Cytoreductive onco-surgery with combined hyperthermic intraperitoneal chemotherapy and hyperthermic intrathoracic chemotherapy: Perioperative challenges

ABSTRACT
Cytoreductive surgeries (CRSs) are the common management modality for advanced cancers. The perioperative period is impacted by major surgical resection and its associated effects. The surgical morbidity is further enhanced when the resection of abdominal and thoracic cavity is required simultaneously. It is added on by the effects of hyperthermic intraperitoneal chemotherapy (HIPEC) and hyperthermic intrathoracic chemotherapy (HITHOC). These procedures are technically challenging with potential for high perioperative morbidity and mortality. We report a case of 56-year-old female diagnosed with carcinoma ovary with pleural metastases and malignant right pleural effusion and scheduled for CRS with HIPEC together with HITHOC.

Key words: Anesthesia; cancer; chemotherapy; cytoreductive surgery; hyperthermic intraperitoneal chemotherapy; hyperthermic intrathoracic chemotherapy

Introduction
Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is currently an accepted treatment modality in the management of gynecological and gastrointestinal malignancies with peritoneal metastases. However, malignant pleural effusion or pleural metastases are difficult to treat due to limited standard treatment options. Hence, it carries a poor prognosis with a median survival rate of 6–18 months. Recently, a combination of systemic chemotherapy and surgery together with hyperthermic intrathoracic chemotherapy (HITHOC) procedure is being tried for management for malignant pleural effusion and pleural metastasis. Like in HIPEC, a combination of intrapleural instillation of chemotherapeutic agent with hyperthermic perfusion may offer an additional benefit as tumor cells are exposed to high local concentration of chemotherapeutic agents with lower incidence of systemic side effects. These procedures are technically challenging with potential for high perioperative morbidity and mortality. The available literature to the best of our knowledge has either HIPEC or HITHOC procedure performed separately, but we did a combined HIPEC and HITHOC procedure, which remains complicated and challenging.

The consent has been provided by the patient for the publication of this case.
Case Report

A 56-year-old female weighing 45 kg, diagnosed case of carcinoma ovary with pleural metastases and malignant right pleural effusion, was posted for CRS with HIPEC together with thoracotomy and HITHOC. She had received three cycles of paclitaxel and carboplatin-based chemotherapy 6 months back. Patient had no other medical comorbidities. Airway and systemic examination were normal except for reduced air entry in the right infra‑axillary and infra‑scapular areas. Investigations including hemogram, coagulation tests, liver function test, renal function test, and electrocardiogram (ECG) were normal. Chest X-ray was suggestive of right‑sided pleural effusion with collapsed right lung [Figure 1]. Contrast enhanced computed tomography chest revealed moderate‑to‑gross loculated right pleural effusion with pleural thickening and nodularity suggestive of pleural metastases. Omental metastases, minimal pelvic‑free fluid, and bulky ovaries were also present. Pulmonary function test revealed restrictive pattern with FEV1 55.21%, FVC 60.76%, and FEV1/FVC 95.77%. Cardiopulmonary exercise testing showed VO\textsubscript{2} (rest 247 ml/min, warm-up 357 ml/min, anaerobic threshold 483), VO\textsubscript{2}/kg (rest 5 ml/kg/min, warm-up 7.4 ml/kg/min, anaerobic threshold 10.1), metabolic equivalent (rest 1.4, warm-up 2.1), and heart rate (rest 111, warm-up 116). Her room air oxygen saturation was 94%. Preoperatively, deep breathing exercise, incentive spirometry, and steam inhalation were started. She was kept nil orally for 8 h and was advised oral ranitidine 150 mg in night and morning of surgery with sip of water.

In the operating room, monitoring included five lead ECGs, noninvasive blood pressure, pulse oximetry, capnography, nasopharyngeal temperature, invasive arterial blood pressure, and central venous pressure. Intravenous access was secured with a 16-G cannulae. After epidural puncture at L3–L4 level, 300 µg morphine with 5 mg of 0.5% bupivacaine heavy given intrathecally followed by epidural catheter placement. After preoxygenation, anesthesia was induced with intravenous morphine 6 mg, propofol 100 mg, and atracurium 30 mg. A 35-Fr left double lumen tube was placed and position confirmed by fiberoptic bronchoscopy. Deep venous thrombosis (DVT) pump was placed. Anesthesia was maintained using oxygen, air, and desflurane (end-tidal concentration of 0.8%). Intravenous morphine and atracurium were administered as and when required.

