyl.

After being admitted to the operation room, EKG, noninvasive blood pressure, and SpO₂ were monitored and induction with thiopental sodium, fentanyl and rocuronium was achieved. Sevoflurane was selected as a maintenance agent. During the early stages of the surgery, the patient's heart rate was maintained at 120-130 bpm, with a tidal volume (TV) of 90mL and a respiratory rate (RR) of 24, resulting in an end-tidal CO₂(ETCO₂) level of approximately 45mmHg.

However, at 2 hours from the start of the anesthesia induction, the heart rate suddenly increased to 160 bpm. Despite the administration of two doses of 10 mcg of fentanyl, there was no significant response. The ETCO₂ level gradually increased, reaching around 50-55mmHg even with a TV 90mL and a RR of 30. After 4 hours and 50 min from induction, the patient's body temperature had risen abruptly to 39.5°C, 3.5 degree higher compared to body temperature at induction and marked hypercapnia (ETCO₂ = 80mmHg) occurred.

To manage the hypercapnia, we changed the soda lime and maintained hyperventilation and high inspired oxygen fraction (TV 90mL, RR 30/min, FiO₂ 1.0). Cold saline hydration and IV paracetamol 1g was given through the peripheral line and alcohol swabs were applied to the patient's body to cool down the body temperature. An arterial line was inserted into the left radial artery for continuous blood pressure monitoring and frequent arterial blood gas analysis.

The prognosis of an MH crisis depends on how soon MH is suspected and how rapidly appropriate treatment is initiated [7]. We considered his high body temperature, hypercapnia, tachycardia and muscular rigidity as early signs of MH. After MH was suspected, at 4 hours and 50 min after induction, we immediately discontinued sevoflurane inhalation. Following the discontinuation of sevoflurane, a decrease in body temperature from 39.5 to 37.3°C was observed. At that time of detection of MH, the operation was already over, so there was no need to switch to intravenous anesthesia. Since there was no dantrolene in our hospital, it could not be administered to the patient in the operating room.

The patient was sent to the ICU after the surgery while remaining intubated, and manual ventilation using an Ambu bag was provided during the transfer. After arriving in the ICU arterial blood gas analysis was immediately obtained (pH 7.37, pCO₂ 31mmHg, pO₂ 215mmHg, HCO₃⁻ 17.9mmHg, Base excess -7.4 mmol/L at FiO₂ 0.4).

Dantrolene was delivered from another hospital 2 hours away from our hospital. After 120 min had passed since the sudden increase in body temperature, dantrolene 25 mg, mixed with normal saline 100mL was given with 25mL/hr in the ICU. Following the administration of dantrolene, the patient's body temperature dropped from 37.6 to 36.7°C. Also, spontaneous respiration was observed with no signs of tachypnea and hypercapnia. As a result, the patient underwent extubation 6 hours after admission to the ICU. The patient stayed overnight to monitor as MH might lead to rhabdomyolysis, acidosis, acute kidney injury or circulatory collapse which is a life-threatening course requiring continuous renal replacement therapy. The next day, feeding was initiated.

His muscle and liver enzymes were normal except creatine phosphokinase (CPK) during hospital stay. On postoperative day (POD) 1, the patient exhibited an elevation in CPK levels, with a peak value of 1062 IU/L. By the next day, the CPK level had returned to

normal, measuring 345 IU/L. Fortunately, clinical signs of MH such hyperkalemia, combined metabolic-respiratory acidosis, rhabdomyolysis, arrhythmia, and circulatory failure were not present in this case.

The patient was transferred from the ICU to the general ward the day after surgery and recovered completely, and then he was discharged two days after surgery with no complication. The patient was followed 5 days after discharge to inform the risk of general anesthesia using a triggering agent and double-check his family history or any overlooked clinical manifestation associated with underlying musculoskeletal disease. The patient's parents refused further evaluation including genetic test due to the costs.

3. CASE REPORT 2

A 5-month-old female infant with alveolar cleft lip was posted to receive cleft lip repair surgery. The patient, of Asian descent, exhibited delayed growth for approximately two months, with a height of 61.7cm and a weight of 6kg.

