Case Report

Malignant Hyperthermia in Postpartum Hemorrhagic Shock: A Case Report

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Malignant hyperthermia is a rare and lethal pharmacogenetic disorder. The susceptible individuals develop hypermetabolic responses when exposed to volatile anesthetic agents and Succinylcholine. The authors reported a Malignant hyperthermia case in postpartum hemorrhagic shock patient scheduled for emergency hysterectomy, eight hours after cesarean section for dichorionic diamniotic twins under spinal block. General anesthesia with endotracheal intubation with rapid sequence induction was performed. After having received Succinylcholine and Desflurane, the patient developed masseter spasm, hypercarbia, hyperthermia, rhabdomyolysis, cardiac arrhythmia, hypotension, and combined metabolic-respiratory acidosis. The clinical symptoms and signs of malignant hyperthermia in this patient were detected early. Symptomatic treatments and dantrolene were administered. The clinical signs improved, and the patient was discharged from intensive care unit on post-operative day 3. The molecular genetic testing was performed and the mutation in RYR1 gene was found in this patient, compatible with Malignant Hyperthermia. Being vigilant and early detection are the key elements for successful Malignant hyperthermia management.

Keywords: Malignant hyperthermia, Hyperthermia, Dantrolene, Hypercarbia

J Med Assoc Thai 2019;102(10):1132-5
Website: http://www.jmatonline.com
Received 31 May 2019 | Revised 1 Jul 2019 | Accepted 5 Jul 2019

Malignant hyperthermia (MH) is a lethal pharmacogenetic autosomal dominant disorder characterized by hypermetabolic responses when susceptible individuals are exposed to the triggering agents such as all volatile anesthetic agents (sevoflurane, isoflurane, or desflurane) and depolarizing muscle relaxant (succinylcholine). The mechanism is the triggering agents that induces prolonged opening of mutated Ryanodine receptor subtype 1 (RYR1), which lead to the uncontrolled release of intracellular calcium from the skeletal muscle sarcoplasmic reticulum. This results in ongoing muscle activation, presenting as rigidity leading to rhabdomyolysis and hyperkalemia, aerobic and anaerobic metabolism activation leading to hypoxia, lactic acidosis, hyperthermia, and hypercapnia. The prevalence of MH worldwide is between 1:10,000 and 1:250,000 and more frequently in males rather than females (2:1)[1]. Only 10.1% of MH cases were Asians[2]. In Thailand, there also have few reports of MH. The incidence of MH in Thailand was between 1:150,000 and 1:200,000[3]. The outcome of MH case depends on early detection and prompt treatments such as discontinuing any triggering agents, symptomatic treatments, and dantrolene administration for specific treatment.

The authors experienced an MH crisis case with successfully treatment and had no long-term sequelae because of early recognition, a good symptomatic treatment, and administering dantrolene drug.

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Case Report

A 40-year-old Thai female with no underlying disease, no known drug allergy, no history of surgery and anesthesia, and no history of family anesthetic adverse event was scheduled for cesarean section due to $G_2P_0A_1$ Gestational age 37^{+2} weeks with dichorionic diamniotic (DCDA) twins. She went on uneventful surgery under spinal anesthesia.

Eight hours post-operative, she developed post-

How to cite this article: Sumphaongern T, Nilyam P. Malignant Hyperthermia in Postpartum Hemorrhagic Shock: A Case Report. J Med Assoc Thai 2019;102:1132-5.

partum hemorrhage, estimated blood loss 2,000 ml unresponsive to high dose oxytocin and sulprostone (nalador). She was diagnosed as uterine atony with hemorrhagic shock grade II and was scheduled for emergency hysterectomy. Her body weight was 70 kilograms and her height was 170 centimeters. The preoperative vital signs were non-invasive blood pressure 92/45 mmHg, heart rate 115 bpm, respiratory rate 22 per minute, and pulse oximetry 100% on oxygen mask with bag 10 LPM. She was conscious, Glasgow coma scale 15 points. Her electrocardiogram was sinus tachycardia rate 110 to 120 bpm.

