



Anesthetic management in patients undergoing hyperthermic chemotherapy

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Purpose of review

Cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has become an important therapeutic option for selected patients with peritoneal surface malignancies. This aggressive multimodality treatment is complex, not only regarding surgical technique, but also regarding anesthesia. The present review represents our experience in anesthetic care.

Recent findings

Improved prognosis compared with systemic chemotherapy alone has recently been demonstrated for cytoreductive surgery when combined with intraoperative intracavitary hyperthermic chemotherapy. Anesthetic management of HIPEC is further impacted by these developments. In addition to the ambitious, long-lasting surgery, HIPEC causes significant fluid, blood and protein losses, increased intra-abdominal pressure, systemic hyperthermia, and increased metabolic rate, leading to relevant pathophysiological alterations, and therefore represents a challenge for anesthetist and critical care physicians.

Summary

Anesthetic management importantly contributes to the containment of the perioperative complications of HIPEC. An appreciation of the technical aspects and physiologic disruptions associated with intra-abdominal HIPEC is critical to ensure effective anesthetic management. Although data on this specialized surgical procedure are scarce, some referral centers have accumulated extensive experience. This article reviews the current knowledge about the anesthesiological and intensive care management of patients undergoing HIPEC. It pinpoints strategies for perioperative monitoring as well as illustrates alterations in hemodynamic, hematopoietic, and fluid hemostasis.

Keywords

anesthetic and intensive care management, hyperthermic intraperitoneal chemotherapy

INTRODUCTION

Hyperthermic intraperitoneal chemotherapy (HIPEC) combined with cytoreductive surgery has been developed in the last years as an effective multimodality treatment option for selected patients with peritoneal surface malignancies [1,2]. HIPEC is performed intraoperatively following peritonectomy procedures. Four drains are placed into the abdomen, one of which represents the inflow and three the outflow catheters. The perfusate is then circulated with a roller pump system into the abdominal cavity at a temperature of 42–43°C. Temperature is monitored during the whole procedure with several probes placed at different sites into the peritoneal cavity. When heated, cytostatic agents are added to the perfusate and HIPEC is performed for 30–90 min, according to different protocols.

Best results can be achieved in selected patients with peritoneal carcinomatosis arising from colorectal cancer. The median survival can be improved compared with systemic chemotherapy alone by 16–24 months with a 5-year survival rate of 30–45% [3–5,6]. Therefore, HIPEC

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Curr Opin Anesthesiol 2012, 25:348–355

DOI:10.1097/ACO.0b013e32835347b2

KEY POINTS

- Maintaining and restoring normothermia and normovolemia during the cytoreductive and the hyperthermic intraperitoneal chemotherapy (HIPEC) phase is of critical importance.
- Supplementary thoracic epidural analgesia can be recommended in HIPEC.
- The anesthesiologist should be familiar with the adverse effects of the chemotherapeutics as well as their resolving solutions.
- Point-of-care testing is a helpful tool for detection and therapy of complex coagulation disorders and salvage of cell saver blood with subsequent irradiation is an established option to spare banked blood in HIPEC.

was performed with an upward trend worldwide as the safety, morbidity rate, and therapeutic considerations are better understood and recognized [7]; at present, there are more than 100 centers in the USA and also in European countries.

HIPEC can be performed as a closed or open abdominal technique. Advantages of the closed procedure are the reduced heat loss, increased tissue penetration due to the increased intra-abdominal pressure, and decreased contamination risk, whereas the advantage of the open abdominal technique is the homogeneous, abdominal distribution of the chemotherapeutics. Up to now, there are no data comparing both techniques; however, most centers perform closed HIPEC techniques.

Depending on the entity of tumors, different chemotherapy strategies are performed intraperitoneally (Table 1).

It has been previously reported that the effects of intraperitoneal chemotherapy can be maximized by delivering the chemotherapy at 42–43°C and thereby heated intraperitoneal chemotherapy achieves high peritoneal concentrations with limited systemic adsorption over the whole time of chemotherapy [8,9]. However, the anesthetist should still be aware of possible side-effects of each applied chemotherapeutic (Table 2) in addition to the usual side-effects, such as allergic reactions, nausea and vomiting, or flush.

