Case Report

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Successful application of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) after intraoperative occurrence of malignant hyperthermia in a patient of uterine leiomyosarcoma for cytoreduction surgery

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ABSTRACT

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is a technique used in combination with cytoreductive surgery to treat various cancers with local spread and not fully resectable. Anaesthetic complications are common during this procedure with disturbances in haemodynamics, coagulation, respiratory gas exchange and impact on various body systems. Sudden increase in temperature may be related to occurrence of Malignant Hyperthermia (MH) and remains a challenge requiring immediate recognition and aggressive management. We hereby report a case of hyperthermia in a patient posted for cytoreduction and HIPEC surgery emphasizing that a prompt identification; rational symptomatic and supportive therapy can be lifesaving.

Key words: Anaesthesia, cytoreduction, hyperthermia, Hyperthermic Intraperitoneal Chemotherapy

INTRODUCTION

Sudden increase in body temperature intraoperatively may be related to Malignant Hyperthermia (MH) and remains challenging for an optimal outcome of the patient[1,2]. Hyperthermic Intraperitoneal Chemotherapy (HIPEC) is a technique used in combination with cytoreductive surgeryto treat various peritoneal, gastrointestinal, and ovariancancers that have spread by transcoelomic metastasisto the lining of the abdomen and peritoneal cavity[3]. Anaesthetic complications are common during this procedure with disturbances in haemodynamics, coagulation, respiratory gas exchange and impact on various body systems (kidney, liver). MH is an autosomal dominant disorder triggered by an exposure to certain anaesthetics agents in susceptible individuals with a mutation at the ryanodine receptor gene RYR. It is a myopathy associated with abnormal skeletal muscle calcium homeostasis. Such clinical scenario of a major surgery and additional occurrence of unexpected complication may jeopardise the patient outcome. We hereby report a case of intraoperative hyperthermia in a patient posted for cytoreduction and HIPEC surgery emphasizing that a prompt identification; rational symptomatic and supportive therapy can be lifesaving.

CASE REPORT

A 27-year-old woman, case of leiomyosarcoma uterus was posted for cytoreduction and HIPEC surgery. Patient did not have any comorbidities preoperatively, no previous history

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of anaesthetic exposure and no family history suggestive of MH. Her preoperative hemogram, renal, liver function, 12 lead Electrocardiogram (ECG) and chest x-ray were within normal limits. She was advised fasting for 6 hours and oral ranitidine (150 mg) in the night and morning of surgery with sip of water. Patient was shifted to operating room on day of surgery and routine monitors including 5 lead ECG, non-invasive blood pressure and pulse oximeter were attached. Baseline parameters were heart rate of 92 beats/min, oxygen saturation of 99% on room air and non-invasive blood pressure of 118/78 mmHg. A peripheral intravenous 18 G cannula was secured. Patient was placed in the left lateral position and combined spinal epidural block was administered in the L2-3 interspace via midline approach. The preservative free morphine (300µg) along with 5 mg of hyperbaric bupivacaine was administered intrathecally. The epidural catheter was inserted and fixed at 10 cm to skin. Anaesthesia was induced with intravenous morphine (6 mg), propofol (100 mg), vecuronium (6 mg) and lung were ventilated using bag and mask with sevoflurane (1.5%) in oxygen along with capnography monitoring. After 3 minutes of ventilation, cuffed endotracheal tube (size 7 mm ID) was inserted, fixed at 19 cm and its correct placement in the trachea was confirmed. The temperature probe was inserted in the nasopharynx. The vitals were stable, End Tidal Carbon Dioxide ($EtCO_2$) was 38 mmHg and temperature was 36.1ºC. The left radial artery was cannulated using 20G arterial catheter. Right internal jugular vein was cannulated under ultrasound guidance using 7 Fr triple lumen central venous catheter. Anaesthesia was maintained with desflurane in oxygen and air (50:50) (Minimum Alveolar Concentration, MAC 1). Forced air warming and fluid warmer was used to maintain normothermia. The surgery was started after cleaning and draping. The total gas flow was reduced from 4 L/min to 800 mL after about 30 minutes of induction. After around 2 hours, the temperature started rising gradually and within a span of around 10 minutes rose from 35.6 to 37.8 ºC. $EtCO_2$ also started to rise gradually and increased from 37 mmHg to 58 mmHg during this period. The heart rate increased from around 80 beats/min to 140 beats min along with an increase in invasive blood pressure from 108/72 mmHg to 160/98 mmHg. Surgery was stopped and surgeon was enquired for any septic focus in the surgical site which they denied. Also, any adrenal mass or suspected secretary lesion in the surgical site was explored but was negative. Forced air and fluid warmer were stopped. The ventilator was found to be working satisfactorily. The ventilation rate was increased to 20 breath/minute to maintain eucapnia. This hyperthermic response appears to be causative factor for hemodynamic and respiratory pertubances. The desflurane was stopped, vaporized removed from mounting rod and gas flow (oxygen nitrous oxide mixture, 50:50) were increased to 10 L/min. Cold fluid (balances salt solution) was administered through central line. The abdominal cavity was lavage with cold saline. Despite these interventions, the temperature and $EtCO_2$ kept on rising and 30 minutes later the temperature reached about 38.8 C, $EtCO_2$ ranged from 60-68 mmHg, HR reached 194 beats/min. Blood pressure further increased to 198/118 mmHg. The cold intravenous solution and abdominal lavage was continued. The ice packs were placed in axilla and groin for vigorous cooling. The intravenous labetalol boluses (5+5+5 mg) were administered. Intravenous lidocaine (100 mg) was slowly infused. The propofol infusion was started for maintenance of anaesthesia. The $EtCO_2$ sampling line and soda lime were changed and ventilatory parameters were adjusted to maintain $EtCO_2$ in normal range. The ABG revealed pH 7.18, pCO_2 47 mmHg, $HCO_3$17.5, lactate2.7, potassium 4.3 meq/L, pO_2 198 mmHg. After about 15 minutes the temperature, heart rate and $EtCO_2$ started decreasing and in next 15 minutes reached to basal values. The surgery was now continued. After surgical resection, HIPEC using open technique was initiated using cisplatin based solution at 42ºC for half an hour. The vitals were monitored during this period and it was discussed with the surgeon to stop the procedure in case hemodynamic instability occurred. However, patient remained stable during this period. After the completion of the surgery which took around 6 hours, the residual neuromuscular blockade was reversed using glycopyrrolate (0.6 mg) and neostigmine (2.5 mg). Once the patient was conscious with adequate respiratory efforts, trachea was extubated and patient was shifted to Intensive care unit (ICU) for further monitoring and management. During ICU stay patient had uneventful course with no recurrent episodes. Blood investigations including hemogram, renal and hepatic function were sent and were in normal range. The CKMB and myoglobin were sent. CKMB was in normal range but myoglobin value was markedly increased (373.7 ng/mL, normal 25-28 ng/mL). The same patient develops bowel perforation on 6th postoperative day and was planned for emergency exploration. This time we took all precautions avoid any agents that incite MH. The perioperative period was uneventful.

