Anesthetic Considerations for Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Kathy Crowley, CRNA [1], Allison Pitroff, PA-C [2], Gregory Adkinsson, MD [1] and Jesus Esquivel, MD, FACS [2]

Department of Anesthesia [1] and Department of Surgical Oncology [2], St Agnes Hospital, Baltimore, Maryland, USA.

Introduction

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) is playing an increasing role in the therapeutic management of patients with peritoneal surface malignancies. It is a complex procedure that includes broad based abdominal and pelvic surgery to remove all visible tumors and HIPEC, a peritoneal perfusion utilizing approximately 3 liters of chemotherapeutic solution heated to 42 degrees Celsius. Heated intraoperative chemotherapy achieves a high peritoneal concentration with limited systemic absorption. [1]

A typical surgery will last between 6 and 10 hours and involves removal of all involved peritoneum, one or several bowel resections with a complete greater omentectomy and in women a bilateral salpingo-oopherectomy. Occasionally, the peritoneum of one or both diaphragms may need to be stripped from tumor. If the diaphragms are stripped, chest tubes will need to be placed on each side operated. The heated chemotherapeutic perfusion normally lasts about 90 minutes. During this time, all the anatomic structures are uniformly exposed to heat and to the chemotherapeutic agents. The heated chemotherapy may be perfused with a closed abdomen technique or

Address correspondence and reprint requests to: Jesus Esquivel, MD. E-mail: jesusesquivel@yahoo.com

an open “coliseum technique”. With the closed technique, which is the method used at our institution, the abdomen is closed at the skin level and two catheters exit through the abdominal wound. A roller pump forces the heated chemotherapy solution into the abdomen through the inflow catheter and pushes it out through the outflow catheter. A heat exchanger keeps the fluid being infused at 44 to 46 degrees Celsius so that the intraperitoneal fluid temperature is maintained at 42 to 43 degrees Celsius[2] Following the heated infusion, the surgeon performs any reconstructive procedures and closes. This phase will vary depending on the number of anastomoses and any other procedures required.

This paper presents a standardized approach that has been successfully utilized in over 80 patients at our center in the last two years and provides an overview of the management of the surgical patient during the HIPEC procedure. This approach will be detailed in terms of preoperative evaluation, intraoperative management and postoperative considerations.

Pre-operative evaluation

In addition to current standard recommendations for preoperative evaluation of patients undergoing major abdominal surgery, specific attention should be paid to conditions that may be exacerbated by the extended time, massive fluid shifts, and a hyperdynamic state that may occur during surgery. Presentation of these patients varies considerably; an increased abdominal girth may or may not be present with up to 10 to 15

liters of ascites possible. Some patients may undergo multiple abdominal paracentesis prior to surgery. The distended abdomen is due to a combination of ascites, tumor, and/or copious mucus production. These patients may also have a severely decreased or limited functional residual capacity secondary to the abdominal contents pushing up against the diaphragm.[3] These factors put these patients at high risk for aspiration and rapid desaturation, therefore a thorough airway evaluation is useful to avoid unexpected difficulty in managing the airway. Specific attention should be paid to the patients' cardiovascular, pulmonary, and renal status for the ability to handle a hyperdynamic state with tremendous volume requirements. A thorough cardiac evaluation with any indicated invasive or noninvasive tests should be conducted in advance of anticipated surgery. Replacement fluids may and frequently do approach 10 to 20 liters of crystalloid along with 1000cc of colloids, blood and blood products. One consideration in the preoperative management of patients with compromised cardiac function and/or low ejection fraction is to run a fluid infusion overnight prior to surgery to counter the effects of the standard bowel prep and greater than normal fluid deficits. Evaluation of all laboratory work including albumin and pre albumin levels is usually assessed.

Intraoperative management

Along with managing a variety of co-morbidities, major concerns during this procedure include tremendous volume requirements due to a combination of major fluid shifts with or without ascites, vasodilation, and a hyperdynamic state that occurs during the hyperthermic phase. Attention to electrolyte balance, coagulation status, hemoglobin

values, and the potential renal toxicity of the chemotherapeutic agents with the subsequent requirements to maintain a steady urine output are also key components. The administration of large volume of any type of intravenous fluids will cause dilution of platelets and coagulation factors and may lead to coagulopathy.[4] During the heated chemotherapy, patients develop a hyperdynamic circulatory state that is characterized by steady increase in heart rate and cardiac output that reaches its maximum between 70-80 minutes of the 90 minute heated chemo. As the body temperature decreases after completion of the heated therapy, the hyperdynamic state begins to normalize, although studies have shown it will still be above baseline 10 minutes after the chemotherapeutic lavage is concluded.[5] When the closed abdomen technique is used, its perioperative toxicity seems to be related to the hemodynamic and cardiac function changes associated with increased body temperature and increased intra-abdominal pressure.[6] The anesthesiologist/anesthetist plays a major role in the management of these patients intraoperatively and a standardized approach to these patients has been developed to minimize potential morbidity and mortality.

