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INTENSIVE CARE MANAGEMENT OF PATIENT AFTER CYTOREDUCTIVE SURGERY AND HIPEC BEYOND THE SCENE

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ABSTRACT Cytoreductive surgery (CRS) and Heated Intraperitoneal Chemotherapy (HIPEC) results in a number of physiological changes with effects on the cardiovascular system, oxygen consumption and coagulation. The Critical Care interventions required by this cohort of patients have not yet been quantified. The chemotherapy is administered in high dosages to the targeted area and washed out, thereby limiting the systemic toxicity. The procedure usually takes long hours and is most commonly used to treat appendiceal, colorectal or mesothelioma tumors including those that have failed standard chemotherapy and/or prior surgeries. Patients face major and life threatening derangements of their hemodynamic, respiratory and metabolic physiologic balance during the surgery and in the immediate postoperative period. Intensive monitoring and timely detection of possible complications and appropriate remedial action is crucial for better surgical results.

KEYWORDS : Intensive care, HIPEC

INTRODUCTION

Treatment of this condition with combined cytoreductive surgery (CRS) and hyperthermic intrapertioneal chemotherapy (HIPEC) has been shown to improve both patient survival and quality of life. Hyperthermic intraperitoneal chemotherapy (HIPEC) in combination with cytoreductive surgery is emerging as an effective chemo therapeutic treatment option for selected peritoneal surface malignancy patients with advanced disease. [1, 2].

HIPEC is performed intraoperatively after surgical cytoreduction and peritonectomy procedures. Usually four drains are placed in the abdominal cavity; one drain is for the inflow and three drains are for the outflow. The perfusate is then circulated with a roller pump system into the abdominal cavity at a temperature of 42-43C. Temperature monitoring is efficiently done during the whole procedure with multiple probes placed at multiple sites in the peritoneal cavity. After reaching the target temperature, chemotherapeutic medications are added to the perfusate and HIPEC is performed for 30–90 min, according to different protocols. Best results with HIPEC can be achieved in selected patients with peritoneal carcinomatosis arising from colorectal cancer. The median survival time can be improved when compared with systemic chemotherapy alone by 16–24 months with a 5-year survival rate of 30–45 % [3–6]. HIPEC was performed at different centers worldwide since its inception as the safety, morbidity rate and therapeutic considerations are better understood and recognized [7]. There are more than 100 centers in the USA and also in European countries routinely performing HIPEC. A few hospitals in India have started their own HIPEC programme. Published Indian data is limited and includes only small case series. 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. Till today there is no data available comparing both techniques; however, most centers perform closed HIPEC techniques. Depending on the type of tumors, different chemotherapy medications are used intraperitoneally

Pathophysiology Of HIPEC from ICU Perspective

Most patients who undergo Cytoreductive surgery and HIPEC treatment have to deal with derangement of normal physiology involving multiple organ systems, very often starting from a non-optimal functioning status pre operatively. In fact, patients undergoing CRS and HIPEC could be pre-operatively hypoxic because of ascites, pleural effusion and atelectasis. Some patients may be malnourished. In addition HIPEC phase promotes an increase in airway pressure and a reduction in functional residual capacity because of the diaphragm shifting cranially [8, 9]. During HIPEC there is an increase of PaCO2 and the concomitant decrease in A-a gradient and arterial pH with noticeable gas exchange deterioration [10]. Reduction in oxygen saturation is common. During Cytoreductive surgery and HIPEC, maintaining the normovolemic state can be difficult due to ongoing blood loss and fluid exudation. Fluid turnover will exceed the well-established 6–8 ml/kg/h for major abdominal surgery [17]. For CRS and HIPEC, up to 12 ml/kg/h fluid may be required [11–14]. HIPEC phase is characterized by an increase in heart rate [11, 14], mean central venous pressure (CVP), pulmonary artery pressure and wedge pressure [8, 14], intrathoracic blood volume index [11] and cardiac index [14–16]; on the contrary, mean arterial pressure and systemic vascular resistance show a reduction [10, 13]. The hypermetabolic state during HIPEC is due to the hyperthermia which is clearly demonstrated by the increase in end tidal CO2 and oxygen extraction and consumption [11, 18]. Coagulation abnormalities are always reported. The prolongation of Prothrombin Time (PT), activated Partial Thromboplastin Time (PTT) and/or pathological reduction of platelet count over the baseline are demonstrated by different studies [9–12]. Platelet count can continue to go down further during the postoperative period due to the effect of cytotoxic drugs used.

The coagulation dysfunction is reported to peak around 24 to 48 h post-surgery [9, 11], with restoration of a normal coagulation profile in 72 h [9]. The two main causes of coagulation abnormalities seem to be the dilutional dysfunction [19] secondary to massive fluid shift and bleeding and the impairment of coagulation factors due to massive ascites [20] and malnourishment. Renal dysfunction, electrolyte disorder and hyperglycemia are frequently observed in the intraoperative and postoperative course [8, 10, 11, 21].

