

Hyperthermic Intraperitoneal Chemotherapy with Cytoreductive Surgery in a High-risk Patient: A Case Report

Annette Rebel^{1*}, Anne N Sloan¹, Brian Wetherington², Sean Dineen³ and Thomas J McLarney¹

¹Department of Anesthesiology and Surgery, University of Kentucky, USA

²Department of Anesthesiology, University of Missouri, USA

³Department of Surgery, University of Kentucky, USA

Abstract

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is an important treatment option for patients with abdominal neoplasms and peritoneal dissemination of disease. However, there are considerable anesthetic risks to the procedure due to the significant temperature fluctuations and fluid shifts. We present a case of a patient with newly diagnosed severe mitral regurgitation who successfully underwent CRS/HIPEC.

A 64 year old male patient presented to our hospital for evaluation for CRS/HIPEC due to mucinous appendiceal neoplasm with peritoneal dissemination. The preoperative assessment found a severe mitral regurgitation with preserved left ventricular systolic function. The patient was asymptomatic and it was decided to proceed with CRS/HIPEC. However, the hyperthermia and significant intraoperative fluid shifts associated with a HIPEC procedure were concerning for potential cardiac decompensation and pulmonary edema. The intraoperative goals were to maintain heart rate, reduce afterload, and avoid volume overload. A preoperative thoracic epidural catheter was placed for pain management. Additional monitoring included the post-induction placement of a pulmonary artery catheter and transesophageal echocardiography probe. Anesthesia was maintained on isoflurane and an epidural lidocaine infusion with intermittent epidural fentanyl boluses. Fluid management was guided by cardiac filling pressures, urine output, serial arterial blood gases, and transesophageal echocardiography. Nitroglycerin boluses and infusion were used to decrease afterload. The patient tolerated the surgery well without any cardiac decompensation; he was extubated in the operating room and taken to recovery. No immediate postoperative complications were observed.

The case report documents that patients with significant cardiac co-morbidities can successfully undergo CRS with HIPEC. Pre-HIPEC systemic hypothermia can be utilized in these patients with advanced hemodynamic monitoring. It appeared advantageous to involve the complete anesthesia team early to allow multi-disciplinary planning of the perioperative course.

Keywords: Hyperthermic intraperitoneal chemotherapy; Mitral valve regurgitation; Perioperative medicine; Anesthesia

Introduction

In selected patients with abdominal malignancy and peritoneal carcinomatosis the use of cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) can improve survival and life quality [1,2]. This treatment approach appears to be very efficacious for neoplasms of the appendix with peritoneal spreading, and has therefore become an established treatment [3]. However, due to the well described hemodynamic stress and fluid shifts associated to HIPEC, patients with significant co-morbidities are usually not seen as good candidates for undergoing this approach [1,4]. HIPEC is associated with marked increase in cardiac output, oxygen consumption and changes in vascular resistance [5-7]. While beneficial effects of CRS with HIPEC have been well described, patient selection criteria are not [8]. Selection criteria appear to be center specific, influenced by the oncological assessment and patient co-morbidities. We describe a patient with significant mitral valve abnormality, posing high vulnerability for changes in vascular resistance and fluid fluctuations, undergoing CRS and HIPEC.

Case Report

A 64-year-old male patient presented to our preoperative clinic for assessment before undergoing CRS with HIPEC. The patient underwent an urgent laparoscopic appendectomy 2 months earlier in an outside hospital without any complications; the previous surgery and histology indicated a low-grade mucinous appendix neoplasm with peritoneal dissemination. During physical exam in the preoperative clinic, a

high grade holosystolic murmur was identified. The transthoracic echocardiography diagnosed a severe mitral regurgitation related to severe mitral valve prolapse secondary to partial frail posterior leaflet, and severe left atrial dilation (Figure 1). Left and right ventricular function was normal. The patient reported no symptoms and he reported his exercise ability as unimpaired in excess of 4METs. After discussion with the surgeon, and consultation of a cardiologist and a cardiothoracic surgeon, it was decided that the oncological urgency for cancer progression superseded the concerns for hemodynamic instability due to severe valve abnormality. The situation was openly discussed with the patient and he decided to proceed despite the increased risk for perioperative complications. The patient was deemed optimized for surgical procedure.

