Pulmonary Insufficiency after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy Procedures for Peritoneal Carcinomatosis in Patients with Colon Cancer: A Case Report and Literature Review

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Abstract

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as an efficient treatment for patients with colorectal peritoneal metastases (PM). Pulmonary adverse events (AEs) are common after CRS and HIPEC. This report covers the case of a pulmonary adverse event, ARDS (acute respiratory distress syndrome), and its effect on the postoperative recovery process. Cytoreductive surgery with HIPEC was performed on a 58-year-old woman E. G. with carcinoma coecum and carcinomatosis. On the first day after surgery, the patient was not extubated because of respiratory insufficiency. We chose the liberal fluid management in order to maintain adequate organ perfusion, but this strategy might have influenced the outcome in this patient. Throughout the procedure that lasted 16 hours and 25 minutes the total dosage of the IV infusion was 19.7 ml/kg/h. ARDS was diagnosed based on chest radiography, oxygenation ratio, and the absence of left atrial hypertension. The patient was extubated after eleven days of ventilation. After that we started using advanced hemodynamic monitoring (esophageal Doppler) as a part of the goal-directed therapy to reduce postoperative complications and get a better outcome. The amount of fluids used during cytoreductive surgery with HIPEC may influence the postoperative pulmonary adverse event; in our case – ARDS. Cardiac output allows safer fluid titration. The goal-directed fluid therapy with advanced hemodynamic management may help in reducing the number of pulmonary adverse events after cytoreductive surgery with HIPEC.

Keywords: Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Pulmonary adverse events; Colorectal peritoneal metastases

Introduction

Since the 1990s, many oncological surgery groups around the world started to apply hyperthermic intraperitoneal chemotherapy (HIPEC) to different types of peritoneal cancers. Over the past decade, cytoreductive surgery (CRS) with HIPEC has emerged as an effective treatment for patients with colorectal peritoneal metastases (PM) [1-3]. HIPEC is also an attractive option when treating patients that are at a high risk of developing PM after surgical management of advanced colorectal cancer [2,3].

CRS and HIPEC involve a large abdominal incision, multiple organ resections, extensive peritoneal stripping and application of heated chemotherapy to the remaining abdominal contents, which often results in major fluid shifts, blood loss, and electrolyte changes. Respiration, hemodynamics and coagulation related disturbances are also common.

The use of HIPEC is increasing, and anaesthetists are required to be familiar with the significant respiratory, hemodynamic, and protein alterations associated with this therapy. Moreover, anaesthetists are involved in pain control, and the metabolic and nutritional support of such patients. Physiologic perturbations during the perioperative period may precipitate multisystem organ failure. Strict patient selection is crucial, and meticulous surgical tumour removal is mandatory for the best clinical outcome [4-7].

Either way, during the surgery and immediate postoperative period, patients face major and life-threatening derangements of their hemodynamic, respiratory, and metabolic physiologic balance.

The post-operative recovery process may be influenced by several factors before, during, and after surgery, and one of these factors is the incidence of pulmonary adverse events [8]. However, there are few reports in the medical literature on pulmonary complications occurring after CRS and HIPEC. The acute respiratory distress syndrome (ARDS) was reported after CRS and HIPEC in two case studies, with a systemic inflammatory response or multiple transusions during major surgery suggested as possible etiologies [9,10].

This report describes a case of pulmonary adverse event, ARDS, and the effect upon the postoperative recovery process after CRS and HIPEC.