Intensive Care Management

Airway And Breathing

Most patients after CRS and HIPEC can be extubated after surgery. A few patients remain intubated and will be shifted to ICU for post op ventilation. As mentioned earlier, patients undergoing CRS and HIPEC could be pre-operatively hypoxic because of ascites, pleural effusion and atelectasis. The patients that required ventilation postoperatively may have been clinically very unstable, had diaphragmatic injury or multiple comorbidities preventing safe extubation.

Postoperative respiratory support is not always necessary even if CPAP periods can be useful [22]. Cooksley et al. had reported to have extubated all the patients in the Operating Room (OR), whereas Miao et al. extubated 62 % before Post Anesthesia Care Unit (PACU) admission [9, 10].

Arakelian et al. had reported the use of early postoperative Continuous Positive Airway Pressure (CPAP) to speed up the recovery [22], during the immediate postoperative period.

Circulation And Hemodynamics

After Cytoreductive surgery and HIPEC, most patients should be transferred to the Intensive Care Unit for monitoring ongoing resuscitation along with fluid and electrolyte management. Due to significant peripheral vasodilatation after HIPEC, vasoactive drugs will be required during the immediate postoperative period.The temperature monitoring is also an integral part of immediate post operative period.

Cooksley et al. had reported that 26 % of the patients still needed vasopressor at the end of the procedure and at arrival in ICU. However, no patients developed renal failure or had a difficult weaning from hemodynamic support [9]. Patients would need fluid requirement because of the fluid loss through the drainages which can reach up to 4 l a day [12].

Postoperative fluid loss during the first 72 h following surgery is very high. It is found that most of the fluid loss after HIPEC occurs via abdominal drains (40 %) due to the severely wounded and exudating peritoneal surface [9, 11, 22].

It is important to maintain an adequate effective circulating volume by constant monitoring and assessment of the fluid loss along with sufficient replacement of intravenous fluids such as crystalloids, colloid solutions or blood products.

Liberal intravenous fluid replacement, mostly crystalloid and colloid, should be guided by hemodynamic changes, CVP, serum electrolytes, urine output and amount of fluid losses from drains and nasogastric tube.

Protein loss is also significant as the exudating fluid is rich in protein. It is very common to see the decline in albumin levels which start during surgery and continue for a few days post operatively, with the need for exogenous administration [9]. Albumin supplementation will be needed for patients to keep serum albumin above 3.0 g/dl, which will help to maintain adequate intra vascular volume.

Blood transfusion should be given together with fresh frozen plasma guided by the drains, hemoglobin percent and hematocrit value, and coagulation profile.

Coagulation

Coagulation abnormalities are always reported after Cytoreductive Surgery with HIPEC. The prolongation of Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT) and/or pathological reduction of platelet count over the baseline is common. During immediate postoperative period, due to high risk of ongoing blood loss from the wound and peritoneal surface, it is important to correct the coagulopathy to minimize blood loss. Fresh Frozen Plasma transfusions will be needed to correct PT and aPTT.

Platelet transfusions are necessary if there is significant thrombocytopenia (<50,000/cumm) with ongoing bleed. Monitoring of coagulation parameters is necessary during the immediate post operative period.

The coagulation profile takes at least 5 days to get back to baseline. Surveillance and eventual transfusions are needed during this period [10].

Electrolyte Balance

Due to significant fluid shift during the surgery and immediate postoperative period, electrolyte imbalance can happen. In the ICU serum electrolyes including Sodium, Chloride, Potassium, Calcium, Magnesium and Phosphate are measured periodically and replacement should be done. Ongoing fluid replacement is guided by static and dynamic hemodynamic parameters.

Glycemic Control

Hyperglycemia in the critically ill has been shown to increase the rate of morbidity, mortality and health care costs. [23] Therefore, glycemic control is necessary in critically ill patients to help reduce the incidence of complications including decreased wound healing, increased infection risk, impaired GI motility, impaired CV function, increased risk of polyneuropathy and increased risk for acute renal failure. [24] The current recommendation for glucose control in critically ill patients is 140–180 mg/dL. [25]. Continuous insulin infusions can be initiated in patients experiencing fluctuations in glucose levels >180 mg/dL or in those patients that are persistently hyperglycemic despite adequate treatment with short-acting insulin injections.

Analgesia

There is increasing evidence that Thoracic Epidural Anesthesia (TEA) with local anesthetics and opioids is superior in the control of dynamic pain. It plays a crucial role in early extubation and mobilization of the patient, in turn reducing postoperative pulmonary complications.

In addition, the duration of ventilation can be significantly shortened and postoperative use of intravenous opioids (leading to complications such as bowel atonia) [26, 27] can be markedly reduced in patients treated with epidural anesthesia.

Some authors summarize that there is a high risk of hemodynamic intolerance and acute episodes of hypotension associated with epidural anesthesia through blockade of sympathetic nerve system being enhanced by systemic effects of HIPEC [28, 29].