Hyperthermic chemotherapy compared with early postoperative intraperitoneal chemotherapy could demonstrate the best effect on overall survival. In agreement, HIPEC also featured better outcome for patients compared with normothermic intraoperative intraperitoneal or early postoperative intraoperative chemotherapy [10,11[■]]. Intracavitary application targets the chemotherapy directly at the sites of recurrence, with higher doses than would be tolerated systemically. Heating the chemotherapy agent increases tumoricidal activity by increasing the permeability and metabolic activity of the cells with additionally direct hyperthermic effects [12–14]. Due to these clear data, the experts during the Sixth International Workshop on Peritoneal Surface Malignancy stated that ‘cytoreductive surgery and HIPEC is standard treatment of peritoneal carcinomatosis ... in experienced multidisciplinary centers’ (Lyon, November 2008).

Table 1. Different intraperitoneally applied chemotherapy strategies

Entity of tumor	Chemotherapeutic solution
Colon	Oxaliplatin 300 mg/m ² BSA i.p. + 5 FU 400 mg/m ² BSA i.v. + 20 mg mg/m ² BSA leucovorin i.v. 5 FU + leucovorin after fascia suture
Appendix	Oxaliplatin 300 mg/m ² BSA i.p. + 5 FU 400 mg/m ² BSA i.v. + 20 mg mg/m ² BSA leucovorin i.v. 5 FU + leucovorin after fascia suture
Rectum	Oxaliplatin 300 mg/m ² BSA i.p. + 5 FU 400 mg/m ² BSA i.v. + 20 mg mg/m ² BSA leucovorin i.v. 5 FU + leucovorin after fascia suture
PMP	Oxaliplatin 300 mg/m ² BSA i.p. + 5 FU 400 mg/m ² BSA i.v. + 20 mg mg/m ² BSA leucovorin i.v. 5 FU + leucovorin after fascia suture
Ovarial	Cisplatin 75 mg/m ² BSA i.p. Doxorubicin 15 mg/m ² BSA i.p.
Stomach	Cisplatin 75 mg/m ² BSA i.p. Doxorubicin 15 mg/m ² BSA i.p.
Mesothelioma	Cisplatin 75 mg/m ² BSA i.p. Doxorubicin 15 mg/m ² BSA i.p.

The strategies applied depended on the entity of tumor (with kind recommendations of Professor Dr Piso). BSA, body surface area; FU, flurouracil; i.p., Intraperitoneally; i.v., intravenous.

Table 2. Chemotherapeutics used during hyperthermic intraperitoneal chemotherapy and possible chemotherapeutic-specific adverse effects

Chemotherapeutics	Adverse effects
Mitomycin C	Nephrotoxicity, pulmototoxicity
Cisplatin	Peripheral neuropathia, myelotoxicity
Doxorubicin	Cardiotoxicity (arrhythmia, cardiomyopathia), myelotoxicity
Oxylipatin	Neurotoxicity (laryngeal/pharyngeal dysesthesia)
Irinotecan	Myelotoxicity

The main challenge is the patient selection for cytoreductive surgery and HIPEC. This is combined with a long learning curve, as many factors may play a crucial role:

- (1) Tumor entity:
 - (a) peritoneal carcinomatosis due to colorectal cancer,
 - (b) peritoneal carcinomatosis due to gastric cancers,
 - (c) peritoneal carcinomatosis due to ovarian/tube/cervix cancer,
 - (d) pseudomyxoma peritonei,
 - (e) malignant peritoneal mesothelioma,
 - (f) peritoneal sarcomatosis,
 - (g) adjuvant HIPEC (RO resection of colorectal/gastric cancer), and
 - (h) palliative HIPEC (due to uncontrolled ascites).
- (2) No extra-abdominal metastases.
- (3) High probability of complete macroscopical surgical cytoreduction, as assessed by computer tomography (CT), PET-CT, and laparoscopy – in particular, to exclude a disseminated small bowel disease.
- (4) Limited tumor extent, with a peritoneal cancer index of less than 20 (maximum 39 possible).
- (5) Good general status with a Karnovsky index of at least 80% and no major co-morbidity.