On the day of surgery, the patient received preoperative midazolam for anxiolysis. A thoracic epidural catheter (T7-8) was placed in the holding area prior to taking the patient to the operating room. After

*Corresponding author: Annette Rebel, Department of Anesthesiology and Surgery, University of Kentucky, USA, Tel: 859-323-5956; Fax: 859-323-1080; E-mail: arebe2@email.uky.edu

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placement of a radial arterial cannula for invasive blood pressure monitoring and preoxygenation with FiO₂ 0.8, anesthesia was induced using intravenous fentanyl, propofol (1.5 mg/kg) and rocuronium. Anesthesia was maintained with isoflurane and epidural lidocaine (1% at 2-5 ml/kg/h) with intermittent epidural fentanyl boluses (100 mcg/h). Post intubation, a pulmonary artery catheter (PAC) was placed. First post induction measurements indicated adequate volume status, cardiac function and low systemic vascular resistance prior to incision (PAP 32/13 mmHg, mPAP 20 mmHg; CI 3.3l/min/m²; SVO₂ 82%; calculated SVRI 1721 dyne s/cm⁵/m²). Additional monitors included a transesophageal echocardiography probe (TEE) with 3-D capability, BIS monitor and temperature sensors for bladder temperature and nasopharyngeal temperature. Warming/cooling devices (water based cooling blanket, forced warm air device for upper and lower body region) were used to actively influence body temperature. Surgical incision was 55 min after anesthesia induction. The cytoreductive surgery portion

required 5.5 h. At the conclusion of the cytoreductive part, the patient was gradually cooled to core temperature of <35°C and ice packs were placed around the neck. Pre HIPEC iatrogenic hypothermia increased systemic vascular resistance (SVR) and reduced contractility without increasing pulmonary arterial pressure or mixed venous oxygen saturation (Table 1). HIPEC related systemic hyperthermia did not lower SVR below measurements at normothermia and cardiac output returned to baseline.

HIPEC with mitomycin was started 6 h after incision (chemotherapy was added 20 min after hyperthermia instillation start and lasted for 120 min). After conclusion of HIPEC, surgical anastomosis was concluded and a gastrostomy tube was placed. After HIPEC was concluded, an intravenous infusion of nitroglycerin was started and titrated from 0.2 to 0.4 mg/kg/min to maintain MAP <80 mmHg. The epidural lidocaine infusion was transitioned to bupivacaine 0.25% (5 ml/h with intermittent 2 ml boluses) to supplement anesthesia and analgesia. The complete surgical procedure time was 9 h and 30 min. The TEE probe was removed before anesthesia emergence.

At the end of the procedure, the patient was successfully extubated and transported to the post anesthesia recovery area and to the ICU after complete recovery from anesthesia. He remained on the nitroglycerin infusion until POD#1. Postoperative pain was well controlled with epidural analgesia (VAS<5) and the patient was able to ambulate with assistance on POD#1. Since the patient was hemodynamically stable, PAC was removed at POD#1 out of concern for increased infection risk in immune-compromised patients. Invasive blood pressure monitoring was discontinued at POD#2 after the patient did not require any antihypertensive medications for >12 h. Serum creatinine concentration increased from baseline before HIPEC 0.8 mg/dL to a peak level of 1.2 mg/dL on POD#2 despite adequate urine output. The patient remained in the ICU until POD#3 to provide adequate fluid resuscitation under close monitoring of hemodynamics, respiratory status and renal function. Volume resuscitation was monitored by intermittent N-terminal Pro Brain Natriuretic Peptide (NT-pro BNP) serum level

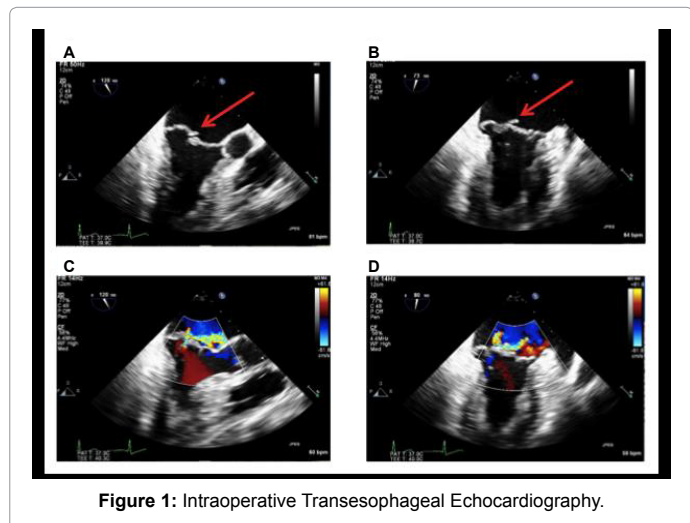


Figure 1: Intraoperative Transesophageal Echocardiography.