During CRS, blood loss was approximately 2 l replaced with 2 units of packed red blood cells (PRBC) and ringer lactate. Temperature was around 35°C using forced air warmer and fluid warmer. The cytoreductive phase which lasted for 5 h consisted of total abdominal hysterectomy with bilateral salpingo‑oophorectomy, lymph node dissection, and total omentectomy. The diaphragm was opened via abdominal approach to excise pleural‑based nodule and hemorrhagic pleural fluid drained. As the patient developed hypotension (BP 80/60 mmHg) intra‑operatively, bolus of ringer lactate was administered, and subsequently, noradrenaline infusion with a dose ranging from 0.04 to 0.2 mcg/kg/min was administered to maintain a mean arterial pressure >65 mmHg. As the pleural‑based nodule could be excised via abdominal approach, thoracotomy was not required. Fluid management was guided by urine output, pulse pressure variation, and arterial blood gas analysis (ABG) [Table 1]. Urine output was maintained at 0.5–1 ml/kg/h during CRS phase and 2–3 ml/kg/h during HIPEC phase. Before the start of HIPEC and HITHOC phase, forced air warmer was kept on ambient mode and fluid warmer switched off. Cold intravenous fluids were administered.

| Table 1: Serial ABG |
|---------------------|
|                     |
| **Postinduction**   |
| **Pre-HIPEC**       |
| **Post-HIPEC**      |
| (30 min)            |
| **Post-HIPEC**      |
| (end)               |
| pH                  |
| 7.43                |
| 7.38                |
| 7.23                |
| 7.26                |
| pO\textsubscript{2} |
| 177                 |
| 169                 |
| 189                 |
| 163                 |
| pCO\textsubscript{2} |
| 32                  |
| 33                  |
| 34                  |
| 33                  |
| HCO\textsubscript{3} |
| 22.5                |
| 18.8                |
| 15.2                |
| 15.8                |
| Lactate             |
| 0.6                 |
| 1                   |
| 3.3                 |
| 3.6                 |
| Na                  |
| 137                 |
| 117                 |
| 138                 |
| 140                 |
| K                   |
| 3.5                 |
| 4.3                 |
| 3.5                 |
| 3.8                 |
| Ca                  |
| 0.92                |
| 0.9                 |
| 1.00                |
| 0.91                |

P\textsubscript{O}\textsubscript{2}: Partial pressure oxygen; P\textsubscript{CO}\textsubscript{2}: Partial pressure carbon dioxide; HCO\textsubscript{3}: Bicarbonate; Na: Sodium; K: Potassium; Ca: Calcium
Semi-Open technique (Coliseum) using cisplatin 100 mg in 2.5 l dialysate at 41°C was circulated for 60 min in the peritoneal cavity and right hemithorax through the diaphragmatic defect at a rate of 1.5 l/min using Sunchip roller pump. Temperature, urine output, hemodynamics, and ABG were monitored. The temperature increased from 35.2°C in the beginning of HIPEC to 38.3°C by the end of the procedure. The ventilatory parameters were adjusted to achieve end-tidal concentration of carbon dioxide between 35 and 40 mmHg. Lung protective ventilation strategies in the form of low tidal volume, recruitment maneuvers were used. Positive end expiratory pressure (PEEP) of 5 cmH₂O was provided to prevent atelectasis and also to increase the surface area of contact between circulating dialysate containing cisplatin and the diseased pleura. Intravenous furosemide and cold ringer lactate were administered to maintain urine output of 2 ml/kg/h. Following the procedure, the diaphragmatic defect was closed, chest and abdominal drains were inserted, and abdomen was closed. The total duration of procedure was 8 h. The total fluids administered were 5000 ml of balanced salt solution along with 2 units of PRBC.

Postoperatively, patient was shifted to intensive care unit in view of hemodynamic and metabolic derangements. Vasopressor support was gradually tapered and stopped. Patient developed mild renal dysfunction from second postoperative day (POD) which was normalized by fourth to fifth POD [Table 2]. Coagulation parameters were also deranged coagulation and fresh frozen plasma was transfused for the same. She was extubated on second POD. Chest physiotherapy and incentive spirometry were started post-extubation [Figure 1]. Analgesia was achieved with epidural morphine and intravenous acetaminophen. She was shifted back to ward on POD 4 and discharged from the hospital on POD 9.

Discussion

Anesthetic management of CRSs with hyperthermic chemotherapeutic treatment (HIPEC, HITHOC) are complex due to major surgical dissection, fluid and blood loss perioperatively, massive fluid shifts, nephrotoxicity, temperature variations in the form of hypothermia during cytoreduction and hyperthermia during HIPEC and HITHOC phase, electrolyte and acid–base disturbances, and deranged coagulation.⁴

Thorough preoperative assessment for chemotherapy-induced toxicity and prehabilitation improve the postoperative outcome and aids in perioperative management.⁵ Chemotherapeutic agents commonly used in HIPEC and HITHOC include cisplatin, doxorubicin, oxaliplatin, and mitomycin C.⁶ These patients can have diminished cardiopulmonary reserve due to the presence of pleural effusion, ascites, or cardiotoxicity from chemotherapeutic agents. The pathophysiological changes in various organs as well as metabolic and electrolyte disturbances are almost similar in HIPEC and HITHOC with a few additional risks related to HITHOC [Table 3]. HITHOC procedure is preceded by pleurectomy/decortication or extrapleural pneumonectomy. This includes additional risks associated with thoracotomy as well as one lung ventilation, lateral position, arrhythmias, and exposure to heated chemotherapeutic agents.⁷ In addition, filling the thoracic cavity with dialysate containing chemotherapeutic agent can cause mediastinal shift leading to inferior venacava and superior venacava obstruction, decrease in venous return, and cardiac output and direct cardiac compression.⁸ Impairment in tissue oxygenation and increase in airway pressure can occur both during HIPEC and HITHOC.

