Learning From Others:

A Case Report From the Anesthesia Incident Reporting System

Anesthesia Quality Institute
ANESTHESIA INCIDENT REPORTING SYSTEM (AIRS)

Detailed review of unusual cases is a cornerstone of anesthesiology education. Each month, the AQI-AIRS Steering Committee will abstract a case and provide a detailed discussion based on a submission to the national Anesthesia Incident Reporting System. Feedback regarding this item can be sent by email to ***r.dutton@asahq.org****. Report incidents to* ***www.aqiairs.org****.*

Case 2013-2: Too Hot to Handle

"Never was anything great achieved without danger."
– Niccolo Machiavelli (1469-1527)

An ASA Physical Status 2, 38-year-old female presented for debulking of appendiceal cancer and hyperthermic intraperitoneal chemotherapy. Her past history included malignant melanoma, chemotherapy-associated pericarditis, and a pericardial window. General anesthesia was planned, and induction and endotracheal intubation were uneventful. The surgical case involved extensive removal of the metastatic tumors. During diaphragmatic stripping of metastases, the old pericardial window was inadvertently opened. The tear in the pericardial window was closed with a nylon suture. The team elected to proceed with chemotherapy infusion. During the hyperthermic intraperitoneal chemotherapy, the patient developed ST elevation but was hemodynamically stable. In the intensive care unit, a 12 lead ECG showed ST elevation in all leads, consistent with recurrent pericarditis. The patient was started on methylprednisolone, and the ST segment changes resolved within 24 hours without further sequelae.

Introduction

This case is illustrative of the systemic toxicity that can occur with aggressive intraoperative treatment of metastatic tumors. Hyperthermic intraperitoneal chemotherapy (HIPEC) joins isolated hyperthermic limb perfusion and radio-frequency ablation of hepatic metastatic tumors as intraoperative cancer treatments that have significant systemic and hemodynamic effects requiring sophisticated anesthetic monitoring and management.

Peritoneal carcinomatosis is a devastating progression of abdominal carcinomas, with widespread seeding of tumors on the surfaces of the bowel, the peritoneum and the mesentery. Until recently, the sheer mass of the tumor burden was thought to make this condition untreatable, with an expected survival of only months. In the mid-1990s, however, Dr. Sugarbaker at the Washington Cancer Institute reported that excision of as many tumors as feasible (cytoreduction) together with hyperthermic intraperitoneal chemotherapy significantly improved survival.[1] The therapy has remained controversial, as only one small randomized controlled trial has been conducted. Other researchers have not demonstrated similar survival rates, and the perioperative morbidity and mortality are significant. However, given the utter lack of alternatives, an increasing number of surgeons in Europe, Australia and the U.S. are advocating this therapy.

A recent systematic review of the literature concerning cytoreduction and HIPEC for ovarian cancer reported on 19 studies.[2] The overall rate of major perioperative morbidity ranged from 0-40 percent, and perioperative mortality varied from 0-10 percent. The overall median survival following HIPEC ranged from 22-64 months; if optimal cytoreduction was achieved, a five-year survival between 12-66 percent was achieved.[2] A similar review of 10 studies of HIPEC in gastric cancer found one-year survival rates to range from 22-68 percent.[3] Although these survival rates appear to be better than that seen without HIPEC, no conclusion can be drawn in the absence of randomized trials that control for patient selection bias. To date, the majority of patients selected for HIPEC have been otherwise healthy.

Surgical Procedure

The procedure involves aggressive resection of as much of the tumor burden as can be accomplished. Typically much of the peritoneum is stripped away, and omentectomy and multiple bowel resections are performed, with the aim of leaving as little tumor as possible. Following resection the abdomen is closed and intraperitoneal catheters are placed for infusion of the heated chemotheraputic. Some surgeons advocate performing the HIPEC with the abdomen open and prior to completion of bowel anastamoses.[4,5] This allows

the surgeon to physically manipulate the viscera to ensure adequate distribution of the heated solution, and it removes the question of metastatic cells being "trapped" in the anastamotic suture line.[4,5]

