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Anaesthesia for HIPEC Surgery: A Case Report

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Abstract: ***Mesothelioma is a malignancy of serosal membranes. Peritoneum is the second most common site of malignant mesothelioma after visceral pleura. The disease presents with diffuse extensive spread throughout the abdominal cavity with rare metastatic spread beyond. This was considered an incurable condition until, Dr Paul Sugarbaker showed that HIPEC surgery (hyperthermic intraperitoneal chemotherapy) improved quality of life and survival of patients. Here, we describe the management of a 33 years old female patient, ASA PS 1 with peritoneal mesothelioma who underwent HIPEC surgery. HIPEC involves exposing the peritoneal surface to a high concentration of heated chemotherapeutic drug to destroy all residual microscopic disease after visceral resection. It consists of 3 phases- the CRS (cytoreductive surgery) phase, HIPEC phase and post HIPEC phase. The anesthesiologist has a crucial position throughout the surgery and post operative period. CRS phase is associated with massive fluid shift, blood loss and hemodynamic alterations. Prior to HIPEC phase, patient is cooled with ice packs and cold fluids to decrease the risks of hyperthermia. The chemotherapeutic agents (oxaliplatin, cisplatin, mitomycin C, and doxorubicin) are delivered mixed in isotonic saline or dextrose-containing fluid. These solutions may enter the circulatory system leading to electrolyte imbalances like hyponatremia and hyperglycemia. Patients have to be kept well hydrated during the procedure, as acute kidney injury can occur. Here we attempt to highlight the challenges we faced and the complications that arose both in intraoperative and postoperative period despite the precautions we took.***

Keywords: Mesothelioma, HIPEC surgery, peritoneal cancer, anesthesiology, chemotherapeutic agents

1. Introduction

Every year, approximately 18 million people worldwide develop some form of cancer[1]. Around 5%-46% of these patients will end up with peritoneal metastasis[2]. Patients presenting with peritoneal spread have a reduced survival rate and poor quality of life[3]. Diffuse metastasis throughout the peritoneal cavity was considered an incurable condition until Dr. Paul Sugarbaker showed that HIPEC (hyperthermic intraperitoneal chemotherapy) surgery improved survival. HIPEC involves perfusing the abdominal cavity with heated chemotherapeutic agents after macroscopic resection of visible tumor.

In 1979, the first patient was treated with hyperthermic thiotepa for pseudomyxoma peritonei. Later in the 1980s, this technique was investigated for various other malignancies including colorectal, ovarian and gastric cancers with isolated peritoneal metastasis. HIPEC combined with CRS (cytoreductive surgery) has developed overtime as an effective multimodal treatment option for selected patients with peritoneal surface malignancies.

CRS and HIPEC are a complex intervention independently associated with morbidity and mortality[4]. The technique itself involves large fluid shifts, blood loss, hemodynamic alterations, electrolyte imbalances and organ damage followed by a challenging postoperative course. The anaesthesiologist has a crucial role throughout the surgery and postoperative phase. Here we attempt to highlight the challenges we faced and the complications that arose both in intraoperative and postoperative period despite the precautions we took.

2. Case Report

Our patient was a 33 years old female with chief complaints of diffuse abdominal pain. An abdominal ultrasound scan revealed a right ovarian tumor for which she underwent an exploratory laparotomy under general anaesthesia outside. Histopathological evaluation of the right salpingo oophorectomy specimen showed peritoneal mesothelioma. She was then referred to our institution for expert oncological care. Further evaluation only showed a mild fatty liver on imaging. Since no other metastatic foci was found, she was considered an ideal candidate for CRS followed by HIPEC.

She was an ASA PS 2 patient with no known comorbidities and a BMI of 17. All routine preoperative investigations including ABG were found to be within normal limits. As it was a major surgery, cardiology and respiratory medicine fitness was obtained. Echo and spirometry showed no obvious abnormalities. Enteral nutritional support was instituted before surgery. Prehabilitation in the form of chest physiotherapy, exercises and incentive spirometry were advised.

