Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy: A Case Report

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Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) is a complex procedure used for the treatment of various types of cancer. Specifically, HIPEC has shown success where treatment failure sites (metastases) thrive. A classic example of one such area is the peritoneal surface, which remains a prominent failure site for patients with gynecologic and gastrointestinal cancer. Traditionally, most patients with advanced stages of cancer have undergone palliative procedures as part of their treatment modality or had no surgery at all. With the advent of cytoreductive surgery with HIPEC, patients with peritoneal cancer have shown increased survival rates. Anesthetic complications are common during this procedure with disturbances in hemodynamics, coagulation, and respiratory gas exchange. A knowledge of what to anticipate anesthetically will guide the practitioner to achieve successful management during and after the case. In this case report, a 71-year-old woman was treated for stage III peritoneal and ovarian cancer by cytoreductive surgery with HIPEC.

Keywords: Cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, ovarian cancer, peritoneal cancer.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) was first described clinically in the treatment of pseudomyxoma peritonei by Spratt et al in 1980. Since then, HIPEC has been used to treat transcoelomic metastasis, which if left untreated, results in the dissemination of malignant tumors throughout organ tissue surfaces of the abdominal and pelvic cavity. Over the past decade, cytoreductive surgery with HIPEC has emerged as an effective treatment for patients with various gastrointestinal cancers, peritoneal mesothelioma, and ovarian cancers compared with IV chemotherapy alone. Current data demonstrate that patients with peritoneal mesothelioma undergoing HIPEC have an improved survival rate, from 12 to 92 months, and those with ovarian cancer have an improved survival rate up to 54 months.

Hyperthermic intraperitoneal chemotherapy is a technique used in combination with cytoreductive surgery to treat various peritoneal, gastrointestinal, and ovarian cancers that have spread by transcoelomic metastasis to the lining of the abdomen and peritoneal cavity. Cytoreductive surgery involves a lengthy exploratory laparotomy with peritoneal stripping and gross tumor resection. After cytoreduction, the abdominal and pelvic spaces are flooded with high-dose heated chemotherapy, resulting in a large exposure of tumor cells to high-dose chemotherapeutic agent. Heated chemotherapeutic solution has been demonstrated to increase the drug’s therapeutic effect by inducing a hyperthermic state that selectively increases the cytotoxicity of malignant cells. This is achieved by increasing membrane permeability in the malignant cell, impairing DNA repair, and triggering protein denaturation. A prospective randomized trial by Verwaal et al in 2003 found that when cytoreductive surgery with HIPEC was combined with modern systemic chemotherapy, survival rates were significantly prolonged compared with systemic chemotherapy alone.

Case Summary
A 71-year-old, 86-kg woman with ASA physical status 3 and stage III peritoneal and ovarian cancer presented for cytoreductive surgery with HIPEC. In addition to the stage III peritoneal and ovarian cancer, the patient also presented with hypertension that was mildly controlled and hyperlipidemia. Preoperative vital signs were blood pressure, 142/72 mm Hg; heart rate, 79/min; respiratory rate, 16/min; and pulse oximetry, 98% on room air. The patient’s physical examination on the morning of surgery found all lung fields clear to auscultation bilaterally and the heart rate rhythm regular. Her airway examination showed unremarkable findings, and the results of all laboratory studies were within normal ranges with the exception of a baseline hemoglobin level of 9 g/dL and hematocrit concentration of 32%. Diagnostic studies included a 12-lead electrocardiogram (ECG), which showed a normal sinus rhythm, and a chest x-ray whose result was unremarkable.

A left hand, 18-g, peripheral intravenous (IV) catheter was placed preoperatively. Before the patient was transported to the operating room, 2 mg of midazolam was administered IV. Intraoperatively, standard monitors
were applied, and preoxygenation was performed. For induction of general anesthesia and for tracheal intubation, the following medications were given IV: fentanyl, 200 µg; lidocaine, 80 mg; and propofol, 160 mg. Following positive pressure ventilation, 10 µg of vecuronium was administered. After loss of train-of-four twitches, a 7.0-mm cuffed endotracheal tube was inserted without difficulty and secured.