Time [min]		BL	-15	HIPEC start	+15	+60	+90	HIPEC end	Surgery end	Emergence	PACU	ICU	POD #1
Temp. Core	°C	36.0	33.7	33.7	35.9	38.9	39.1	38.5	37.9	37.5	36.8	36.4	36.2
Temp. NP	°C	35.8	34.4	34.5	34.4	37.1	36.8	36.4	36.6	37.7			
HD													
MAP	mmHg	78	80	82	75	84	75	80	72	78	75	80	84
SPAP	mmHg	32	34	29	31	35	33	27	23	24	29	32	22
DPAP	mmHg	13	15	13	14	14	19	13	14	17	10	16	16
MPAP	mmHg	20	24	20	21	24	22	20	19	19	16	22	20
CI	ml/min/m ²	3.3	2.1	1.8	2.4	3.0	2.5	3.4	2.4	2.7	2.4	2.6	3.0
SVO ₂	%	82	90	92	85	83	82	82	83	82	78	73	75
SVRI	dyne s/cm ⁵ /m ²	1721	2740	3241	2198	2141	2046	1669	2198	2131	2297	2121	2184
ABG													
P _a O ₂	mmHg	225	322				190		215		127	84	75
P/F ratio		312	367				292		390		453	300	267
Lactate	Mmol/L	0.6	1.8				2.0		2.2		2.3	2.7	1.6
Bicarb	Mmol/L	25	22				20		21		22	21	22
BNP	pg/ml										74	82	133

Time in minutes expressed in relation to HIPEC/hyperthermia instillation start: BL = baseline, measurements before incision, surgery end = closure of abdominal incision, Anesthesia emergence = last measurement before extubation, PACU = at arrival in postanesthesia Care Unit, ICU = at arrival in Intensive Care Unit, and POD#1 = first postoperative day.

Mean arterial blood pressure [MAP], pulmonary artery pressures [SPAP/DPAP and MPAP]; Cardiac index [CI]; venous saturation [SVO₂], and systemic vascular resistance index [SVRI]. Arterial blood gas analysis was used to monitor P_aO₂, lactate, bicarbonate levels and NT-pro Brain natriuretic peptide [BNP].

Blue: systemic hypothermia (<36°C), Red: systemic Hyperthermia (>38°C)

Table 1: Temperature related changes of hemodynamic and circulation parameters.

measurements (Table 1). Creatinine concentration normalized on POD#3 prior to discharge from the ICU. The remainder of the hospital course was uneventful and the patient was discharged home on POD#7.

The patient was readmitted 1 week after initial discharge (POD#15 post HIPEC) because of significant nausea and vomiting. The patient responded to conservative therapy, but the workup indicated concerns for malnutrition (prealbumin concentration 8 mg/dL) and leukocytosis. The patient stayed hospitalized for 8 days to complete antibiotic therapy, to avoid dehydration and to provide intensified nutritional support before being discharged to a rehabilitation facility. An ambulatory follow up appointment 6 months after HIPEC indicated that the patient had recovered and was doing well by returning to his regular life activities. Radiographic workup did not show any evidence of neoplasm recurrence.

Discussion

The presented case describes the perioperative management of a patient with advanced valvular heart disease undergoing CRS with HIPEC without major complications. In addition to providing more information about patient selection criteria for this invasive surgical approach of disseminated abdominal malignancy, this case describes the influence of intentional temperature manipulation (from significant hypothermia to hyperthermia) on systemic vascular resistance, cardiac function and oxygen utilization.