Thrombocytopenia and alterations in blood coagulation profile are often observed during HIPEC and are a risk factor of spinal epidural hematoma after epidural analgesia [30]. Nevertheless, thoracic epidural anesthesia for cytoreductive surgery and HIPEC should be considered because of the above-mentioned positive effects.

Stress Ulcer Prophylaxis

Stress-related mucosal damage (SRMD) is a form of hemorrhagic gastritis that can occur in critically-ill patients. Patients with SRMD have much higher mortality rates than those without (57 % vs. 24 %) [31]. Two risk factors have been shown to be independently associated with SRMD: respiratory failure necessitating mechanical ventilation for at least 48 h and coagulopathy defined as a platelet count <50,000/cumm, an INR > 1.5 or a partial thromboplastin time of >2 times the control value [32]. The use of certain medication (corticosteroids, non-steroidal anti-inflammatory drugs, vasopressors) and hypotension can predispose the patient to stress related mucosal damage. Considering all these factors, all patients after CRS and HIPEC should be started on either

H2 receptor antagonists or Proton pump inhibitors.

Thromboprophylaxis

Specific thrombotic risks for HIPEC patients include long surgery, immobility, pre existing malignancy, age, pre existing heart or respiratory failure, obesity, smoking and presence of central venous catheters [33, 34]. All patients need to be placed on mechanical devices (graduated compression stockings (GCS), intermittent pneumatic compression (IPC) devices and the venous foot pump -VFP) to prevent DVT and need to start pharmacological agents (Heparin/LMWH) as soon as the bleeding risk and coagulopathy has been resolved.

Feeding/Nutrition

The effect of HIPEC on small bowel physiology is quite unknown. However, patients should be treated basing on the guidelines for perioperative nutritional support after major surgery [35]. Most of the patients will be commenced on TPN. Enteral feeding should be started as soon as possible. Early postoperative enteral feeding is considered to be beneficial in reducing infective complications in general surgical patients, but consideration should be given to the complex nature of CRS and HIPEC with multiple anastamoses. A naso-jejunal catheter can be a valuable option to start early enteral feeding in selected patients [8]. This issue of feeding and nutrition should be correctly evaluated because malnourishment has been identified as a major adverse determinant of surgery success and recovery of quality of life.

Antibiotics

Routine postoperative surgical prophylaxis is recommended. Choice of antibiotics is generally based on the institutional protocol. The Surgical and Intensive Care teams should be watchful for possible infective complications due to immunosuppression and should have a low threshold for escalating to higher antibiotics if and when it is necessary after appropriate cultures.

Watch for Complications

The most common complications after Cytoreductive surgery and HIPEC include anastamotic leaks, intra-abdominal sepsis, pancreatitis, intestinal fistula, renal failure and haematological toxicity. There is also denaturation of proteins which leads to wound infections and dehisence so serum albumin levels are done along with liver function tests to assess the prognosis. The treating team should be aware of the potential side effects of the Chemotherapeutic agents used during hyperthermic intraperitoneal chemotherapy [Mitomycin C- Nephrotoxicity, pulmotoxicity; Cisplatin-Peripheral neuropathy, myelotoxicity; Doxorubicin-Cardiotoxicity (arrhythmia, cardiomyopathy), myelotoxicity; Oxyliplatin- Neurotoxicity (laryngeal/pharyngeal dysesthesia); Irinotecan-Myelotoxicity.] The Surgical and Intensive Care teams should be watchful of these possible complications and

Summary

Given the well described physiological abnormalities that occur during cytoreductive surgery and HIPEC the degree of organ support required is minimal. Early extubation is efficacious with the aid of epidural analgesia. Critical Care monitoring for 48 hours is still desirable in view of the challenges of fluid management, low albumin state, coagulopathy and potential complications. Hyperthermic intraperitoneal chemotherapy (HIPEC) in combination with cytoreductive surgery is emerging as an effective chemo therapeutic treatment option for selected peritoneal surface malignancy patients with advanced disease. A few centers in India are performing HIPEC even though our data is limited [36]. Considering the promise emerging from this novel method of therapy, it is expected that more hospitals will be considering this treatment option in future.

Most patients who undergo Cytoreductive surgery and HIPEC treatment have to deal with derangement of normal physiology involving multiple organ systems. Intensive monitoring along with adequate fluid and electrolyte replacement is necessary during the immediate postoperative period. It is of utmost importance to restore a normovolemic volume status. Avoiding both hypovolemia and hypervolemia is crucial for preventing postoperative complications. 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.

Patients face major hemodynamic, respiratory and metabolic derangements during the procedure and postoperative period that need to be timely addressed. From an Indian perspective, ideally these patients should be monitored in an ICU unless there is a well-equipped and staffed High Dependency Unit (HDU) or Post Anesthesia Care Unit (PACU) for better surgical results and patient outcomes.

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