On the preoperative day, a high risk informed consent was obtained. Adequate blood and blood products was arranged. Nebulisation with bronchodilators and steroids was given. Ice packs and cold fluids were kept ready. Patient was given adequate premedication and kept well hydrated. Thromboprophylaxis with LMWH single dose 12 hours before procedure and pneumatic compression stocking was given.

On the day of surgery, the patients ECG, blood pressure and SpO2 were monitored upon entry into the operating room. A thoracic epidural was placed at T9- T10 level under local

anaesthesia. General anaesthesia was induced as routine with titrated dose of propofol followed by controlled ventilation. Anaesthesia was maintained with sevoflurane, intravenous morphine and epidural 0.2% ropivacaine. Intravenous vecuronium infusion was given for adequate muscle relaxation. Post induction monitors include intra arterial blood pressure, central venous pressure, cardiac output, bispectral index, peripheral nerve stimulator and nasopharyngeal temperature. Two large bore IV cannulas were placed in peripheral veins. BIS was maintained between 45- 52 throughout the procedure.

CRS Phase - The blood loss during resection of the macroscopic tumor was managed with IV fluids, albumin, blood and blood products. IBP was maintained above 90/60 mm of Hg with IV dopamine infusion. CVP only showed mild fluctuation between 8-13 mm of Hg. Cardiac output, stroke volume variation and pleth variability index were in the normal range throughout this phase. There was a urine output of 250-1000 ml/hr. All electrolyte abnormalities were corrected based on ABG and serum electrolyte values. Normothermia was maintained using forced air warmer and warm fluids. After completion of cytoreduction, the PCI score was calculated to be 12 and therefore decided to proceed with HIPEC. Personal protection in the form of gowns, gloves and masks were used by all theater personnel.

HIPEC Phase - HIPEC was performed for 90 minutes at 42 degrees Celsius using Cisplatin 110 mg by the closed method. It was converted to open technique for the last 10 minutes due to block in outflow tube. Temperature was maintained between 35.3 to 35.8 degree Celsius using 6 litres of cold saline rapid infusion and ice packs which were replaced every 15 minutes. Urine output was 500- 750 ml every 15 minutes. Dopamine infusion was continued.

Post HIPEC Phase - After the chemotherapeutic agent was drained, abdomen was washed with saline and closed in layers. Rewarming was started with forced air warmer and cold fluids. All electrolyte abnormalities were corrected. The patient was hemodynamically stable and dopamine infusion was tapered and stopped.

The surgery lasted for around 11 hours. The total input was 13 litres and output was 9 litres. Blood loss was around 1 litre. The patient was electively ventilated in the postoperative period in view of prolonged surgery and massive transfusion.

TIME	ph	pco2	po2	hco3	Na	K	Ca	Lac	Glu
9 am	7.363	48.5	257	25.9	135	3.2	4.06	3.2	196
2 pm	7.358	46	264	24.4	136	3.7	4.40	4.2	270
3 pm	7.367	46	248	24.5	137	3.2	3.95	4.4	205
6 pm	7.345	43.6	227	22.7	139	4.2	4.34	3.9	191

Figure 1: Intraoperative ABG

Postoperative period- All invasive monitoring was continued. Analgesia was maintained with epidural 0.2% ropivacaine infusion and intravenous fentanyl infusion. The postoperative period was stormy. Patient developed bradycardia in the immediate postoperative period which responded to IV atropine. Dopamine infection had to be restarted in view of persistent hypotension. On postoperative day 1, patient was extubated after a successful T piece trial. Patient was hemodynamically stable and dopamine was tapered and stopped. Total parenteral nutrition and thromboprophylaxis was commenced on the next day itself. Later patient developed bilateral pleural effusion for which bilateral intercostal drainage was placed. Patient slowly went in for sepsis with persistent fever spikes and appropriate antibiotics were started based on culture and sensitivity testing. On postoperative day 6, patient developed tachypnoea which was not responding to noninvasive ventilation and had to be reintubated. CT pulmonary angiography showed doubtful thrombus in right middle lobe segmental vessel with bilateral basal collapse and consolidation. Heparin was started in therapeutic dose. Prone ventilation was done for 2 days in view of poor oxygenation after which it improved. On postoperative day 8 elective tracheostomy was done and by postoperative day 12 she was successfully weaned off from ventilator. Tracheostomy was decannulated by postoperative day 18 and discharged on day 21.