Regarding safety data with the handling of intraperitoneal chemotherapy during and following surgery, lots of articles have been published that summarize that adhering to instructions regarding the use of chemotherapeutics reduces occupational risk of exposure for collaborators (surgeon/perfusionist) executing the procedure during HIPEC [15,16]. This was demonstrated by ambient air and biological monitoring. Furthermore, established in-vitro methods showed that wearing doubled gloves of natural rubber latex can prevent a breakthrough of

chemotherapeutic agent. The closed abdomen technique reduces the potential for the operating room staff and is used for HIPEC in most institutions [17].

Marked effects on the cardiovascular status, oxygen consumption, and hematopoietic parameters of patients during HIPEC have been described in the literature and are often observed in practice [18–21]. Therefore, knowledge of pathophysiological changes accompanying extended debulking and HIPEC is of utmost importance to abide or restore physiological homeostasis perioperatively.

This review concludes results from the literature and experiences from specialized centers dealing with pathophysiological alterations during cytoreductive surgery and HIPEC, and emphasizes the important ‘HIPEC-specific’ concerns beyond the standard anesthetic management issues for intra-abdominal surgery. Furthermore, recommendations for special anesthetic attendance and care as well as suggestions for therapeutic approaches to combat HIPEC-specific perioperative problems are given.

MAINTENANCE OF TEMPERATURE BALANCE

Perioperative management of patients undergoing cytoreductive surgery with HIPEC is a challenge for the anesthetist, even though many patients are young and without relevant comorbidity. During cytoreductive period, the anesthetist is confronted by substantial fluid losses due to drainage of ascites, the drawn-out procedure, and extreme surface exposure [21]. Despite the extensive debulking procedure and the large abdominal surgical access, hypothermia has to be prevented by all means by using forced air warming with blankets, and warmed infusions, as coagulation, metabolic homeostasis, anti-inflammatory cascade, and neurological status are all dependent on thermal homeostasis [22–24].

However, due to the hyperthermic intraperitoneal solution administered during HIPEC, body temperature – measured esophageally, vesically, or tympanically – rises up to 40.5°C (mean 37.7°C) [7,19,25,26], leading to a significantly increased metabolic rate. Hence, the anesthetist should note that vesically measured temperature rises rapidly after administration of hyperthermic solution intraperitoneally.

In consequence, patients develop a rising systemic oxygen demand [19], bringing forth an increase in heart rate and end tidal CO₂ levels with concomitant metabolic acidosis and elevated arterial lactate values reaching their maximum at the end of the HIPEC phase [18,19,21,25,26].

Therefore, the aim of the anesthetist should be the restoration of normothermia by using cooled infusions and the perpetuation of metabolic standard values by adjusting respiratory ventilation to the hypermetabolic conditions during HIPEC [2⁷].

FLUID MANAGEMENT AND VOLUME STATUS

In addition, maintaining and restoring a normovolemic status during the cytoreductive period by using crystalline and colloid solutions as well as blood substitutes before starting HIPEC procedure is important to be prepared for the excessive pathophysiological alterations during the HIPEC phase. Intraoperative fluid turnover significantly exceeded the established levels of 6–8 ml/kg per h fluid loss by fluid turnover for major abdominal interventions with values up to 12 ml/kg per h depending on the degree of debulking. Blood loss can also be extensive in some patients.

Abdominal filling with saline solution enriched with chemotherapeutics causes an increase in intra-abdominal pressure with cranial shift of the diaphragm resulting in a reduction in the functional residual capacity and an increase in airway pressure. These effects are analogous to those seen in patients with pneumoperitoneum [27–29]. These changes in turn lead to a decrease in oxygenation ratio and an abrupt rise in the central venous pressure [19,21]. It is well known that small changes in intra-abdominal pressure affect cardiac output [30–32] due to the reduction in the venous return by narrowing of the vena cava associated with a reduction of the abdominal blood volume and an increase in splanchnic vascular resistance [33,34]. Not only macrocirculation, but also microcirculation will be affected during HIPEC period with a significant increase in gastric $p\text{CO}_2$ and decrease in gastric pH during HIPEC.