At operating room, the attending anesthesia resident planned to do general anesthesia with endotracheal intubation with rapid sequence induction and cricoid pressure. The patient was induced by thiopental 200 mg, ketamine 75 mg, fentanyl 50 mcg, and succinylcholine 125 mg intravenously. After induction, she developed masseter muscle spasm, but the endotracheal tube was successfully placed in one attempt with laryngeal view grade 3. The operation was going on and the patient was maintained with oxygen, air, desflurane, and atracurium. The attending anesthesia resident observed that the end-tidal CO_2 was 39 mmHg and the minute ventilation increased. After that, she felt that the patient had high body temperature then the temperature probe was placed in the oropharynx and measured about 37.0 degree Celsius. The temperature and end-tidal CO_2 were still rising. The temperature rose from 37.0 to 39.3-degree Celsius in one hour and the maximum end-tidal CO_2 was 58 mmHg. Hematuria was observed. The MH crisis was suspected.

The attending anesthesia resident called for help to the anesthesia staff and notified the obstetric surgeon to finish the case as soon as possible. Desflurane was shut off and 100% oxygen was administered. Total intravenous anesthesia (TIVA) with propofol infusion was used. The minute ventilation was increased three times normal for hyperventilation. The soda lime was exchange and the patient was cooled down by irrigating nasogastric tube with cold water and applying cold packs. Dantrolene drug and intensive care unit (ICU) reservation was requested. Then the electrocardiogram (ECG) changed to supraventricular tachycardia rate approximately 160 bpm with blood pressure 80/50 mmHg. The synchronized cardioversion 100 Jules was delivered, and the ECG turned to sinus rhythm rate 140 bpm.

The arterial line was inserted, and the blood sample was collected for measurement of serum electrolyte, creatinine phosphokinase (CPK), arterial

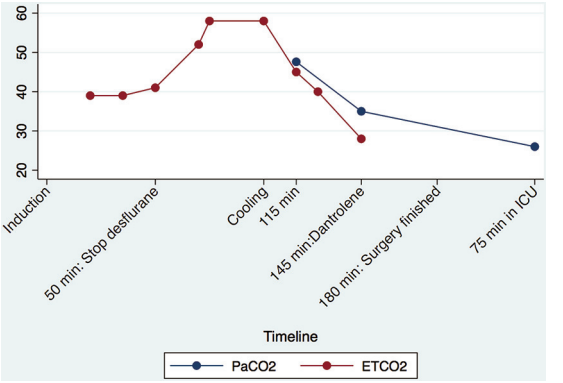

Figure 1. Timeline of $PaCO_2$ and $ETCO_2$ level.

blood gas, coagulation, complete blood count, and renal and hepatic functions. The arterial blood gas showed severe mixed metabolic and respiratory acidosis and hyperkalemia (pH 7.061, $PaCO_2$ 47.6 mmHg, PaO_2 243 mmHg, sodium 137 mmol/L, potassium 7.32 mmol/L, calcium 0.97 mg/dl, bicarbonate 11.9 mmol/L, base excess –17.1). Two doses of regular insulin 10 unit with 50% glucose 20 ml, 7.5% $NaHCO_3$ 100 ml and 10% calcium gluconate 4 gm intravenously was administered. Dantrolene 180 mg (2.5 mg/kg) was well mixed with 60 ml of sterile water per vial and was given intravenously. The crystalloid fluid and blood products were adequately infused. The temperature and end-tidal CO_2 began to decrease. The final temperature was 37.4-degree Celsius and end-tidal CO_2 was 28. The vital signs were more stable with norepinephrine (4:250) intravenously 25 ml/hour. The operation finished with operative time of about 02.40 hours, anesthetic time 03.15 hours, received crystalloid 4,130 ml, packed red cell 3 units, platelet concentration 6 units, urine output 400 ml (2 ml/kg/hour), and estimated blood loss was approximately 1,500 ml. The patient remained intubated and transferred to ICU for close monitoring.

