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Case Report

Successful management of malignant hyperthermia without dantrolene – A case report

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ABSTRACT

Malignant hyperthermia (MH) is a rare inherited genetic disorder implicated in a life-threatening catastrophic event under general anaesthesia. In India, the total number of reported cases are of the magnitude of single digit due to lack of reporting. The mortality of MH is dramatically decreased from 70-80% to less than 5%, due to an introduction of dantrolene sodium for treatment of MH, early detection of MH episode using capnography, and the introduction of diagnostic testing for MH.[1] In India, there is enormous dependence on clinical grading scale rather than halothane caffeine contraction test due to the lack of availability of accredited testing facilities. In addition to this, the drug of choice dantrolene, is not readily available everywhere in India. The scarcity of quintessential monitoring techniques cannot be ignored in peripheral areas. Despite these limitations many reported cases have survived with vigilant monitoring, prompt diagnosis and aggressive supportive care.

1. Introduction

Malignant hyperthermia (MH) is a rare yet potentially fatal pharmacogenetic disorder of the skeletal muscle. It is inherited as an autosomal dominant characteristic with variable expression and incomplete penetrance. It presents as a hypermetabolic response in susceptible individuals to potent volatile anaesthetics with/without depolarizing muscle relaxants; in rare cases, to stress from exertion or heat stress. MH symptoms include increased end-tidal carbon dioxide, tachycardia, skeletal muscular stiffness, hyperthermia, acidosis, and mortality.[1] The present article describes a successful management of MH patient and emphasizes attentive surveillance, timely diagnosis, and intensive supportive measures for successful outcomes. There is also a need to address the lack of availability of dantrolene in most centres so as to have better outcomes whenever a suspected case of MH determined by clinical grading is presented.

2. Case Report

A 14-years-old male presented with scoliotic deformity with gradual progression to the Cobbs angle of 33 degrees. Pre-anaesthetic evaluation for scoliotic correction surgery of the patient did not reveal any comorbidities with good effort tolerance. Informed high-risk consent was obtained in view of nature of surgery. General anaesthesia was induced with intravenous Fentanyl, Propofol and Atracurium with O_2+Air. Patient was intubated with flexo-metallic cuffed endotracheal tube (ETT)no.6mm ID orally. Anaesthesia was maintained on O_2+Air+Sevoflurane+Dexmedetomidine infusion (0.5μg/kg/hr) and propofol infusion (25μg/kg/min). A radial artery cannula, central venous catheter and nasopharyngeal temperature probe were put. The patient was turned prone with well protected eyes and pressure

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points and the procedure was started. After one and half hours of induction, the $ETCO_2$ (end tidal CO_2) started trending upwards. Despite initial corrective measures like hyperventilating the patient, changing the CO_2 absorbent and increasing the total flow rates, the $ETCO_2$ levels continued to rise. At the same time, the temperature of the patient showed an upward trend along with tachycardia and hypotension. (Figure 1) No significant changes in the muscle tone and skin appearance were noted. With the clinical suspicion of MH, the surgeon was alerted and requested to abandon the procedure immediately. Immediately sevoflurane was discontinued, the vaporizer and soda lime were removed. Fresh gas flows with 100% O_2 was increased and anaesthesia circuit was changed to open circuit to flush out remaining sevoflurane. Anaesthesia was maintained with intravenous agents. Dantrolene, drug of choice for MH could not be used due to unavailability at our institute. Active cooling measures were instituted to accessible body parts. Cold intravenous fluids were administered and noradrenaline infusion was started to maintain the blood pressure. Patient was turned supine after surgical closure and cold ice packs were placed in the axilla, groin, chest and abdomen. Blood gas analysis showed respiratory acidosis. (Table 1) After achieving normothermia and hemodynamic stability, the patient was shifted to the ICU on ventilatory and inotropic support. During the course of treatment in the ICU the ABGs trended towards normal. Next day the patient was extubated once normotensive and normocapnic and satisfied all the criteria for extubation. The patient and the family were informed of the clinical diagnosis of MH. They were counselled that future anaesthesia exposure involved risk of recurrence in the patient as well as the family members. The patient was discharged and for future reference, the incident was documented in his anaesthesia records as well.