3. Discussion

Mesothelioma is a malignancy of serosal membranes. Peritoneum is the second most common site after visceral pleura. [5]Malignant peritoneal mesothelioma (MPM) commonly presents with diffuse, extensive spread throughout the abdomen with rare metastatic spread beyond the abdominal cavity.[5] The combined treatment of CRS with HIPEC has the potential for cure but with acceptable morbidity and mortality risks in selected patients. Since our patient was a young female in good general condition with no known comorbidities, no solid organ metastasis and a low PCI (peritoneal cancer index) score, she was an ideal candidate for this procedure.

The peritoneal cancer index (PCI) score was developed by Sugarbaker in 1996 and is used to assess the extent of peritoneal cancer throughout the peritoneal cavity.[6] The peritoneal cavity is divided into 13 well-defined regions(abdomen and pelvis are divided into 9 regions and intestines are divided into 4 regions), with each region given a score from 0 to 3 depending on the extent of tumour present (LS-0 denotes absence of cancer; LS-1 tumor size <0.5 cm in diameter; LS-2 tumor deposit 0.5-5 cm and LS-3 tumor deposit >5 cm).[7] The maximum score is 39. In patients with a PCI score more than 20, HIPEC is not advisable.[8]

The aim of CRS is to eradicate all macroscopic tumours using a laparotomy approach. The surgical procedure involves removing all or part of any affected organs and the lining of the peritoneal cavity.[7] During HIPEC, the abdominal cavity is perfused with chemotherapy solution heated to between 40 and 43 degree Celsius for 30 to 120 minutes.[7] The rationale involves direct delivery of high concentrations of the cytotoxic drug to the local tumor-bearing peritoneum while keeping the systemic drug levels low. Hyperthermia causes selective destruction of malignant cells by inhibiting RNA synthesis. Also heat increases drug uptake by the malignant cells.[9] The intraperitoneal chemotherapy penetrates tissues up to a depth

of 5mm only. So before HIPEC, adequate peritoneal resection should be performed to remove visible tumour mass to ensure penetration of the chemotherapy into the remaining tumor cells.[10] Chemotherapeutic drugs used commonly include mitomycin C, cisplatin, oxaliplatin and 5-fluorouracil. Dose calculations of these agents are based on body surface area.[7] Although the low systemic uptake of these drugs appears to reduce the toxic effects, cisplatin is associated with an increased incidence of postoperative renal impairment and oxaliplatin is associated with a higher risk of postoperative bleeding.[11]

The procedure may be performed by two techniques: open and closed. The open technique allows more uniform distribution of the drug but it is difficult to achieve and maintain hyperthermic state due to the heat dissipation by the exposed abdomen.[8] Also there is a potential risk of contamination of the operating field and aerosolisation and inhalational exposure to theater personnel. In closed technique, after cytoreduction the temperature probes and catheters are placed to instill chemotherapy and abdomen wall is sutured prior to infusion.[8] The advantage of closed technique is that there is minimal exposure of the operating theatre personnel to aerosolized chemotherapy. However, it may lead to uneven distribution of the hyperthermic drug.