The patient was born small for gestational age, weighing 1.81kg at 36 weeks and 6 days of gestation, because of maternal preeclampsia. At 1 minute after birth, her APGAR score was 9, and at 5 minutes after birth, her APGAR score was improved to 10, and SpO₂ level was maintained above 90% without the application of oxygen. She stayed in the neonatal ICU for 10 days.

The patient was born with a perimembranous-type ventricular septal defect (VSD), atrial septal defect (ASD), and cor triatriatum. A consultation with the pediatric cardiology and pulmonology department concluded that there were no significant concerns regarding the surgery. The patient had not experienced general anesthesia previously.

After being admitted to the operation room, EKG, noninvasive blood pressure, SpO₂, and body temperature were monitored. Glycopyrrolate 0.02mg and dexamethasone 1 mg was given to the patient as a premedication. An induction with sevoflurane, fentanyl and rocuronium was achieved. Sevoflurane was used as a maintenance agent. During the early stages of the surgery, the patient's heart rate was maintained at 130-140 bpm, with a peak inspiratory pressure of 13mmHg, RR of 26, resulting in an ETCO₂ level of approximately 45mmHg.

During the surgery, despite increasing the RR setting to 30, there was a continuous upward trend in the patient's ETCO₂ level. After 2 hours from the start of the induction, the patient's ETCO₂ level increased to 52mmHg and body temperature rose to 37.0°C. Despite turning off the warming machine, the patient's body temperature continued to rise abruptly, reaching 37.6°C. We considered high body temperature, hypercapnia as an early sign of MH. So, we decided to discontinue the administration of sevoflurane and then applied 100% oxygen to the patient. Instead, we administered ketamine 3 to 5mg and fentanyl 5 mcg at a time to maintain anesthesia since the surgery was ongoing. Fortunately, immediately after the discontinuation of anesthesia gas, a decrease in body temperature to 35.5°C was observed.

After 80 min following the abrupt rise in body temperature, dantrolene was delivered from another hospital. Then dantrolene 15mg was mixed with 100mL of normal saline and was given to the patient at a rate of 25mL/hr in the operating room. Following the administration of dantrolene, the ETCO₂ level dropped from 50 to 33mmHg.

Although there was no sign of an abrupt increase of heart rate, it generally showed an increasing trend, and it had increased up to 155 bpm 3 hours after induction. After the administration of dantrolene, the surgery was concluded 30 min later. Despite the patient's stable vital signs, she did not regain spontaneous respiration then. So, we decided to transfer the patient to the ICU without extubation.

Upon admission to the ICU, immediate venous blood gas analysis was performed, which revealed the presence of respiratory acidosis (pH 7.16, pCO₂ 60mmHg, pO₂ 21mmHg, HCO₃⁻ 21.4mmHg, Base excess -3.9 mmol/L at FiO₂ 0.4). After the administration of sodium bicarbonate 840mg, a follow-up venous blood gas analysis demonstrated an improvement in the previous acidosis. (pH 7.38, pCO₂ 43mmHg, pO₂ 36mmHg, HCO₃⁻ 25.4mmHg, Base excess 0.3 mmol/L at FiO₂ 0.4)

The postoperative laboratory tests conducted in the ICU showed a slight increase in muscle enzyme levels as follows: The lactate dehydrogenase (LDH) was measured at 740 IU/L, creatine kinase-myocardial band (CK-MB) at 10.5ng/mL, and CPK at 295 IU/L. The myoglobin level was 31ng/mL and the potassium level was at 4.8mmol/L, both were within normal range.

During the follow-up laboratory tests, LDH, CPK, and CK-MB all gradually decreased and returned to the normal range. Throughout the ICU stay, there were no prominent findings indicating significant muscle destruction, such as a sudden increase in muscle enzyme, or hyperkalemia. The patient's vital signs also remained stable. Spontaneous respiration was observed with no signs of hypercapnia.

The patient was extubated and transferred from the ICU to the general ward the day after surgery. Eight days after the surgery, the patient was discharged without any complications.