Lung protective ventilation strategy includes low tidal volume, PEEP, and recruitment maneuvers. Maintaining

**Table 2: Hematological and biochemistry parameters**

|                      | Pre-op | POD 0 | POD 1 | POD 2 | POD 3 | POD 4 | POD 7 |
|----------------------|--------|-------|-------|-------|-------|-------|-------|
| Hb (g/dl)            | 12.2   | 18.3  | 16.3  | 11.4  | 9.6   | 10.8  | 10.4  |
| Hct (%)              | 39.1   | 55.8  | 47.5  | 32.1  | 31.7  | 3.1   | 30.8  |
| TLC                  | 5470   | 21,000| 21,140| 20,000| 11,000| 8580  | 11,250|
| Platelet count       | 181,000| 150,000| 108,000| 42,000| 53,000| 63,000| 87,000|
| PT (s)               | 13.4   | 14.7  | 23.5  | 20.3  | 16.4  | 15.7  | 13.6  |
| INR                  | 1.2    | 1.32  | 2.1   | 1.85  | 1.4   | 1.43  | –     |
| Urea (mg/dl)         | 21     | 23    | 44    | 37    | 24    | 27    | 13    |
| Creatinine (mg/dl)   | 0.6    | 1.7   | 1.2   | 0.7   | 0.7   | 0.7   | –     |
| Sodium (mEq/l)       | 137    | 147.8 | 147   | 148   | 141   | 142   | 137   |
| Potassium (mEq/l)    | 3.8    | 5.1   | 4.5   | 3.2   | 2.7   | 3.4   | 3.1   |
| Bilirubin (mg/dl)    | 0.8    | 2.2   | 0.8   | 0.8   | 0.7   | 0.5   | 0.5   |
| Total protein (g/dl) | 8.0    | 4.4   | 4.2   | 4.4   | 4.7   | 4.5   | 4.9   |
| Albumin (g/dl)       | 4.3    | 2.5   | 2.4   | 2.4   | 2.7   | 2.8   | 3.0   |

Hb: Hemoglobin; Hct: Hematocrit; TLC: Total leucocyte count; PT: Prothrombin time; INR: International normalized ratio
optimal volume status and adequate tissue perfusion during HIPEC/HITHOC and CRS is the key to the successful management. Both hypovolemia and hypervolemia can be detrimental.\cite{9,10} Urine output measurement could be a noninvasive, reliable surrogate marker of renal perfusion and goal of urine output of 0.5 ml/kg/h during cytoreductive phase; 4 ml/kg/h during HIPEC and 1–2 ml/kg/h in post-HIPEC phase are required.\cite{11} ABG measurements may guide fluid therapy by lactate levels as well as provide information about acid–base and electrolyte status.

Optimal analgesia is imperative as the surgery involves large incision and extensive tissue manipulation. We used combined spinal epidural technique for perioperative analgesia and the patient received epidural morphine and intravenous acetaminophen as a part of multimodal analgesia. Core body temperature monitoring remains essential. In addition, temperature monitoring of the dialysate used during the hyperthermic phase is also required. It is essential as temperature fluctuations may lead to metabolic derangements, coagulation abnormality, and inflammatory cascade. We used forced air warmer and fluid warmer during cytoreductive phase to prevent hypothermia and cold infusions and ice packs during HIPEC/HITHOC phase to prevent hyperthermia.

These patients require intensive monitoring in the postoperative period along with possible need of ventilation.\cite{2,12,13} Coagulation dysfunction peaks around 24–48 h following surgery with restoration of normal coagulation in 5 days.\cite{13} Protein loss can occur and albumin supplementation might be needed.\cite{14} Renal dysfunction, dyselectrolytemia, and hyperglycemia can occur especially in first 48 h.\cite{15} Serum electrolytes (sodium, potassium, calcium, magnesium) are to be measured periodically and replaced. Mechanical thromboprophylaxis should be used to prevent DVT and pharmacological agents can be started as soon as the bleeding risk and coagulopathy resolve.

Conclusion

CRS with either HIPEC or HITHOC is complex and technically challenging procedure with profound pathophysiological alterations which can significantly affect the perioperative management more so in the combined technique as it requires proper planning, coordination with surgeons, and vigilance in perioperative period for a successful outcome [Table 3].\cite{16‑29}

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.
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