Blood volume plays a major role in establishment and maintenance of adequate systemic as well as regional perfusion [25]. Therefore, to prevent systemic hemodynamic disorders or reduction of regional perfusion leading to acute renal failure – aggravated by administration of chemotherapeutics (cisplatin) – [35] during HIPEC, adequate fluid therapy should be one of the main goals for the anesthetist. By considering this aspect and by checking urinary output, the standardized use of furosemide (mean dose of 25 mg) [25] or low doses of dopamine [36] to improve urinary output and prevent renal dysfunction is inadvisable as previous studies demonstrated unaltered perioperative creatinine values in patients with cytoreductive surgery and HIPEC just by maintaining normovolemia and

adequate urinary output [26]. Furthermore, in the last decade, several trials have shown a lack of benefit of low-dose dopamine in improving renal function [37,38]. The choice of crystalloid or colloid infusions for intraoperative fluid management in abdominal surgery is subject of debate within the anesthesia community [39]. The authors prefer a balanced infusion strategy to maintain both colloid oncotic pressure and urinary output. Drainage of ascites and extensive debulking are associated with an enormous perioperative protein loss up to 700 g per day [40]. To cover these protein deficits, it is often necessary to administer human albumin and/or fresh frozen plasma. How liberal or restrictive substitution regimes might influence the outcome of these patients is still unknown and requires further evaluation. We prefer a restrictive regime and substitute albumin only in the case of a profound decrease in albumin plasma levels (<15 mg/dl), and the transfusion of fresh frozen plasma is restricted to patients with a clinically evident bleeding disorder in accordance with the European and German guideline for transfusion.

To ensure colloid oncotic intravascular pressure, artificial colloids are a good alternative. Iso-oncotic hydroxyethyl starch of the third generation (6% HES 130/0.4) could demonstrate a reliable volume effect of 90–100% [41] and is nowadays also available as a balanced solution. Furthermore, in contrast to previous studies, even during severe sepsis, recent data could not demonstrate negative effects of new colloid preparations (CRYSTMAS-Studie, www.clinical-trials.gov) either on lethality or on kidney function. On the contrary, intravascular volume effects of isotonic crystalloid compound amount to less than 20%, which causes significant interstitial edema being an outcome-relevant risk factor for increased lethality [42,43] influencing renal tubulus cells negatively [44].

Furthermore, in analogy to hypovolemic effects, clinical data could clearly outline that intravascular fluid excess is associated with serious adverse effects concerning organ functions and recovery [45] by destroying the endothelial glycocalyx [46], so that the anesthetist is confronted with the balancing act to prevent hypovolemia and hypervolemia. The difficulty in estimating the absolute lack of intravascular volume in each individual condition of surgical procedure may be one reason for this dilemma [45,47].

Taken together, both during debulking and HIPEC, the anesthetist should be aware of the great intraoperative fluid turnover and should initiate an aggressive therapeutic fluid regime for the establishment and maintenance of adequate systemic as well as regional perfusion. However, a fine line between

hypovolemia and hypervolemia should be aspired to, as an 'over-soaking' influences patient's outcome negatively [45].

Moreover, the anesthetist should catch up on the composition of resolving solutions for chemotherapeutics, as significant electrolyte disturbances can result. Oxaliplatin is resolved in glucose 5%; consequently, 3–5 liters of glucose 5% is administered intraperitoneally during HIPEC, resulting in some cases in pronounced hyperglycemia and/or hyponatremia [48,49^{***}].