Post-operative day 1, the dantrolene drug was continuously administered for 48 hours (1 mg/kg every 6 hours). The metabolic acidosis, electrolyte imbalance and rhabdomyolysis were observed and corrected. The timeline of $PaCO_2$, end-tidal CO_2, serum potassium, pH, creatinine, and creatinine phosphokinase level are showed in Figure 1, 2, and 3. Patient awoke with good consciousness. Post-operative day 2, dantrolene was tapered off and mechanical ventilator was weaned. Patient was discharged from the ICU on post-operative day 3. Genetic counselling and advice were settled and molecular genetic test for RYR1 mutation was done. The mutation in RYR1 gene was found in this

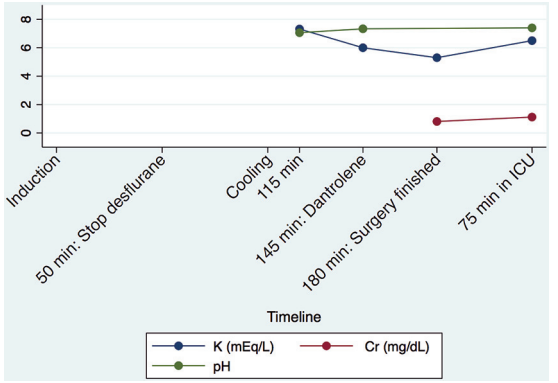

Figure 2. Timeline of serum potassium, pH, and creatinine level.

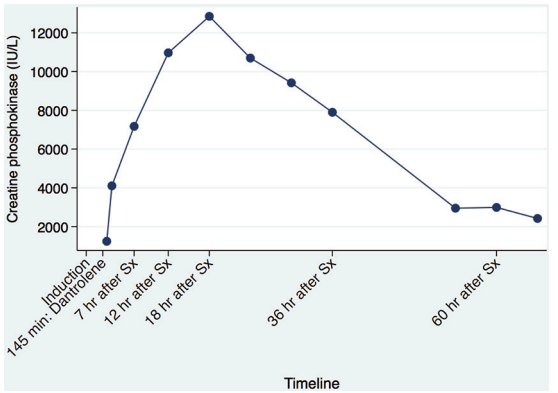

Figure 3. Timeline of Creatinine phosphokinase level.

patient, compatible with MH. The twins were advised to evaluate the DNA genetic testing. Due to minor abdominal wound infection treatment and wait for her twins' condition, patient was discharged from the hospital on post-operative day 14 with good conditions of herself and both of her sons.

Discussion

The diagnosis of MH was based on clinical presentation, genetic test, and contracture test. There were many clinical signs of MH shown in the present case. The early signs were masseter spasm, tachycardia, hypercapnia, and combined metabolic-respiratory acidosis. The late signs were hyperthermia, rhabdomyolysis, cardiac arrhythmia, and hypotension. Larach et al gave a clinical grading scale using clinical indicators for determining the MH raw score[4]. In the present patient, the clinical indicators are listed in Table 1. The total point was 86, which was more than 50 points, placed her into almost certain MH.

Halothane and caffeine contraction test have been

Table 1. Clinical indicators for calculating clinical grading MH raw scale in this patient

Clinical indicator	Points
Masseter spasm after succinylcholine administration	15
Serum K >6 mEq/L	3
$ETCO_2$ >55 mmHg with appropriately controlled ventilation	15
Inappropriate rapid increase in body temperature	15
Temperature >38.8 celsius	10
Inappropriate sinus tachycardia	3
Base excess > –8 mEq/L	10
Arterial pH <7.25	10
Rapid improvement after administration of dantrolene	5
Total	86

$ETCO_2$=end-tidal CO_2

the gold standard of the diagnosis MH susceptibility, but it needs invasive surgical muscle biopsy. Therefore, the molecular genetic testing is developed. The DNA analysis will be done from a small amount of blood sample of the patient. Both methods are approved for the diagnosis of MH. The contracture test will be done to confirm or exclude of MH when the molecular genetic test gives uncertain answer[5]. In the present case, the diagnosis was made by calculating the MH Raw Score and the confirmation of diagnosis was made by molecular genetic test.