In a recent review of 24 reports of HIPEC, the duration of HIPEC ranged from 30-120 minutes and the temperature of the chemotherapeutic solution ranged between 39-44 degrees C.[6] The chemotherapy solution used varies by type of cancer: for peritoneal surface malignancies, mitomycin C; for colorectal cancer, mitomycin C and oxaliplatin; in gastric cancer, mitomycin C; and in ovarian cancer, cisplatin. The reported series cite dose ranges for mitomycin C of 10-120 mg/m^2, and for cisplatin 50-250 mg/m^2. Intraperitoneal instillation of the chemotherapeutic agent allows for a much higher chemotherapeutic dose than could be tolerated systemically; heating the solution has been shown to have a synergistic effect. The extensive surgical resection and hyperthermic chemotherapy, however, have systemic effects requiring careful anesthetic management.[7,8]

Operative and Anesthetic Management

Fluid shifts and protein loss are extensive and continual, beginning with the loss of ascites in many patients. The extensive peritonectomy and stripping of tumor plaques results in further significant fluid and protein loss from the raw surfaces, and manipulation of the bowel may result in third-space losses due to bowel edema. The protein loss due to removal of ascites and extensive debulking can reach 700 gm per day.[8] Taken in total, the fluid requirements may reach 12-15 mL/kg/hr, exceeding the 8-10 mL/kg/hr typically expected for abdominal procedures, and may include significant blood loss.[7,9,10] One report of 76 patients noted that the median duration of surgery was 10 hours (mean 9:51 hrs, range 3-16 hrs), the average blood loss was 2,384 mL (range 50 – 14,000 mL), with a mean of 12,220 mL of crystalloids and 4,791 mL of colloids administered.[10] The anesthesiologist must take care to not only replace volume but also to replace colloid oncotic pressure with colloid solutions, albumin and/or plasma.

Blood loss can result in significant coagulopathy. A recent report of 78 patients demonstrated increased INR, aPTT and antithrombin III with decreased platelet count.[7] Cell saver use can decrease the requirements for transfusion, but the recovered red cells must be irradiated to ensure elimination of metastatic cells. Administration of plasma can be beneficial for both maintenance of colloid oncotic pressure and adequate coagulation factor levels. Use of a point of care viscoelastic monitor can assist with identification of fibrinolysis, thrombocytopenia and Factor XIII deficiency.[8]

Extensive fluid shifts and protein loss can lead to non-cardiac pulmonary edema; the increased abdominal pressure associated with closed intraperitoneal perfusion can shift the diaphragm cephalad, reducing pulmonary excursion and resulting in decreased oxygenation and increased airway pressure.[7] Increased abdominal pressure during this period can lead to impairment of venous return and an increase in splanchnic vascular resistance.

Patients are at risk of becoming hypothermic during the extensive period of cytoreduction, and then hyperthermic during the peritoneal perfusion period. Instillation of the hyperthermia solution (39-42 degrees C) induces a hypermetabolic state, with peripheral vasodilation (adding to the challenges of maintaining fluid balance), increased heart rate and increased cardiac output.[4] Systemic temperature quickly reaches 40 degrees or more centigrade, even with use of cooling blankets and cooled I.V. solutions. Oxygen demand increases and may be associated with a combined respiratory and metabolic acidosis.[7,8]

Perioperative pain management is often a challenge. Many patients with abdominal carcinomatosis have chronic pain and significant preoperative opioid use. The use of thoracic epidural anesthesia (TEA) is advocated, as there is significant pain both intra- and postoperatively.[7,8] Although one author has pointed out the potential issue of peripheral sympathectomy in the face of significant fluid shifts, and the potential for epidural hematoma with coagulopathy,[11,12] the majority of patients do receive epidural analgesia intraoperatively and for up to five days postop, without reported morbidity due to the TEA.[7,9,10] In a recent survey of 29 centers performing HIEPC, 72 percent reported use of TEA intra- and postoperatively, and 69 percent used PCA opioid infusions; despite this aggressive approach, only 28 percent reported that they achieved excellent pain control. Of note is that the incidence of epidural abscess was 2/4,276 patients.[13]

Finally, the specific effects of the chemotherapeutic agents must be considered. Cisplatin is administered in 5 percent glucose, and as much as 3-5 L of this solution may be administered, resulting in hyperglycemia and/or hyponatremia. Systemic absorption can lead to cardiotoxicity. One case report of intraperitoneal cisplatin details onset of intermittent (30 seconds) pulseless ventricular tachycardia that was refractory to amiodarone. Electrolytes were normal, but hypomagnesemia was present with a prolonged QT interval. The intraperitoneal cisplatin fluid was drained with prompt resolution of the arrhythmia. The authors concluded that the direct cardiotoxic effects of unbound cisplatin were responsible for the tachyarrhythmia. The case reported here demonstrates the local toxicity of chemotherapy on either the myocardium or the pericardium.