HEMODYNAMIC STATUS

Based on the hyperdynamic metabolic rate during HIPEC, an increased cardiac output (CO) and heart rate are on display measured by a pulmonary artery catheter or transesophageal echocardiography [18,21,33]. It is well recognized that one of the body's initial responses to heat stress is dilatation of the peripheral vasculature, which increases heat loss from the core to the environment. Heart rate increases in order to maintain cardiac output in the face of decreasing peripheral vascular resistance [18,25]. As body temperature decreases after completion of HIPEC with normalization of the hyperdynamic circulatory state [21,26], the routine use of extended invasive hemodynamic monitoring such as Swan-Ganz catheters, transesophageal echocardiography, or pulse-contour devices cannot be recommended. However, by implementing amplified hemodynamic monitoring in individual cases with specific problems, the anesthesiologist can get additional auxiliary information, for example, is there an increase in extravascular lung water, estimated by single transpulmonary thermodilution measurement using the PiCCO device, as an alert for a noncardiac lung edema in patients with low levels of serum albumin after aggressive long-lasting cytoreductive surgery [50]. In addition to the standardized monitoring devices (arterial line, central venous catheter, urinary catheter), less-invasive hemodynamic monitoring devices such as the esophageal echo-Doppler [21,25] or the FloTrac/Vigileo device [51] are interesting tools to obtain more information about the patient's fluid and hemodynamic 'real-time' status with an appropriate risk/benefit ratio. Especially as central venous pressure is a poor indicator of cardiac preload and patients' volume state due to the increased intra-abdominal pressure and changes in the operating table's inclination during HIPEC [25], the possibility of monitoring dynamic parameters of cardiac preload and fluid responsiveness (SVV, aortic blood flow, left ventricular ejection time) is of utmost importance for the anesthesiologist to maintain

fluid homeostasis and prevent acute renal failure [21,25]. Furthermore, the entity of tumors also influences patient's hemodynamic status and should therefore be incorporated in anesthetist's master plan of perioperative hemodynamic management [52].

If dealing with hemodynamic function, the anesthetist should not disregard chemotherapy-induced cardiac side-effects. Case studies report about pulseless amiodarone-refractory ventricular tachycardia occurring after intraperitoneal cisplatin application [53]. As a result of direct cardiotoxicity (half-life of unbound cisplatin 20–30 min in patients with normal renal function), of selective renal magnesium wasting by cisplatin, and of prolongation of QT interval dispersion through cisplatin therapy, the anesthetist should search for perioperative QT interval prolongation and measure perioperatively magnesium plasma levels in patients with intraperitoneal cisplatin therapy.

COAGULATION

Major surgery is often associated with significant blood loss with values between 200 and 9000 ml. Transfusion of packed red blood cells and fresh frozen plasmas is necessary in about 50% of all patients intraoperatively and in about one-third of all patients postoperatively [26]. Salvage of cell saver blood with subsequent irradiation (50 Gy) to assure elimination of cancer cells is an established option to cut down on banked blood as salvaged blood contains higher levels of morphologically intact and long-life red blood cells with more physiological pH, higher levels of 2,3-diphosphoglycerate, and lower levels of K⁺ [54,55]. However, further prospective studies have to be performed to investigate the long-term effects of irradiated salvaged blood of cancer patients. Blood loss is not only due to surgical reasons but also due to an increased bleeding tendency; however, the reasons for this are unknown so far. Impairment of coagulation due to the large volume shift and protein loss with high fluid turnover and possibly due to the hyperthermic chemotherapy is conceivable. Laboratory analysis revealed disturbance of coagulation with increased international ratio (INR), decreased AT III and fibrinogen values, as well as prolonged activated partial thromboplastin time (aPTT) and a reduced number of thrombocytes [26]. Additionally, coagulation could be defective due to decreased levels of coagulation factors, which are not measured by standard coagulation tests, such as factor XIII.

Furthermore, the adoption of advanced coagulation monitoring such as thromboelastography with the rotation thromboelastometry and/or

thrombocyte function analyzer multiplate seems to be a helpful tool for detecting complex coagulation disorders such as hyperfibrinolysis, thrombocytopenia/penia, or factor XIII deficiency.