DISCUSSION

The sudden increase in intraoperative temperature remains a challenge for anaesthesiologist as it leads to various systemic responses. MH is a rare life-threatening

entity characterized by rapid rise in body temperature, heart rate and muscle rigidity triggered by exposure to certain anaesthetic agents like succinylcholine and volatile anaesthetics. The increased intracellular calcium activates the myosin ATPase resulting in an increased ATP consumption, oxygen consumption, carbon dioxide production, hyperthermia and rigidity. Early recognition of an impending MH crisis and its immediate treatment is essential for the patient's optimal outcome. As the clinical signs associated with MH syndrome are not unique, anaesthesiologists must be able to recognize a pattern of signs to make a rapid diagnosis. Any patient may develop MH during or shortly after an anaesthetic where trigger agents are used, this can occur even in patients who have had uneventful general anaesthesia previously[4]. The onset of MH after the exposure to triggering agent is variable. Usually onset of clinically recognizable signs manifests in 45-55 minutes after exposure, but first sign may appear in 5 minutes or even after 6 hours of anaesthetic agent exposure in postoperative period. The usual signs of MH like sustained muscle activity, rigidity of limbs and abdomen may not manifest under anaesthesia with neuromuscular blockade as happened in our case. However, increased sympathetic tone that occurs in MH was manifested with increase in heart rate and blood pressure and increased metabolism that was manifested with increased carbon dioxide levels and rapidly rising temperature. The other signs of MH include respiratory acidosis, metabolic acidosis, increase myoglobin, and creatinine phosphokinase levels. The acidosis was manifested in our patient as well.

The potent inhalation agents are the principal triggers and there is evidence that the modern agents, desflurane, sevoflurane, and isoflurane, can cause florid MH reactions in the same way as halothane but also are associated with reactions whose onset is delayed for several hours into anaesthesia. There is evidence that the triggering of MH by drugs is dose-dependent but the minimum dose that will trigger the condition is unknown[5]. The clinical presentation in this case conformed to a typical episode of malignant hyperthermia. Larach et al gave a clinical grading scale using clinical indicators for determining the Malignant Hyperthermia Raw Score[6]. This score has been a definitive diagnostic indicator of MHS based on clinical findings and biochemical tests. The total score in our patient was 43 which puts it in MH Rank 5 and makes the diagnosis of malignant hyperthermia very likely. The other probable diagnoses were ruled out in our case. Thyroid storm was ruled out as thyroid function test done postoperatively were normal and no history was suggestive of thyroid disease or pheochromocytoma. Computed tomographic scan of the patient was discussed again to rule out any other hormone secreting tumour such as carcinoid. Neuroleptic malignant syndrome was ruled out as the patient was not on any of the implicated drugs for this syndrome. The iatrogenic hyperthermia was not possible yet hyperthermic chemotherapy instillation was not started and Forced air warming was being used appropriately with functional monitoring of temperature on these equipments[7].

The conducting HIPEC after the event was a dilemma. There is no literature published on this issue for concerns related to MH and subsequent management of HIPEC for a cancer surgery. Since patient was hemodynamically stable with normothermia and onco-surgery could not be postponed, we continued with the technique of HIPEC and completion of surgery.

The standard diagnostic test is the "caffeine-halothane contracture test" along with genetic findings. A muscle biopsy is carried out and the fresh biopsy is bathed in solutions containing caffeine or halothane and observed for contraction; under good conditions, the sensitivity_is 97% and the specificity 78%[8]. However, cases have been reported with negative caffeine halothane contracture test that had full blown clinical episode of malignant hyperthermia under anaesthesia hence the importance of the MH Raw Score[9]. The published standards for this test were not available at our centre; hence this test was not done.

We managed the case intraoperatively by early recognition and symptomatic treatment including ventilatory changes, cooling, maintenance of haemodynamics, and stoppage of inciting agents. Since the dantrolene was not immediately available and could not be procured, its immediate administration was not possible. But we arranged the drug to prepare for any recurrence of the signs of MH. Our patient did not have any recurrence and in second surgery all precaution were taken.

CONCLUSION

To conclude, we want to emphasize the late occurrence of hyperthermia in a major surgery leading to hemodynamic compromise. HIPEC requires cautious monitoring and vigilance during onco-surgery. Appropriate and aggressive management may prevent any morbidity and mortality.

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