HEMODYNAMIC CHANGES ASSOCIATED WITH HIPEC

1. Increased cardiac output
2. Decreased systemic vascular resistance
3. Increased heart rate
4. Increased end tidal CO2

Appropriate hemodynamic monitoring and urinary monitoring is essential to properly identify and treat intravascular hypovolemia and oliguria. Standard monitors are applied along with a triple lumen central venous catheter, an arterial line, and large bore peripherals. Central venous pressure and intra-arterial monitoring are essential for the large fluid shifts and importance of urinary output. In specific cases a pulmonary artery catheter and/or transesophageal echo (TEE) may be indicated or required. In addition, most of these patients are at high risk for pneumothorax with all central line placements secondary to the large distended abdomen. The use of long acting antihypertensives is avoided due to the changing nature of the procedure. For example, following a long open procedure where body temperature tends to fall, the patient will be exposed to heated agents and they will tend to vasodilate significantly. Heart rate is maintained below 90 bpm. Our preferred agent is metoprolol given in 1mg increments. This will give adequate heart rate control while having minimal effect on blood pressure. There is increasing evidence that perioperative use of beta-blockade will reduce both short and long term cardiovascular complications in high risk patients.[7] In high risk patients beta blockers are recommended in the 2002 update of the American College of Cardiology and American Heart Association.[8,9] Blood loss in our procedures typically ranges from 300 to 500cc but can vary widely.

Fluid management is a critical component. As surgery begins and progresses, the HIPEC patients require large amounts of volume taking into account bowel prep, NPO, third space (10 to15cc/kg/hr), maintenance IV fluids, blood loss, ascites, and copious amounts of mucus production. Along with the patients' history and co-morbidities, the

urinary output and CVP guide the fluid administration throughout the case. Of these two parameters, the urinary output is more important using the CVP as a trend rather than an absolute number. At the beginning of the case, some patients require as much as 5 liters of crystalloids along with 500-1000cc of albumin over the first two to three hours just to establish urine output, while other patients have good urine output from the start.

As the surgery progresses, the peritonectomies and stripping of the diaphragms are very stimulating portions of the surgery. Narcotic/epidural management is an important adjunct for HIPEC procedures. A fentanyl infusion is maintained between 100-200mcg/hour with a total dose approximately 1000-1500mcg. If an epidural is placed, consider that the incision extends from xyphoid to pubis and a thoracic epidural will be of more benefit.

After the patients initial preoperative labs, the next labs are drawn approximately one hour prior to the heated chemotherapeutic infusion unless otherwise indicated. Chemistries, ABG, coags, and CBC with platelets are drawn. Ninety five percent of all patients will require electrolyte replacements, most commonly calcium, magnesium, and potassium. Calcium is an important electrolyte as well as a necessary cofactor at several points in the coagulation process and for normal platelet function.[4] Acidosis is rare but if it occurs, the acidosis must be addressed. All fluid warmers must be turned off and the bair hugger should be placed on ambient. There are a few studies looking at the perioperative safety concerns for HIPEC patients. Studies by Kanakoudis et al encouraged extensive hemodynamic monitoring and found perioperative complications

and changes in cardiac and hemodynamic functions were related to acute change in body temperature and increased abdominal pressure.[6] The study by Esquivel et al suggests that the hemodynamic and cardiac function alterations observed during the heated intraoperative intraperitoneal chemotherapy seems to be determined by the thermal stress induced in the patient with its subsequent hyperdynamic circulatory state. The increase in the patients temperature causes (1) increased cardiac output (2)decreased systemic vascular resistance (3) increased heart rate and (4)increased end tidal CO2.[5] To avoid perioperative complications from the hyperdynamic state, we utilize hemodynamic monitoring as stated earlier, liberal fluid administration, and heart rate control.

INTRAOPERATIVE ELECTROLYTE IMBALANCES

1. Hypocalcaemia
2. Hypomagnesaemia
3. Hypokalemia
4. Anemia

During the heated perfusion, the chemotherapeutic agent Mitomycin C is nephrotoxic so a steady urinary output is required to avoid renal damage. The goal is to maintain 100cc every 15 minutes of urine output for the duration of the 90 minutes of hyperthermic perfusion, although patients with reduced cardiac function, a smaller amount 50 to75cc/ 15 minute period may be acceptable. The patients must be adequately hydrated to avoid hypovolemia. This is addressed by adjusting fluid administration of both colloid and crystalloids, along with starting a dopamine infusion at 0.5 to 3