Case Report

Cytoreductive surgery with HIPEC was performed on a 68-year-old woman (weight 68 kg) with ASA physical status 2 due to arterial hypertension, overweight (BMI 26, 56) and carcinoma coecii with carcinomatosis. Her history included a right hemicolecctomy and...
In addition to the carcinoma coeci with carcinomatosis, the patient was presented with hypoalbuminemia 34 g/l (total protein 70 g/l) related to the patient’s eating habits (vegetarian). The preoperative vital signs included: blood pressure 130/70 mmHg, heart rate 69/min, respiratory rate 16/min. According to the results of the patient’s physical examination on the day before the surgery, all lung fields were clear to auscultation bilaterally and the heart rate rhythm was regular. The patient’s airway examination did not reveal anything remarkable, and the results of all laboratory studies were within normal ranges with the exception of an albumin level (34 g/l). The electrocardiogram (ECG) showed a normal sinus rhythm; cardiopectoscopy and chest X-ray results were unremarkable as well. A left hand, 18g, 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, a thoracic epidural catheter was inserted to achieve a sensory blockade from about T4 to L2. Preoxygenation was performed. For induction of general anesthesia and for tracheal intubation, the following medications were given IV: fentanyl, 200 μg; propofol, 160 mg; and atrovent, 4 mg. After loss of train-of-four twitches, a 7.0 mm cuffed endotracheal tube was inserted without any difficulty, and secured. Following endotracheal intubation, sevoflurane was initiated and carefully titrated. Volume controlling mechanical ventilation was initiated, with a mean tidal volume of 450 ml, respiratory rate of 10/min, and a positive 5 cm H₂O end-expiratory pressure. A right radial arterial line, an 18 F nasogastric tube, an esophageal temperature probe, and a Foley catheter were placed without difficulty. A forced-air heating blankets were applied to the upper and the lower parts of the body, and heated IV fluids were initiated in an effort to maintain normothermia. General anaesthesia was maintained with 1.0% to 1.2% end-tidal sevoflurane, 60% oxygen (O₂) at 1 L/min, and an infusion of atracurium according to neuromuscular monitoring (TOF). Additional opioids were administered IV, and epidural ropivacaine as needed, based on the patient’s hemodynamical parameters. Central venous and arterial O₂ saturation, and central venous pressure were monitored. Hemodynamic stability was maintained with crystalloid, 4% modified fluid gelatine, 500 ml, epidrane (total dose 25 mg); dopamine infusion 5–8 μg/kg/min was started during the HIPEC phase. We had to choose to use the liberal cristalloids infusion and conservative colloids infusion during this operation in order to maintain fluid balance and to avoid the most frequent post-HIPEC complication - chemotherapy related renal insufficiency. 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 10 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 periportal cavities were explored for tumors. The liver capsule, multiple bowel resections, a hysterectomy and an adnexectomy, a splenectomy, and a cholecystectomy were performed, and the peritoneum was excised. Upon completion of the cytoreduction, the patient was prepared for HIPEC. One hour before HIPEC, a 5-FU 12 mg and a carboplatinum 35 mg IV were administered. HIPEC was started using the Sun Chip Hyperthermic Intra – peritoneal Chemotherapy System, with 86 mg of oxaplatin 640 mg added to the circuit. HIPEC was delivered via an open coliseum technique for 30 minutes. During this time, the forced-air heating blanket was turned to an ambient setting, and the heated IV fluids were discontinued. Throughout the chemotherapeutic phase, we did not use cool intravenous fluids and ice packs on the patient’s body to avoid extremes of core temperature (the highest recorded temperature reached 39°C). If the patient’s core temperature exceeded 39°C, the chemotherapy temperature was decreased. Nearing the conclusion of the operation, the patient’s temperature decreased to 37.5°C compared to her preoperative baseline temperature of 35.7°C; however, the temperature before the chemotherapeutic stage was 36.9°C. The electrolytic disturbance was performed before the chemotherapeutic stage: 25 g of magnesium sulfate was administered IV based on a magnesium laboratory value of 0.49 mmol/l, 1,000 mg of calcium gluconate was administered IV based on a calcium laboratory value of 1.79 mmol/l. After 60 minutes of the heated therapy, the abdomen was flushed with large amounts of dialysis fluid and drained. The abdomen was inspected for hemostasis, and closed. The entire intervention lasted for 985 minutes, including preparation for surgery (anesthetic induction, patient positioning) which lasted 75 minutes, and the HIPEC procedure that lasted 60 minutes. Throughout the procedure which lasted 16 hours and 25 minutes, the patient received 21 L of IV crystalloid and 500 ml of IV 4% modified fluid gelatine, the total IV infusion being 19.7 ml/kg/h. The urine output was 4,890 ml and the estimated blood loss was 500 ml; the loss with ascitis was 1,500 ml. After subtracting intraoperative output from input, the median balance of infused fluids was 14.8 ml/kg/h. The oxygenation ratio was 307% during the cytoreduction, declined to 176% with FiO₂>60% during HIPEC, and reached 156% with FiO₂>70% after HIPEC. Comparing pH and base excess values during the cytoreduction, before HIPEC and after HIPEC, revealed a decrease in pH and ABE. pH – from 7.4 to 7.30, base excess – from 1.5 to 6.4. The values of arterial lactate were as follows: 2.4–5.2. The albumin values were 34 g/l before surgery and decreased to 12 g/l after surgery, remaining low throughout the whole post-operative period. The hemoglobin and hematocrit values were 118 g/l and 32% before the chemotherapy. The laboratory analysis revealed disturbances in the coagulation system, with increased INR and prolonged APTT. The creatinine values remained unchanged. The patient was transported to the intensive care unit (ICU) for standard monitoring, where she remained intubated and sedated overnight.