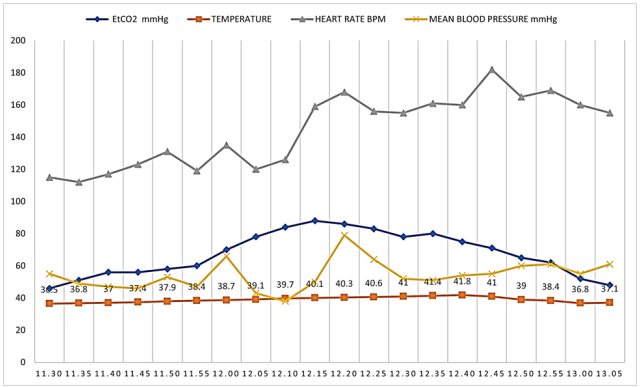

Figure 1: Vitals chart

3. Discussion

Malignant hyperthermia is a pharmacogenetic disorder which presents as a hypermetabolic response after exposure to inhalational agents or to depolarizing muscle relaxant succinylcholine. The most common genetic mutations associated with MH are RYR1(Ryanodine receptor-1) and less commonly CACNA1S gene (calcium voltage-gated channel subunit alpha 1S). An abnormal ryanodine receptor that controls calcium release causes a buildup of calcium in skeletal muscle, resulting in a massive metabolic reaction. The uncontrolled release of calcium from the skeletal muscle sarcoplasmic reticulum leads to sustained muscle contraction. The sustained muscle contraction produces a depletion of adenosine triphosphate (ATP) and dramatically increases oxygen consumption, carbon dioxide production, and heat. The depletion of ATP stores leads to membrane integrity failure and cell content leakages such as potassium, creatinine kinase, and myoglobin into the circulation. Therefore, the clinical manifestations are unexplained elevation of $ETCO_2$, muscle rigidity and rhabdomyolysis, hyperthermia, tachycardia, acidosis and hyperkalemia.[1]

After the first case reported by Denborough in 1960,[2] many cases were reported around the world. The diagnosis of malignant hyperthermia is based on clinical presentation, contracture test and genetic studies. The Indian studies largely rely upon the clinical grading scale (CGS) of Larach et al. In India the gold standard for diagnosis i.e., caffeine-halothane muscle contracture testing has limited availability and the genetic testing is not economical. The clinical grading scale of Larach et al. allocates points to the presenting clinical features and aids in the diagnosis of the event as Malignant hyperthermia.[3]

As per the clinical grading scale, clinical features of the present case scored 68 which suggests it was an almost certain case of MH. (Table 2). The clinical presentation in the present case under general anaesthesia was observed after one and half hours of induction. The ETCO2 continued to rise despite corrective measures and temperature of the patient showed an upward trend along with tachycardia and hypotension. No significant changes in the muscle tone and skin appearance were noted. The timeline of vital signs and ABGs is as depicted in the Figure 1 and Table 1 respectively. The peak $ETCO_2$ levels attained was 88 mmHg and Temperature rose to maximum of 41.8°C. Electrocardiogram revealed occasional premature ventricular contractions and sinus tachycardia with maximum Heart rate of 180 beats per minute. Arterial blood gas analysis revealed respiratory acidosis. Attempts were targeted at maintaining mean arterial blood pressure of 70 mmHg by titrating an infusion of inj. Noradrenaline.

The prognosis of an MH crisis depends on early detection and how rapidly appropriate treatment is initiated. The principles of treatment are firstly to reverse the reaction

Table 1: Timeline of blood gas analysis

	Timeline of Blood Gas Analysis					
Time	11:30 (ABG)	12:17 (ABG	12:54 (ABG)	14:56 (ABG)	18:16 (VBG)	18:22 (ABG)
pH	7.22	7.18	7.21	7.57	7.44	7.47
PCO2	55.4	69	61.7	23.7	40.1	32.3
PAO2	154	149	456	309	35.2	124
HCO3	22.2	25.2	23.8	21.9	27	23.8
Sat O2%	98.2	98.5	99.8	99.7	67.7	98.6
Lactate	3.9	2.7	1.1	1.9	1.1	0.6
Glucose	130	88	301	120	123	113

Table 2: Clinical grading scale for MH. Clinical features of the present case scored 68 which suggests it was an almost certain case of MH

Muscle rigidity			
Generalized rigidity		15	
Masseter rigidity		15	
Elevated CK >20,000 (after succinylcholine administration)		15	
Elevated CK >10,000 (without exposure to succinylcholine)		15	
Cola-colored urine		10	
Myoglobin in urine >60 mg/L		5	
Blood/plasma/serum K+ >6 mEg/L		3	
Respiratory acidosis			
ETCO2 >55 with controlled ventilation		15	√
PACO2 >60 with controlled ventilation		15	√
ETCO2 >60 with spontaneous ventilation		15	
PaCO2 >65 on spontaneous ventilation		15	
Inappropriate hypercarbia		15	
Inappropriate tachypnea		10	
Temperature increase			
Rapid increase in temperature		15	√
Inappropriate temperature >38.8°C in perioperative period		10	√
Cardiac involvement			
Inappropriate tachycardia		3	√
Ventricular tachycardia or fibrillation		3	
Arterial base excess more negative than−8 mEq/L		10	
Arterial pH <7.25		10	√
Rapid reversal of signs with IV Dantrolene		5	
Total Score Calculated		68	
Score:	**MH rank**	**Likelihood**	
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 √	

and secondly to treat the consequences of the reaction. There are three approaches to reversing the MH process: (1) eliminate the triggering agent; (2) give i.v. dantrolene; and (3) start active body cooling. The primary management involves elimination of the triggering anaesthetic agents. The vaporiser should be turned off and removed from the anaesthetic machine, 100% oxygen should be delivered at maximum flow and the patient's minute ventilation should be increased to 2–3 times normal. Activated charcoal filters introduced in recent times can be placed on the inspiratory and expiratory limbs of the anaesthesia machine which can adsorb inhalational anaesthetic agents.