mcg/kg/min 15 to 30 minutes prior to initiating the heated chemotherapy, and furosemide is used in small doses (2.5mg to 5mg) as needed to ensure and maintain adequate urine flow. Judicious fluid administration both before and during the heated chemotherapy is of great importance. In Esquivel's study, a noninvasive esophageal Doppler was used to evaluate preload, in the study the mean infusion rate per hour of intravenous fluids was 1781cc/hr during the heated perfusion. This large amount of fluid was shown to maintain an adequate effective circulating volume, allowing the patients to handle the hyperdynamic state and thermal stress. The data also showed that the most physiological maneuver to minimize intraoperartive complications is maintaining an adequate effective circulating volume by giving liberal fluids to counteract the increased venous capacitance.[5] Experience has shown that colloids have been very beneficial during the HIPEC portion of the surgery if urine output is sluggish and/or to maintain good urine output especially in hypoalbuminic patients. The osmotic activity of the high molecular weight substances in colloids tends to maintain these solutions intravascularly. Most colloid solutions intravascular half lives is between 3-6 hours versus 20-30 minutes for crystalloids.[3] Dopamine is only infused for the 90 minutes of heated perfusion. Dopamine is a non selective DA1 and DA2 agonist and has multiple effects. Although there is a lack of definitive evidence, low dose dopamine (0.5 to 3 mcg/kg/min) has been widely used as a renal protective agent. It is likely in many cases that dopamine benefits the kidneys by its beta adrenergic actions like increased cardiac output, increased renal blood flow and increased perfusion pressure.[10,11] In addition, stimulation of DA1 receptors causes renal vasodilation as well as inhibition of active sodium transport in the proximal tubule, leading to natriuresis and diuresis.[12] The small doses of furosemide

generally allow for steady flow without significant rebound effect following surgery and the subsequent need for a large amount of fluid to catch up later. In most HIPEC procedures furosemide is not necessary, the liberal fluid administration and low dose dopamine almost always allow the patient to produce good urine output. Communication between the surgeon, anesthesia provider, and perfusionist is vital. The temperature and urine output must be documented every 15 minutes and communicated to the surgeon and perfusionist. When the patient's core temperature starts to reach 39 degrees Celsius, the surgeon/pefusionist will start to decrease the temperature of the perfusate.

CHECKLIST 15 MINUTES PRIOR TO STARTING

HYPERTHERMIC PERFUSION

1. All fluid warmers off
2. Bair hugger placed on ambient
3. Lab results are evaluated / pending
4. Dopamine started at 0.5 to 3 mcg/kg/min
5. Open fluids with the approximate infusion rate of 1800cc/ hour to overcome venous capacitance
6. Start evaluating/documenting temperature and urine output every 15 minutes
7. Ensure antibiotics are repeated
8. Administer 5% Albumin as needed

Postoperative considerations

At the end of surgery, the patients are transported to the ICU with the endotracheal tube in place. Chemotherapy precautions must be utilized by all personnel coming in contact with the HIPEC patient. Extubation occurs after the patient has had time to equilibrate from temperature changes and volume administered, which varies depending on the duration of surgery, extent of surgery, volume required, and any intraoperative difficulties. Most patients are extubated within 1-4 hours after arrival in the ICU.

Cytoreductive surgery with HIPEC is becoming an increasingly important adjunct in the therapy of peritoneal surface malignancies. Anesthetic management of these cases requires a thorough pre-op evaluation with an understanding of the significant fluid and electrolyte changes and the hyperdynamic state induced by thermal stress during the heated perfusion as well as optimizing co-morbidities to minimize the risk of morbidity and mortality during the perioperative period.

References

1-Sugarbaker,PH: Heated Intraoperative Intraperitoneal Chemotherapy (HIIC). www.surgicaloncology.com.

2-Sugarbaker PH: Management of Peritoneal Surface Malignancies using Intraoperative Heated Perfusion and Cytoreductive Surgery: A Manual for Physicians and Nurses. www.surgicaloncology.com

3- Morgan GE, Mikhail MS: Clinical Anesthesiology, Appleton & Lange, 1992.

4-O Malley CMN, Bennett-Guerrero E: Does the Choice of Fluid Matter in Major Surgery. Evidence- Based Practice of Anesthesiology 2004: 136-143.

5-Esquivel J, Angulo F, Bland R, Stephans A, Sugarbaker P: Hemodynamic and Cardiac Function Parameters During Heated Intraoperative Intrperitoneal Chemotherapy using the Open "Colliseum Technique". Ann Surgical Oncology 1998(4) 296-300.

6-Kanakoudis F, Petrou A, Michalooudis D, Chortaria G, Konstantindou A. Anaesthesia for intra-peritoneal perfusion of hyperthermic chemotherapy; haemodynamic changes, oxygen consumption and delivery. Anaesthesia 1996;51: 1033-6.

7-Fleisher L: Should Beta-Adrenergic Blocking Agents be given Routinely in Noncardiac Surgery? Evidence-Based Practice of Anesthesiology 2004: 163-167.

8-Eagle KA, Berger PB, Calkins H, et al: ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery—Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Anes Analg 2002; 94: 1052-64.

9-Sladden R, Preoperative Evaluation of the Compromised Patient: University of Utah, Park City 52nd Annual Postgraduate Course in Anesthesiology and TEE. Feb 11th-16th 2007. p.60-68.

10-Sladden R. Preoperative Oliguria: Is There a Magic Bullet?: University of Utah, Park City 52nd Annual Postgraduate Course in Anesthesiology and TEE. Feb 11th-16th 2007. p. 90-106.

11-Bailey IM : Dopamine: One Size does not Fit All. Anesthesiology 2000; 92: 303-5.

12-Lokhandwala MF, Amenta F: Anatomical Distribution and Function of Dopamine Receptors in the Kidney. FASEB Journal 1991;5: 3023-30.