Perianesthesia Care of the Oncologic Patients Undergoing Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (CRS+HIPEC): A Retrospective Study

Purpose: This study was to understand the perianesthesia care for the patients under cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS+HIPEC) through the electronic medical record data from 189 surgical cases.

Method: Retrospective study.

Design: The perioperative electronic medical records of 189 CRS+HIPEC surgical cases at a hospital of west Pennsylvania from 2012 to 2018 were analyzed to study the characteristics of perianesthesia care for CRS+HIPEC surgery.

Findings: The patients' median age was 57 (range 21–83) years, and 60% were male. The mean anesthesia time was 10.47 ± 2.54 hours. Most tumors were appendix or colorectal in origin, and the mean peritoneal cancer index (PCI) score was 16.19± 8.76. The mean estimated blood loss was 623 ± 582 ml. The mean total intravenous crystalloid administered was 8377 ± 4100mL. Fifty-two patients received packed red blood cells during surgery. Postoperatively, 100% of the patients needed to stay at intensive care unit. 52% of patients were extubated in the operating room. Median lengths of hospital and intensive care unit stays were 13 and 2 days, respectively. The invasive procedure and prolonged hospital stay posed challenges for perianesthesia care. Even if all CRS+HIPEC patients were pre-screened for medical conditions, 73% of patients had one or more postoperative complications and 29% of patients experienced major postoperative complications (Clavien–Dindo grade III or higher) during the hospital stay. Prolonged hospitalization was due to gastrointestinal dysfunctions and respiratory failure related to atelectasis and pleural effusion.

Conclusions: CRS+HIPEC is a major surgery with numerous challenges to the perinesthesia care team regarding hemodynamic adjustment, pain control and postoperative complications, which once again demand training and ongoing studies from the perinesthesia care team.

Keywords: Perianesthesia care, hyperthermic intraperitoneal chemotherapy, postoperative complications.

Introduction

Peritoneal Carcinomatosis

Peritoneal carcinomatosis (PC) is defined as cancer affecting the peritoneum, the thin membrane surrounding your abdominal organs. Most PCs are secondary to the tumors originating from the peritoneal surface, gynecological *and* gastrointestinal systems.[1,2] In the past, PC might cause death, and it was a terminal disease for some patients.[1,3-5] Cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) (hereafter, CRS+HIPEC) is a promising therapy for improving quality of life and survival for PC patients.[6] However, CRS+HIPEC surgery causes substantial hemodynamic, metabolic, pulmonary, hematological instabilities and postoperative complications during perioperative periods due to aggressive visceral resections during CRS, the high temperature chemotherapy drug during HIPEC, and prolonged surgical duration.[7-10] The perioperative management of these adverse factors poses challenges for healthcare providers who need to establish strategies to avoid postoperative complications and maintain adequate normovolemia, normothermia, homeostasis, tissue perfusion and pain management.[11]

CRS+HIPEC Surgery

CRS+HIPEC is a complicated abdominal and pelvic surgical procedure that involves a degree of associated tissue injuries. The CRS portion of the procedure plans to remove all macroscopic tumors and may require extensive organ resection.[12-16] The possible resected organs include the uterus, ovaries, gastrointestinal tract, pancreas, spleen, gallbladder, and portions of the liver—not to mention extensive peritonectomy (i.e., resection of the affected peritoneal lining of the peritoneal cavity).[17] Once the surgical tumor and organ resection is completed, 3–4 liters of chemotherapy solution (e.g., oxaliplatin diluted with 5% dextrose) are infused into the abdominal cavity through inflow and outflow catheters placed in the abdomen. The chemotherapy solution is heated to temperatures of up to 42°C. Infusing heated chemotherapy to abdomen provides up to a 100-fold increase in the concentration of cytotoxic drugs in the peritoneal cavity compared to systemic chemotherapy. The abdomen is manually shaken by surgeons for more than one hour to allow the chemotherapy to bathe all peritoneal surfaces and prevent pooling of the heated chemotherapy solution. HIPEC is a targeted therapy to eradicate microscopic implants left by CRS.[18-27] After HIPEC, abdominal lavage, reconstruction of the gastrointestinal tract, drainage placement, and abdominal closure are performed at the last stage of surgery.