As described in previous publications, the perioperative HIPEC management of otherwise healthy patients presents significant challenges due to fluid shifts, extensive surgical exposure and temperature manipulation [8,9]. Considering the well documented benefits of cytoreduction and HIPEC for life quality and survival, anesthesia providers will be asked to consider patients with significant co-morbidities for this procedure. Non-ischemic mitral valve regurgitation (MR) due to mitral valve prolapse is not an uncommon finding. The hemodynamic impact of the valvular abnormality is rarely severe under normal circumstances and is usually managed medically [10]. According to AHA/ACC recommendations, surgical repair or replacement is recommended in patients with severe MR when patients develop symptoms (shortness of breath, palpitations, fatigue), asymptomatic patients with mild to moderate LV dysfunction, new onset atrial fibrillation, pulmonary hypertension or if repair has a high likelihood of success without residual MR [11]. However, impact of the described valvular abnormality on hemodynamic function and needs during HIPEC are different.

Our patient presented with asymptomatic severe non-ischemic MR related to mitral valve prolapse and would have fallen in the patient category to be managed medically until the valvular abnormality would progress. He recently underwent a less invasive procedure (laparoscopic appendectomy) without any perioperative complications. However, HIPEC imposes different anesthesia and surgical challenges. The temperature shifts before HIPEC can cause an afterload increase and therefore induce LV function compromise and pulmonary edema [5,6,9]. Based on previous studies the systemic response to HIPEC-related hyperthermia are increased heart rate, elevated cardiac output and >50% drop in systemic vascular resistance [5,9]. The hyperdynamic state and increase in filling pressures during systemic hyperthermia could induce arrhythmia (atrial fibrillation) or heart function compromise [6,9]. The hemodynamic and metabolic changes may last longer than the hyperthermia [9]. Although the presented patient was asymptomatic, he presented an increased risk for decompensation during or after HIPEC. Meticulous advanced

monitoring and continuous adjustments of anesthesia technique/ vasoactive medications were needed.

Recent publications have shown the advantage of epidural analgesia for perioperative management of HIPEC patients [12,13]. Owusu-Agyemang et al. demonstrated that epidural use decreased blood loss and fluid requirements, optimized postoperative analgesia and was not associated with significant complications [12]. Osseis et al. documented the postoperative benefits of epidural analgesia after HIPEC for patient ambulation and recovery [13]. We utilized the preoperatively placed epidural catheter with intraoperative local anesthesia and opioid to use the associated sympatolysis for blood pressure and afterload management in addition to postoperative analgesia. Based on our novel and aggressive approach, our patient tolerated pre-HIPEC associated hypothermia followed by HIPEC hyperthermia well. Since the reported changes in SVR, cardiac output and pulmonary artery pressures are slightly different from previous reports [9], we consider the possibility that the epidural anesthesia with lidocaine and fentanyl may have mitigated temperature related SVR changes.

Iatrogenic hypothermia before HIPEC is not routinely practiced in all centers [14,15]. While the avoidance of pre-HIPEC hypothermia may have decreased the systemic hemodynamic stress, the risk of systemic and cerebral hyperthermia would have been increased [8]. Considering the valvular abnormality of the presented patient, we could have chosen to omit the pre-HIPEC hypothermia. However, this would have created a less aggressive oncological procedure (by decreasing the HIPEC temperature) and the threat of cerebral hyperthermic injury [8,16]. Therefore, we decided to induce the hypothermia stage under advanced hemodynamic monitoring.

Another observation of the presented case deserves to be commented on, directed towards the perioperative process and the role of the anesthesiologist as perioperative physician. Although the patient presented as an otherwise healthy individual with recent anesthesia exposure without any problems, the systematic and thorough workup in the preoperative anesthesia clinic revealed a significant abnormality, changing the anesthesia approach used for this patient. The presented case documents the role and value of the anesthesiologist as the perioperative constant of patient care [17,18]. The preoperative evaluation in the anesthesiology-run PreOp clinic identified the cardiac abnormality and initiated the workup. The intraoperative and postoperative care teams were included in these discussions preoperatively, resulting in a perioperative care plan for this patient prior to surgery. While some recent publications have provided evidence that questionnaire based patient screening could make the preoperative process more efficient, it is possible that patients similar to the presented case may not be recognized in a less personal screening process since our asymptomatic patient was not aware of any health care problems [19,20].

In conclusion, this case emphasizes the need for the early involvement of the complete anesthesia care team in the perioperative process for patients undergoing aggressive oncological procedures, independent of the subjective health status of the patient. With appropriate planning, patients with significant cardiac co-morbidities can successfully undergo cytoreductive surgery with HIPEC.

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