CRS combined with HIPEC is an invasive abdominal surgical procedure with additional intraoperative temperature changes and fluid shifts over and above conventional laparoscopic or open surgical approaches.[12] The pathophysiological effects associated with this procedure can precipitate organ failure in some patients. Therefore an extensive preoperative assessment including thorough evaluation of the patients cardiac and pulmonary systems is of utmost importance. Preoperative malnutrition with a BMI <18.5 may lead to prolonged hospital stay, increased complications and cost of care.[13] Nutritional support preferably enteral should be instituted to improve anemia and albumin. Thromboprophylaxis should be started preoperatively in view of increased chances of thromboembolism.[8]

Patients with peritoneal mesotheliomas may often present with ascites. In such patients rapid sequence induction may be considered.[14] Since these patients have a large laparotomy incision, adequate analgesia in the form of epidural block and intravenous opiods should be provided.[15] Due to extreme variations in temperature, patients undergoing HIPEC are prone to coagulation abnormalities.[15] Point of care coagulation testing like thromboelastography may prove to be useful in such situations. Invasive monitoring like IBP and CVP is of utmost importance. The addition of dynamic measures of cardiac preload and fluid responsiveness, such as CO, SV, and SVR, may help us to implement goal directed fluid therapy.[8] Thermoregulation is a crucial step. Temperature probes should be placed in the esophagus in addition to 4 probes placed in the abdominal cavity during HIPEC phase.[16]

During CRS phase, due to large fluid shifts replacement at the rate of 8-12 ml/kg / hr may be required. [16] Goal directed fluid therapy will help to reduce postoperative complications. In case of massive blood loss, it should be corrected with adequate colloids, blood and blood products. A minimum of 0.5ml/kg/hr urine output should be maintained.[17] Normothermia should be maintained using forced air warmer and warm fluids. All electrolyte abnormalities must be corrected based on frequent ABGs.

Dopamine infusion at the rate of 1-2 mcg/kg/min may be started before the start of HIPEC phase to maintain the MAP within 20% of the patient's preoperative baseline and the stroke volume variation below 10%.[7] Urine output should be maintained at the rate of 2-4ml/kg /hr.[17] During HIPEC phase the patients usually develop raised core body temperature (nasopharyngeal) of up to 40.5°C due to the hyperthermic perfusate.[8] This leads to hypermetabolic phase and hyperdynamic circulation. The anesthesiologist must maintain normothermia by setting the warming device to ambient or off mode and using the underbody mattress to cool the patient. Cold intravenous fluids (2-3 litre bolus) and placement of ice packs in the axillae of the patient may be required to normalize the temperature. If despite all these measures, core body temperature rises to ≥39°C then the perfusionist should be advised to reduce the instillate temperature.[8] Hyperthermic chemotherapeutic agents can cause hyponatremia, hypomagnesemia, hypocalcemia, hyperglycemia and lactic acidosis which should be corrected based on ABG and serum electrolyte values. Any coagulation abnormalities should be corrected using FFP or cryoprecipitate. End tidal CO2 may rise during this phase.
Active rewarming should be started in the post HIPEC phase. A urine output of 1-2 ml/kg/hr should be maintained.[17]

Postoperative elective ventilation should be considered in patients with unstable intraoperative parameters. All invasive monitoring should be continued. Postoperative epidural infusion and opioids provide excellent analgesia. Fluid loss during initial 72 hours after surgery may be as high as 4.1 litres per day due to oozing of protein-rich fluid from the raw surface area due to peritonectomy.[18] Vasopressors may be required to maintain BP and albumin to maintain intravascular volume. Coagulation dysfunction can continue in the postoperative period which should be corrected with FFP or platelets.[19] Electrolyte abnormalities should be corrected and thromboprophylaxis initiated as early as possible. Early enteral feeding should be considered in patients who do not have bowel anastomoses.[8] Postoperative complications include intraabdominal fluid collection, pleural effusion, cytopenia, hypomagnesemia, hypokalemia, renal failure and sepsis. Aggressive chest physiotherapy and incentive spirometry should be initiated to prevent pulmonary complications.

4. Conclusion

Cytoreductive surgery followed by HIPEC is a major surgery that presents with multiple challenges for the anesthesia team during both intraoperative and postoperative period. But we should not refrain from offering this treatment to patients who are otherwise fit and with a high probability of long-term survival.

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