4. DISCUSSION

In the first case, the patient had previously undergone two times of general anesthesia without any complications. When comparing the previous records, the same anesthetic agents were used, and the only difference with the current anesthesia was the anesthesia duration. In the previous two times of anesthesia, the duration from the start to the end of anesthesia was 170 and 85 min, respectively. However, in the current anesthesia, it took 330 min until the termination of anesthesia, and the point at which a temperature rise was observed occurred 290 min after the induction.

Although the initial clinical signs of MH typically occur within one hour of anesthesia induction, the onset of MH can occur at any time during the administration of triggering agents [8]. Therefore, we suggest that the longer the duration of anesthesia, the higher the risk of MH occurrence.

It is also noteworthy that MH can occur even in patients without an episode of MH in previous surgery [4,9]. It was difficult to suspect MH at first because the operation had been done without any anesthetic problems previously. However, MH can develop even after several trouble-free surgeries [4,9], so we should always be mindful of early intervention when there are clinical symptoms suspected of MH.

In both cases, patients were born via cesarean section due to maternal preeclampsia, and they were initially born with low birth weights of 1.5kg and 1.8kg, respectively. They both had a congenital anomaly, with one having a cleft palate with a cleft lip and the other having a cleft lip. Both patients underwent surgery for their respective conditions and then

experienced MH. One patient exhibited chromosomal abnormalities associated with physical anomaly, while the other had normal findings.

However, it should be noted that this testing method using PHA-stimulated T-lymphocyte culture, may not detect genetic defects, subtle structural abnormalities in chromosomes not observable under a microscope, or extremely rare chromosomal abnormalities. The RYR1 gene mutation is inherited in an autosomal recessive pattern and it is likely that their myopathy is mild and has minimal progression[7]. We suspect the patients might have predisposition of myopathy caused by RYR1 gene mutation and minimally affected resulting in no clinical symptoms. This RYR1 gene mutation results in functionally altered calcium channels causing uncontrolled release of calcium from the sarcoplasmic reticulum and MH crisis.

These case series are meaningful in that we should consider the possibility of MH with no MH-associating underlying diseases or family history of MH. During the pre-anesthetic interview and double check after discharge, we confirmed the patient had no clinical symptoms related to MH.

In these patients, some clinical features regarded as signs of MH were ambiguous to diagnose MH. But, only early management including dantrolene administration prevents the detrimental, life-threatening course and allows early recovery without permanent damage. We should not wait until the extremely high body temperature, urine color change or poor urine output that imply rhabdomyolysis or acute kidney injury. In both cases, there were no prominent findings suggesting significant muscle destruction, such as marked elevation of muscle enzymes or hyperkalemia.

According to MH Clinical Grading Scale, Case 1 patient scored 38 points, indicating a risk level of 5 (fairly likely), while Case 2 patient scored 33 points, corresponding to a risk level 4 (more than likely) [10]. As this scoring system is in many parts based on the subjective judgment of the anesthesiologist, it is important to suspect MH on an early basis. This could be attributed to the prompt measures taken to address the situation. If possible, in vitro contracture test or genetic test might be helpful to determine the patients' future anesthetic plans[1].

5. CONCLUSION

These case series shows an importance of early intervention for suspicious MH. One of the patients had experienced uneventful anesthesia twice. As there is no related underlying disease or family history, it was difficult to suspect whether the symptom was MH, but with MH in mind, early treatment was possible at an appropriate time after quick diagnosis. Prompt management, including dantrolene administration, is crucial to prevent severe complications. Early suspicion of MH is important, and scoring systems like the MH Clinical Grading Scale can support in risk assessment.

Also, both patients born with low birth weights and congenital anomalies underwent surgery and experienced MH. One patient had chromosomal abnormalities associated with a physical anomaly, while the other had normal findings. Genetic testing may not always detect underlying genetic defects. Further assessments, such as confirming the presence of RYR1 gene mutations, can assist in determining the anesthesia plan in the future for these patients.

CONSENT

Written consent obtained from the patient has been collected and preserved by the authors.

ETHICAL APPROVAL

It is not applicable.

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