On the first day after surgery, the patient was not extubated because of low oxygenation, hemodynamic instability (noradrenaline infusion 0.01 μg/kg/min), remarkable electrolyte balance disturbance, and a very low albumin leve, 12 g/l. During the first day after surgery, the patient’s hemodinamic status was stabilized, and electrolyte and coagulation disturbances were corrected (blood, albumin and frozen plasma transfusion were used), and the excess of infused crystalloids was removed using diuretics,total dose of furosemid was 150 mg, applied on the day of the cytoreductive surgery with HIPEC, however, the respiratory insufficiency remained, the oxygenation ratio was between 135-197 mmHg with FiO₂>70% with 14 cm H₂O end-expiratory pressure. On the second day after operation, ARDS was diagnosed with the help of chest radiography, the observance of the oxygenation ratio and the absence of clinical evidence of left heart failure. After eight days of supported ventilation with 10-14 cm H₂O end expiration pressure and strict fluid balance control (the aim was to maintain a neutral fluid balance), a positive progress was reached, i.e. the patient was successfully extubated after 11 days of ventilation, when her oxygenation ratio was 312. We chose a conservative fluid management strategy, maintaining a relatively low central venous pressure in order to reach better results in respiratory failure and shorten the duration of mechanical ventilation in our case of ARDS.
Our findings suggest that therapy with diuretics and colloids might be of benefit in the treatment of ARDS too. After 18 days of treatments in ICU, the patient was transferred to the oncosurgical department. After 11 days of treatment in this department, the patient was discharged from the hospital in good condition. The patient was treated at our institution for 36 days.

Literature review

Fluid administration

Maintaining and restoring normovolemia during the cytoreductive and hyperthermic intraperitoneal chemotherapy (HIPEC) phase, is of critical importance. A balance of crystalloid and colloid solutions are required to maintain volume status and colloid oncotic pressure.

Optimizing organ perfusion and reducing morbidity through adequate fluid therapy is a significant challenge during CRS with HIPEC because inadequate fluid therapy leads to hypovolemic results in impaired perfusion of major organs (kidneys, gastrointestinal tract, and skin) with subsequent postoperative morbidity [11]. In order to maintain end-organ perfusion, general fluid management includes a continuous baseline infusion of crystalloids, aiming at a urinary output of at least 0.5 (CRS phase), 2 (HIPEC phase), and 1 (reconstruction phase) ml/kg/h, respectively. Replacement of these fluid losses is achieved through a combination of crystalloid, colloids, and albumin solutions. In our institution, we prefer a balanced infusion strategy that helps to maintain both colloid oncotic pressure and urinary output.