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Whether expedited drainage of the chemotherapy solution was performed is not noted, but this should be considered in any case of intraoperative cardiac dysfunction. Cisplatin can cause renal wasting of magnesium, and prolongation of the QT interval. Local effects of chemotherapeutic solutions also include neurotoxicity with gastric and bowel atony in the postoperative period. Exposure of the operating room staff to aerosolized mitomycin and cisplatin is decreased with the use of closed hyperthermic perfusion; surgeons need to be careful to double glove (latex gloves are recommended) to avoid personal systemic absorption of the chemotherapy agents.[8]

Discussion

In the case reported to AIRS, the ST segment elevation is presumed to have resulted from entry of the hyperthermic chemotherapeutic agent across the suture line of the pericardial window. There is no mention of a discussion or concern of the potential risk, or of how the decision was made to proceed. There are no reports in the literature similar to this, and the anesthetic and surgical team could not have based a decision on the literature. However, unexpected developments occur every day in the surgical suite, and anesthesiologists can-not simply focus on the anesthesia machine and monitors. Effective anesthesia

Table 1: Multi-Institutional Experience with HEIPC

Management Practice (International survey of practice, Sept 2010)[13]	Percent Reporting Practice
Preoperative Testing	
Routine Labs	100%
Electrocardiogram	93%
Echocardiography	24%
Pulmonary Function Tests	28*
Anesthesia Set-up*	
Arterial line	100%
Intubation/mechanical ventilation	100%
Large bore peripheral I.V.	100%
Central line	90%
Cardiac output monitoring (varied types)	45%
Thoracic epidurals intra- and postoperative	72%
Temperature probe (predominantly esophageal)	100%
Fluid Management	
Trigger for blood transfusion (typically 7-8 g/dL)	62%
Use of albumin solutions	55%
Coagulopathy Monitoring (q 2-4 hrs)	
Standard laboratory testing (APTT, PT, INR)	93%
Thromboelastogram (TEG, ROTEM)	21%
Fresh frozen plasma prophylactically	48%
Transexamic acid	14%
Use of FFP for coagulopathy	90%
Temperature Management	
Forced air warming	79%
Active cooling during HIEPC (mean target 39.2°C)	62%
Renal Protection	
Furosemide	28%
Dopamine infusion	17%

*No note made of intraoperative ECG; recommend 5 lead.

care requires a keen "situational awareness" and a willingness to speak up when concerned. It certainly would have been appropriate for the anesthesiologist in this case to enter into a discussion with the surgeon of the advisability of moving forward with the hyperthermic chemotherapy, given the open pericardial window. The discussion should have included a risk/benefit analysis, with a clear decision made to proceed with a full understanding of the increased risks.

Conclusions

The use of HIPEC is increasing, and anesthesiologists need to be familiar with the significant hemodynamic, and serum chemistry and protein alterations associated with this therapy. As in this case, excellent resources for management can be found in recent publications and should be reviewed in advance by the care team.

Table 2. Key Management Points (adapted from Raspe et al[8])

Maintaining and restoring normothermia and normovolemia during the cytoreductive and the hyperthermic intraperitoneal chemotherapy (HIPEC) phase is of critical importance.
A balance of crystalloid and colloid solutions will be required to maintain volume status and colloid oncotic pressure.
Expect and manage hypothermia during cytoreductive phase; expect and manage hyperthermia and hypermetabolic state during HIPEC.
Supplemental thoracic epidural analgesia can be recommended to HIPEC patients.
The anesthesiologist should be familiar with the adverse effects of the chemotherapeutics as well as their carrier solutions.
Point-of-care testing is a helpful tool for detection and therapy of complex chemical and coagulation disorders.

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