POSTOPERATIVE CARE

Postoperatively, most patients should be transferred to the ICU, as postoperative fluid loss during the first 72 h following surgery is still very high with values up to 4.1 liters per day, whereas most of the fluid loss occurs via abdominal drains (40%) due to the severely wounded surface [26,56[■],57[■]]. Therefore, it is important to maintain an adequate effective circulating volume by supplying sufficient intravenous fluids such as crystalline, colloid solutions or blood solutes. It is obvious that protein loss is also remarkable with decreased albumin levels starting to decline during surgery with the frequent need for exogenous administration [57[■]]. Average time on the ICU of the patients lies between 1 and 2 days, as the comorbidity of patients with cytoreductive surgery and HIPEC is low and patients are young [26]. Especially during the first 3 days, close-meshed monitoring of fluid loss and turnover is of critical importance for the patient's convalescence. Additionally, Arakelian *et al.* [56[■]] could demonstrate that the use of continuous positive pressure (CPAP) after extubation was related to better postoperative recovery, likely by recruitment of basal atelectasis and keeping those lung areas open that have been collapsed due to prolonged mechanical ventilation, ascites amounts, and HIPEC procedure.

PERIOPERATIVE PAIN MANAGEMENT

There is increasing evidence that thoracic epidural anesthesia (TEA) with local anesthetics and opioids is superior in the control of dynamic pain, playing a key role in early extubation and mobilization, reducing postoperative pulmonary complications, and having the potential to decrease the incidence of postoperative chronic pain syndrome. Also for patients undergoing HIPEC, supplementary TEA is an adequate tool for sufficient pain management. In addition, duration of ventilation can be significantly shortened and postoperative use of intravenous opioids – leading to complications such as bowel atonia [58,59] – can be markedly reduced in patients treated with epidural anesthesia. Furthermore, as patients undergoing cytoreductive surgery and HIPEC have frequent chronic pain with bad quality of life and opioid tolerance [51], an adequate prolonged pain management is essential. Hence, the exclusive method to sufficiently combat perioperative pain in patients on chronic opioids is to

continue their regular analgesics and to provide a preoperative supplementary TEA.

Some authors summarize that there is a high risk of hemodynamic intolerance and acute episodes of hypotension through blockade of sympathetic nerve system being enhanced by systemic effects of HIPEC [60,61[■],62[■]], as well as that thrombopenia and perturbations in blood coagulation are often observed during HIPEC and are a risk factor of spinal hematoma after epidural analgesia [63].

Nevertheless, we highly recommend thoracic epidural anesthesia for cytoreductive surgery and HIPEC because of the above-mentioned positive effects. Regarding our patients with a median age of less than 55 years and healthy conditions apart from their malignant underlying disease, there was no significant drop in hemodynamic blood pressure induced by supplementary epidural anesthesia during surgery [64].

Indeed, we and others [56[■],57[■]] also detected disturbances of coagulation with increased INR and decreased AT III values as well as prolonged aPTT and a reduced number of thrombocytes [64]. Hematoma formation in the spinal canal due to epidural anesthesia is a serious but very rare complication. However, the chief cause of spinal hematoma is the insertion of a catheter and a difficult or traumatic procedure. For prevention of epidural hematoma, preoperative assessment of the patient's bleeding anamnesis and drug therapy seems to be essential in addition to an atraumatic epidural puncture and catheter insertion by an experienced anesthetist without enforcing this supplementary procedure [61[■]]. Following the general guidelines for neuraxial anesthesia, the above-mentioned benefits of perioperative epidural anesthesia outweigh, in our opinion, its very rare side-effects [65]; however, recent data with a higher incidence of severe adverse effects after TEA should be considered when performing TEA [66[■]]. Finally, data from animal studies and retrospective clinical trials indicate an improvement of long-term outcomes and a reduction in metastatic growth after neoplasm surgery by supplementary epidural anesthesia [67[■]].

CONCLUSION

In patients undergoing HIPEC, the anesthetist is challenged by relevant fluid, blood, and protein losses, increased intra-abdominal pressure, systemic hyperthermia, and increased metabolic rate. It is of utmost importance to restore a normovolemic volume status by aggressive substitution of intravenous fluids, avoiding both, hypovolemia and hypervolemia. Supplementary thoracic epidural analgesia can be recommended to guarantee

adequate pain therapy and reduce the rate and duration of postoperative ventilation as well as postoperative intravenous opioid administration. Before starting HIPEC, the anesthetist should be informed about the content of intraperitoneal resolving solution and the choice of chemotherapeutic, to sufficiently combat adverse events. For coagulatory diagnostics point-of-care tools are expedient devices to quantify the level of dysfunction and to establish an appropriate therapy.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 395).

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