Fluid shifts and protein loss are extensive and continual, beginning with the loss of ascites in many patients. Due to a combination of ascetic drainage, debulking surgery, and increased capillary leakage, hypoalbuminemia is common with mean levels falling from 42.6 to 15.7 g/l during CRS as reported by one retrospective review [12]. The protein loss due to removal of ascites and extensive debulking can reach 700 mg per day [7]. While hypoalbuminemia signals of increased morbidity in surgical and critically ill patients, the use of albumin in such cases is still debated [13]. When covering the albumin used to correct hypoalbuminemia, some studies show improved organ functions, while others report almost no benefit or reduced survival rates [14,15]. We prefer a restrictive regime, and substitute albumin only in the case of a profound decrease in albumin plasma levels (<15 g/l). Transfusion of fresh frozen plasma is based on the coagulation studies, and transfusion of packed red blood cells is based on both clinical signs and laboratory data suggesting inadequate oxygen delivery. In total, the need for fluid may reach 12–15 ml/kg/h, depending on the degree of debulking, exceeding 8–10 ml/kg/h normally expected during abdominal procedures, and may include significant blood loss [4,16]. According to one report (76 patients), the average duration of surgery was 10 hours (app. 9.51 hrs., range being 3–16 hrs.), the average blood loss was 2.384 ml (range being 50–14,000 ml), with the average of 12.220 ml of crystalloids and 4.791 ml of colloids administered [17]. The anesthetist must take care not only to replace volume but also to replace colloid oncotic pressure with colloid solutions, albumin and/or plasma.

Extensive fluid shifts and protein loss can lead to noncardiac pulmonary oedema. Cardiac output monitoring is recommended as a managing aid to help avoid noncardiogenic pulmonary oedema [18]. Abdominal filling with saline solution enriched with chemotherapeutics causes an increase in intra-abdominal pressure with cranial shift of the diaphragm, reduces pulmonary excursion, and results in decreased oxygenation and increased airway pressure [12]. These effects are similar to those seen in patients with pneumoperitoneum [16,19,20]. Increased abdominal pressure during this period can lead to impairment of venous return and an increase in splanchic vascular resistance. Furthermore, by analogy with hypovolemic effects, clinical data could clearly outline that the excess of intravascular fluid is related to serious adverse effects concerning organ functions and recovery [21], through destroying the endothelial glycocalyx [22], so that the anesthetist is confronted with a balancing act as a means to prevent hypovolemia and hypervolemia.

When maintaining and restoring a normovolemic status during the cytoreductive period by using crystalline and colloid solutions as well as blood substitutes before starting the HIPEC procedure, it is important to be prepared for excessive pathophysiological alterations during the HIPEC phase.

Thermal homeostasis

Hypothermia should be expected and controlled during the cytoreductive phase; also, hyperthermia and hypermetabolic state should be expected and controlled during HIPEC.

Patients are at risk of becoming hypothermic during the extensive period of cytoreduction, and then hyperthermic during the peritoneal perfusion period. Despite the extensive debulking procedure and extensive abdominal surgical access, hypothermia is 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 all depend on thermal homeostasis [23-25]. Instillation of the hyperthermia solution (39–42°C) induces a hypermetabolic state with peripheral vasodilatation (which adds to the overall challenges of maintaining fluid balance), increased heart rate and increased cardiac output [26]. In addition, hyperthermia may cause consumptive coagulopathies, arrhythmias, liver/renal injury, peripheral neuropathies, and seizures [27]. As a consequence, patients develop an increasing systemic oxygen demand [28] 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 [12,28-31]. The Systemic temperature quickly reaches 40°C or higher, even with the use of cooling blankets and cooled intravenous solutions. The permitted increase in core temperature with a mean accepted core temperature 39.2°C (range of 36–41°C).