MH is associated with some diseases, such as Duchenne muscular dystrophy, King-Denborough syndrome, periodic paralysis, myotonia congenita, and central core syndrome[6]. As a result, every patient undergoing general anesthesia should be asked about their underlying diseases, anesthetic history, and family anesthetic complications, especially history of MH-susceptible families. The present patient had no underlying disease and no family history of MH-susceptibility. She underwent general anesthesia for the first time, and she had MH crisis. MH can develop when exposed to triggering agents not only for the first time but can also develop in some patients with history of uneventful general anesthesia too[7]. Naive of anesthetic complications does not mean that MH will not occur.

Like in the present patient, MH crisis mostly developed after induction. When MH is suspected, the other possible causes should be considered and excluded, such as sepsis, thyrotoxicosis, and light anesthesia[8]. Sepsis might be in this patient, but the

pattern of fever and tachycardia were not compatible with the setting of acute and abrupt severe fever, tachycardia, and muscle rigidity after exposed to triggering agents. MH may also develop during peri-operative or post-operative periods and may be recurrent. Therefore, patient should be closely observed at least for the first 48 hours after being exposed to the inhalation of anesthetic agents and succinylcholine.

From thirty years ago, the mortality of MH decreased from 80% to less than 5% in 2006[1]. The keys of the successful treatment in MH crisis are awareness and early recognition, symptomatic treatment and specific treatment. In the present case, MH was suspected early, then the dantrolene and symptomatic treatments were administrated early. The symptomatic treatments include stopping the triggering agents, change to TIVA, 2 to 3 times normal minute volume hyperventilation with 100% oxygen, calling for help, decreasing body temperature, correcting of metabolic acidosis and hyperkalemia, keeping urine output at more than 2 ml/kg/hour, and proper cardiac dysrhythmias treatment.

The symptomatic drugs administering in MH crisis must be carefully prescribed. Calcium channel blocker is contraindicated in tachyarrhythmia treatment in MH because it can cause hyperkalemia when prescribed with dantrolene. Digoxin, calcium salts and all medications that increase calcium level should be avoided. The drugs that are considered to be safe in MH patients are barbiturates, narcotics, benzodiazepines, propofol, non-depolarizing muscle relaxant, nitrous oxide, and local anesthetics without adrenaline[8].

The specific treatment for MH is dantrolene sodium, diphenylhydantoin analogue. Its mechanism of action is to inhibit calcium release from the sarcoplasmic reticulum[9]. This drug comes in dry powder 20 mg/vial and must be hardly dissolved with sterile water 60 ml per vial. The new formula of more hydrophilic dantrolene mixture (Ryanodex™) is already launched in some countries but in the authors' hospital has only the former form of dantrolene drug.

The initial bolus dose of dantrolene is 2 to 3 mg/kg and can be repeated up to a total of 10 mg/kg every 5 minutes. As a result, at least 36 vials of dantrolene (total dosage of 10 mg/kg in a 70 kg patient) should be stored in the operating room supply for immediate use in MH crisis. As mentioned before, MH can be recurrent, 1 mg/kg of dantrolene should be prescribed every 6 hours for at least the next 48 hours during close observation[6,8,9].

To conclude, being vigilant, early detection, having knowledge, and good non-technical skill to communicate with team and patient's family are the key elements for MH management. Furthermore, clinical practice guideline must be developed for emergency situations and dantrolene should be readily available for use in MH crisis.

What is already known on this topic?

MH is life-threatening and rare pharmacogenetic autosomal dominant disorder, triggered by inhalation anesthetic agents and/or succinylcholine. Dantrolene is the specific treatment for this crisis.

What this study adds?

Early recognition of MH and prompt treatment, together with good communication and teamwork are the keys to achieve a good outcome in MH crisis.

Conflicts of interest

The authors declare no conflict of interest.

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