Dantrolene Sodium is an antidote for MH and it binds to the RYR1 receptor thereby inhibits the release of calcium from the sarcoplasmic reticulum and reverses the negative cascade of effects.[4]

Due to the unavailability of dantrolene the case was aggressively resuscitated using active cooling measures.

These included intravenous cold saline infusion, gastric lavage with cold fluids, along with cold sponging. Other supportive measures include ionotropic support, correction of acid-base and electrolyte imbalances and forced diuresis using fluid and furosemide to prevent acute renal failure.

The differential diagnosis for symptoms of hyperthermia, hypercarbia and tachycardia in the perioperative period commonly are thyrotoxicosis, anaphylaxis and phaeochromocytoma and to eliminate these causes investigations like thyroid function tests and urinary VMA were done which were found to be within normal limits. The neuroleptic malignant syndrome was ruled out due to the absence of history of antipsychotic medications. Our patient had a rise in CPK of 2999 IU/L. the expected rise in CPK after cardiac or great vessel surgeries can be up to 1100 IU/L hence ruling out any cardiac pathology.[5]

The first case reported in India by Punj et al in 2001 was in a 21-year-old man from Nepal who got operated for thyroid surgery.[6] The patient developed tachycardia, hypercarbia, hyperthermia, acidosis, hyperkalaemia and increased creatine kinase concentration. Later, he succumbed to disseminated intravascular coagulation. The diagnosis of MH was based on the clinical presentation and the Larach clinical grading scale. Similar case reports were published by Gupta et al. in 2010 and Pillai et al. in 2015 wherein the patients couldn't be saved despite aggressive supportive measures.[7,8]

Indian literature has examples of reported cases of malignant hyperthermia that survived this ordeal with early diagnosis and supportive management. In 2007 Saxena et al published a case of almost certain diagnosis of malignant hyperthermia with CGS of 61 where the patient survived and the triggering agents used were halothane and succinylcholine.[9] In 2010 Gopalakrishnan C V et al reported a case with CGS of 63 and the agent used was sevoflurane.[10] Gulabani et al. reported a case with CGS of 43 wherein isoflurane was the suspected triggering agent in 2014.[11] In 2017 and 2019 cases by Iqbal et al and Ramanujam et al published cases with almost certain diagnosis of malignant hyperthermia.[12,13] All these cases that survived were symptomatically managed without having received the drug of choice i.e. dantrolene.

However, in 2016 Raut et al published a case report that illustrated a case of malignant hyperthermia triggered by isoflurane with CGS of 61 in a post-operative patient and saved by prompt administration of intravenous dantrolene and supportive treatment.[14]

These instances demonstrate the prevalence of MH in India although the actual numbers may probably be much higher. The lack of reporting is the primary reason for meagre numbers. Although some of the cases have been successfully managed by supportive treatment, the use of the antidote dantrolene has resulted in the mortality rates being greatly reduced. There is need for better availability of dantrolene and resource sharing amongst tertiary care centers. The European Malignant Hyperthermia Group has recommended the availability of dantrolene in centers where volatile anaesthetics and succinylcholine are used.[15]

The successful management of MH without dantrolene emphasizes the need for stringent monitoring, early detection and immediate and effective treatment. Essential monitoring especially temperature and $ETCO_2$ should be used so that early warning signs can be detected in all cases where volatile anesthetic agents and other triggering agents are used. There is a need to develop awareness amongst anesthesiologists and the supporting staff about MH through regular training by mock drills, protocol development and patient education. Ready reference charts or posters showing the management of MH can be kept in the vicinity of the operations theatres.

The rapid progression of the condition and the potentially fatal outcomes necessitate the need for active case reporting, record keeping of susceptible patients and data sharing amongst institutes. The need for approved testing facilities for genetic and contraction testing is highlighted by these case studies.

4. Conclusion

Contrary to conventional belief, MH is not restricted to the western world. Early diagnosis and active supportive care are essential for good results. Every case of general anesthesia requires stringent monitoring measures, including ETCO2 and temperature. Positive outcomes may be achieved by early case reporting, the establishment of testing centers, and the speedy distribution of MH kits. Although MH may only occur once in a lifetime for anesthesiologists, it is no longer a myth in the Indian context, thus we must be well-prepared to handle it.

5. Abbreviations

RYR: Ryanodine Receptor; **CACNA1S**: Calcium Voltage-gated Channel Subunit Alpha 1 S; **ATP**: Adenosine Triphosphate; **VMA:** Vanillyl Mandelic Acid; **CPK**: Creatine Phosphokinase; **CGS:** Clinical Grading Scale

6. Source of Funding

None.

7. Conflicts of Interest

None.

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