Pain management

Supplemental thoracic epidural analgesia can be recommended to HIPEC patients. Perioperative pain management is often a challenge because of the extent of CRS and the significant use of preoperative opioids; also, because many patients with abdominal carcinomatosis suffer chronic pain. Patients often have stripping of diaphragmatic peritoneum with insertion of chest drains as well as extensive pelvic dissection requiring analgesia from approximately T4 down to low lumbar or sacral nerve roots. There is increasing evidence that thoracic epidural anaesthesia (TEA) with local anaesthetics and opioids is superior when controlling dynamic pain, plays a key role in early...
Effects of chemotherapeutic agents

Finally, specific effects of chemotherapeutic agents must be considered. Cisplatin is administered in 5% glucose, which, considering the fact that as much as 3-5 L of this solution may be administered, results in hyperglycemia and/or hyponatremia. Systemic absorption can lead to cardio toxicity. One detailed case report on intraperitoneal cisplatin, includes the onset of intermittent (30 seconds) pulseless ventricular tachycardia that was refractory to amiodarone. Electrolytes were normal, but hypomagnesemia with a prolonged QT interval was present. The intraperitoneal cisplatin fluid was drained using prompt resolution of arrhythmia. The authors concluded that tachyarrhythmia was caused by the direct cardiotoxic effects of unbound cisplatin [7]. The case described demonstrates the local toxicity of chemotherapy on either the myocardium or the pericardium. It is not specified whether expedited drainage of the chemotherapy solution was performed, 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 during the postoperative period. While toxicities of cisplatin include ototoxicity, gastro toxicity, myelosuppression and allergic reactions, the main side effect of dose-limiting is nephrotoxicity. To prevent this cytostatica-induced tubular nephrotoxicity, the anesthetist should aim at a forced perioperative hydration and diuresis. Therefore, a urine flow greater than 0.5 mL/kg/h should be achieved, although no randomized studies acknowledge this approach. Exposure of the operating room staff to aerosolized mitomycin and cisplatin is reduced through the use of the closed abdomen technique; surgeons need to be careful and use double gloves (latex gloves are recommended) to avoid personal systemic absorption of the chemotherapy agents [7]. The anesthetist should be familiar with the adverse effects of the chemotherapeutics as well as their carrier solutions.

Coagulation disorders

Impairment of coagulation due to the large volume shift and high protein loss with high fluid turnover (and possibly due to the hyperthermic chemotherapy) is conceivable.

Blood loss can result in significant coagulopathy. A recent report of 78 patients demonstrated increased INR, aPTT and antithrombin III with a decreased platelet count [12]. The cell saver can decrease the requirements for transfusion, but the recovered red cells must be irradiated in order to ensure elimination of metastatic cells. Administration of plasma can be beneficial for maintaining both colloid oncotic pressure and adequate coagulation factor levels. Viscoelastic point-of-care monitoring can be used when assisting with identification of fibrinolysis, thrombocytopenia, and Factor XIII deficiency [7].

Post-operative management

After HIPEC, patients are often admitted to an intensive care unit or remain in a post-anesthesia care unit for the purpose of monitoring their organ function, management of intraoperative complications, and correction of coagulopathy. Physiologic perturbations during the perioperative period, affect the duration of the patient’s stay in the intensive care unit. The post-operative fluid loss during the first 72 hours after surgery remains very high. Therefore, it is important to maintain an adequately effective circulating volume by supplying sufficient intravenous fluids such as crystalline, colloid solutions, or blood solutes. The decrease of albumin is remarkable and is often needed for exogenous administration. These patients are at risk for bowel perforations, anastomotic leakage, bile leakage, fistula formation, pancreatitis, postoperative bleeding, wound dehiscence, deep vein thrombosis, and pulmonary embolism [39].