Following endotracheal intubation, isoflurane was initiated and carefully titrated. Volume control mechanical ventilation was initiated, with a mean tidal volume of 650 mL, respiratory rate of 8/min, and zero positive end-expiratory pressure. An 18F nasogastric tube, an esophageal temperature probe, and a Foley catheter were placed without difficulty. A right radial arterial line was subsequently placed and a right internal jugular venous catheter was inserted using ultrasound guidance. Because of the expected prolonged length of surgery and large surgical exposure required, a forced-air heating blanket was applied to the upper part of the body, and heated IV fluids were initiated in an effort to maintain normothermia. General anesthesia was maintained with 0.8% to 1% end-tidal isoflurane, 100% oxygen (O2) at 2 L/min, and an additional 30 mg of vecuronium throughout the case to maintain 1 of 4 twitches. Additional opioids were administered IV as needed based on the patient’s hemodynamics, for a total of 250 µg of fentanyl, and 7 mg of morphine. Cardiac output, central venous O2 saturation, and stroke volume variation were calibrated in vivo and were monitored (Vigileo with FloTrac sensor and PreSep oximetry catheter, Edwards Lifesciences). Hemodynamic stability was maintained with crystalloid, packed red blood cells (RBCs), 250 µg of phenylephrine, 5 mg of labetalol, and 7.5 mg of furosemide as required. No ECG changes were noted throughout the procedure. The heart rate and mean arterial pressures remained within baseline values throughout the chemotherapeutic phase. A substantial increase in central venous pressure, from 8 to 12, was noted 60 minutes after the initiation of HIPEC.

Following induction of general anesthesia and surgical preparation, the surgeon made a vertical surgical incision from the suprapubic bone to the xiphoid process. The peritoneal cavity was accessed, and the abdominal and peritoneal cavities were explored for tumors. Portions of the liver, sigmoid colon, and peritoneum were excised, and a total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. On completion of the cytoreduction, the patient was prepared for HIPEC.

At this time, the forced-air heating blanket was turned on to a ambient setting, and the heated IV fluids were discontinued. Two inflow catheters and a temperature probe were placed above the dome of the liver (Figure). Outflow catheters were placed at the inferior aspect of the incision, with a temperature probe extending from the pelvis (see Figure). The incision was whipstitch closed. The catheters were connected to a perfusion pump circuit. The peritoneal cavity was infused slowly with 3 L of heated dialysis fluid. A roller pump forced the heated solution into the abdomen through the inflow catheter and out the abdomen through the outflow catheter (see Figure). A heat exchanger was used to maintain the infused fluid at 44°C to 46°C, allowing the intraperitoneal fluid to be maintained between 42°C and 43°C. Once the temperature of the fluid reached 41°C, 150 mg of cisplatin was added to the circuit. The flow of heated chemotherapeutic agent was maintained at 1,100 mL/min at 42°C. Continuous rocking and agitation of the abdomen was performed by the operating room nursing staff. During the chemotherapeutic stage, 4 g of magnesium sulfate was administered IV based on a magnesium laboratory value of 0.7 mEq/L measured by a handheld blood analyzer (i-STAT System, Abbott Laboratories).

After 120 minutes of heated therapy, the abdomen was flushed with large amounts of dialysis fluid and drained. The abdomen was reopened, inspected for hemostasis, and closed. Throughout the 10-hour procedure, the patient received 12 L of IV crystalloid and 2 U of packed RBCs to treat hemoglobin and hematocrit values of 7 g/dL and 28%, respectively; the urine output was 1.4 L, and the estimated blood loss was 450 mL. Throughout the chemotherapeutic phase, cool IV fluids were infused and ice packs were applied to the patient’s groin and bilateral axilla to avoid extremes of core temperature (highest recorded temperature reached 38.9°C). At the conclusion of the procedure, the patient’s temperature decreased to 37.5°C, compared with her preoperative baseline temperature of 35.7°C.

The patient was transported to the intensive care unit (ICU) on standard monitors, and she remained intubated and sedated overnight. On postoperative day 1, she was successfully extubated. She was discharged to home on postoperative day 6, with no further complications. To our knowledge, no standard guidelines are currently available to guide the anesthetic management for cytoreductive surgery with HIPEC. Therefore, the references were used as a guide for anesthetic management throughout the procedure.

Discussion
Cytoreductive surgery with HIPEC has the potential to produce unique intraoperative challenges for the anesthesia provider. It is a long and complex surgical procedure that often results in major fluid shifts, blood loss, and electrolyte changes. Disturbances in hemodynamics, coagulation, and respiratory gas exchange are also common. In addition to the current standard recommendations for preoperative evaluation of patients undergoing major abdominal surgery, a thorough preoperative evaluation exploring all body systems should be performed. The evaluation should focus on comorbid...
conditions that may become exacerbated by the large fluid shifts that occur during the heated chemotherapeutic phase. Results of preoperative laboratory, electrocardiography, and diagnostic studies should be reviewed. Cardiac and pulmonary clearance should be obtained when necessary.