Discussion

This case was one of the first cases of cytoreductive surgery with HIPEC conducted at our institution. As recommended by earlier studies, we choose liberal fluid management in order to maintain adequate organ perfusion, circulating volume, and urine output based on evaluation of the blood loss, blood pressure, pulse rate, central venous pressure, urinary output, and body temperature, but this strategy could have influenced outcomes in this patient. Many studies addressed the connection between intra-operative fluid therapy and post-operative complication in colorectal surgery. The post-operative recovery process may be influenced by several factors before, during and after surgery, and one of these factors is the incidence of pulmonary adverse events (AEs) [8]. Factors that can cause the pulmonary adverse events include perioperative fluid therapy. Only on the first day of cytoreductive surgery and HIPEC, did the patient have a positive fluid balance. This patient had a post-operative chest radiography, which showed no atelectasis or pneumonia. On the first day after surgery, the oxygenation ratio was between 135–197 mmHg with FiO$_2$>70% with 14 cm H$_2$O end-expiratory pressure, and remained similar – 145–200 with FiO$_2$>60% 10 cm H$_2$O end-expiratory pressure – until the eighth day after surgery. A noticeable increase in the oxygenation ratio was achieved after eight days of treatment (it reached 244) and three days after the patient was extubated. On the day of extubation, the oxygenation ratio was 312.
Recent studies and reviews have repeatedly demonstrated a strong correlation between liberal fluid administration and incidence of postoperative lung oedema or acute respiratory distress syndrome (ARDS) – a permeability pulmonary oedema characterized by increased permeability of pulmonary capillary endothelial cells and alveolar epithelial cells, leading to hypoxemia that is refractory to usual oxygen therapy. Clinically, ARDS is characterized by severe hypoxemia, bilateral radiographic pulmonary infiltrates, and no clinical evidence of cardiogenic pulmonary oedema. In 2012, in an update of the AECC definition [40], an empirical ARDS classification was proposed that is based on three PaO2/FiO2 cut-off values on PEEP ≥ 5 cm H2O at ARDS onset: severe (≤ 100 mmHg), moderate (>100 - ≤ 200) and mild (>200 - ≤ 300). Recognition of ARDS risk factors and avoidance of aggravating factors during general anesthesia (e.g., non-protective mechanical ventilation, multiple blood product transfusions, positive fluid balance, ventilator-associated pneumonia, gastric aspiration, and major trauma), can help in decreasing its incidence. Due to vascular and epithelial permeability increasing during ARDS, fluid is one of the most difficult measures that it is necessary to manage. A conservative fluid management strategy maintaining a relatively low central venous pressure is associated with the need for fewer days of mechanical ventilation compared with a liberal fluid management strategy in ARDS [41]. The occurrence of postoperative pulmonary adverse events is seen more frequently if the intraoperative infusion rate of fluids exceeds 6 ml/kg/h [42]. On the other hand, an adequate perioperative fluid therapy is important in cytoreductive surgery with HIPEC because it helps to reduce the risk of chemotherapy-related postoperative renal insufficiency. Goal-directed fluid therapy reduced the number of pulmonary and pneumonia cases compared to liberal fluid therapy without hemodynamic goals. After this case, we started using advanced hemodynamic monitoring as a part of the goal-directed therapy in order to reduce postoperative complications and obtain a better outcome. Our choice was to use esophageal Doppler. Despite being non-invasive, echocardiography enables us to directly visualize the heart and assess cardiac function. It has been widely demonstrated that it accurately prognosticates fluid responsiveness. Currently, it is a complete non-invasive tool able to accurately determine the hemodynamic status in case of circulatory failure. Up to this point (i.e. a year later), our institution has successfully performed fifteen cytoreductive surgeries and HIPEC procedures, using advanced hemodynamic monitoring.

**Conclusion**

The anesthetist helps in restoring an adequate circulating volume by giving intravenous fluid to a patient that undergoes cytoreductive surgery with HIPEC. The amount of fluids used may influence the postoperative pulmonary adverse event in patients, in our case – ARDS. Cardiac output allows safer fluid titration. Goal-directed fluid therapy with advanced hemodynamic management may help in reducing the number of pulmonary adverse events after cytoreductive surgery with HIPEC.

**Conflict of Interest**

The authors have no conflict of interest to declare.

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**Consent**

A written informed consent for publication was obtained from the patient described in this paper.

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