Major hemodynamic changes during the heated chemotherapeutic phase result in a hyperdynamic circulatory state because of the thermal stress that is induced. Fluid management becomes a critical component before, during, and following the heated chemotherapeutic phase. Increased circulating volume becomes necessary during peritoneal stripping and tumor excision to counteract the increase in venous capacitance that occurs during the chemotherapeutic phase. Hemodynamic monitoring is recommended to properly treat intravascular hypovolemia and oliguria. Although not substantial in the current case report, blood loss can be considerable, especially during the cytoreductive phase. Replacement fluids may approach 10 to 20 L of IV crystalloid, this in addition to IV colloids and blood products that may also be given in an effort to maintain cardiovascular stability. Coagulopathy is a potential concern secondary to the administration of large volumes of IV fluids and the resulting dilution of platelets and coagulation factors that occur. Because blood loss can be considerable, blood product replacement must be anticipated and all products readily available for the patient at the blood bank. Hetastarch is contraindicated during HIPEC, because of an increased risk of coagulopathies. Alterations in respiratory gas exchange may also occur because of decreased O₂ delivery to the microcirculation that may have been destroyed by the tumors. In addition, these patients may have decreased functional residual capacity secondary to increased abdominal girths that may result from tumors or ascites, putting them at risk of aspiration and rapid desaturation.

An excessive systemic body temperature resulting from the hyperthermic intraperitoneal solution is of great concern because of the potential for an increased metabolic rate. Extremes of body temperature and increased metabolic rate lead to a steady increase in heart rate, cardiac output, and end-tidal carbon dioxide, with an overall decrease in systemic vascular resistance. The peripheral vasculature dilates in response to heat stress, resulting in an increase in heat loss from the core to the environment. In the face of decreasing peripheral vascular resistance, the heart rate increases in an effort to maintain cardiac output. Therefore, before the chemotherapeutic phase, the anesthesia provider must ensure that all fluid warmers are turned off and blanket warmers turned to an ambient setting to avoid dangerous extremes of hyperthermia. Typically, a core temperature goal of 35°C before the introduction of the hyperthermic perfusion is sufficient to keep the core body temperature below 38°C once the heated chemotherapeutic agent is initiated. The anesthesia provider must be aware that both extremes of temperature can affect patient outcome, and therefore keeping the patient as normothermic as possible remains a viable goal.

Adequate IV fluid hydration before the initiation of the chemotherapeutic phase is imperative. As stated
previously, replacement fluids may approach 10 to 20 L in an effort to counteract the increase in venous capacitance that occurs during the heated chemotherapeutic phase. In addition, heated cisplatin has been demonstrated to cause nephrotoxicity. In an effort to avoid systemic hemodynamic fluctuations and hypovolemia leading to potential complications related to decreased perfusion, the anesthesia provider should have adequate fluid therapy as a primary goal. During the heated chemotherapeutic phase, the goal is to maintain 100 mL of urine output every 15 minutes for the duration of the treatment. Furosemide and mannitol are recommended in small doses to ensure maintenance of adequate urine output. This allows the patients to tolerate the hyperdynamic and thermal state induced by this phase. It is imperative that the anesthesia provider continually assesses electrolytes during the case. At the conclusion of HIPEC, the body temperature begins to decline and the hyperdynamic circulatory stage begins to normalize.

Postoperatively, patients are typically transported to the ICU with an endotracheal tube in place. Most patients are extubated 1 to 4 hours after their arrival in the ICU once they have demonstrated hemodynamic stability.

Cytoreductive surgery with HIPEC is a complex and long surgical procedure with the potential for substantial fluid shifts and blood loss. This procedure has demonstrated improved outcomes in patients with peritoneal and ovarian cancers, allowing surgeons to completely remove all visible tumors and directly treat the peritoneal cavity with chemotherapeutic agent. The long-term (5-year) survival of patients with peritoneal cancer before the introduction of HIPEC was historically only 20% to 30%. Cytoreductive surgery with HIPEC has improved 5-year survival rates to 52% to 96%, with a median survival rate up to 156 months. Median survival rates have also improved for patients with ovarian cancer, from 17 months for patients treated only with systemic chemotherapy to 54 months for those treated with HIPEC.

An understanding of the pathophysiological changes that accompany HIPEC is important in guiding the anesthesia provider toward optimal anesthetic management of these patients and the avoidance of potentially life-threatening intraoperative complications.

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