Perianesthesia Care for CRS+HIPEC

CRS+HIPEC associated with mortality and morbidity rates of 0.8%–4.1% and 5%–34%, respectively.[28-30] Although the surgical techniques and chemotherapeutic agents used for CRS+HIPEC vary among institutions, all might lead to multiple postoperative complications and hemodynamic and metabolic instability. To take care of patients safely and achieve the best outcomes for CRS+HIPEC surgeries, the perianesthesia clinicians need to understand the mechanism of CRS+HIPEC and the characteristics of CRS+HIPEC patients throughout perianesthesia phases.[8, 31-33] Previous CRS+HIPEC research focused on the surgical and anesthetic aspects of the procedure, leaving the research about postoperative care aspect under-addressed in most studies. All perianesthesia clinicians, especially nurses, need evidence-based studies to provide insight into knowledge about CRS+HIPEC patient care.

Our study retrospectively analyzed the data for perianesthesia management and postoperative course of patients undergoing CRS+HIPEC over seven years. We aimed to describe patients' characteristics, surgical procedures, anesthesia management, and postoperative complications to provide information for clinicians including nurses to improve perianesthesia care. We discussed the roles of perianesthesia nurses in the context of CRS+HIPEC surgeries.

Method

Patient Information

We conducted a retrospective study to identify patients who underwent CRS+HIPEC for colorectal cancer, appendiceal cancer, ovarian cancer, uterine cancer, gastric cancer, gastrointestinal cancer and peritoneal mesothelioma from one hospital in western Pennsylvania. The perianesthesia data, records, and clinical notes from 2012 to 2018 for CRS+HIPEC patients from this hospital were used for this study. This hospital implemented Electronic Medical Record (EMR) system and the Anesthesia Information Management System (AIMS) to replace paper charting in 2011. Since then, most patient information was recorded in digital format, and could be retrieved for research purposes. All clinical data for this study were retrieved by Health Record Research Request (R3) service by the Department of Biomedical Informatics (DBMI) of the University of Pittsburgh. The retrieved data included patient demographic information, medical history, medical data (e.g., lab values, vital signs, fluid, and medication management), and nursing care data through the duration of the

hospital stay. Our study was approved by the University of Pittsburgh, Human Research Protection Office, Institutional Review Board.

Perianesthesia Management

Patients were identified in AIMS and EMR with the keywords of surgery name "chemoperfusion" in our study. Generally, patients who are less than 80 years old and without severe comorbidity are selected for CRS+HIPEC due to the invasive nature of surgery. Anesthesia management for CRS+HIPEC is conducted with general anesthesia combined with regional anesthesia for intraoperative and postoperative pain management.[11] The central venous catheter and arterial catheter are routinely placed for fluid infusion and hemodynamic monitoring.[11] In CRS, both peritoneal and visceral resections are performed to remove all macroscopically visible tumor tissue from the peritoneal surface.[16] After CRS, surgeons perform HIPEC by using the 3~4 liters of diluted chemotherapy solution (e.g., mitomycin C, doxorubicin or oxaliplatin, and cisplatin) based on the types and origins of tumors. After surgery, patients are transferred to the intensive care unit (ICU). Some patients stay at the post anesthesia care unit (PACU) for recovery if they are extubated in the operating room (OR). Patients are discharged from the hospital when their status meets the defined criteria (e.g., hemodynamic and metabolic stability).

Clinical Parameters

The anesthetic protocol comprises of the complete monitoring of ventilation, anesthetic depth, and neuromuscular relaxation. Non-invasive hemodynamic monitoring (FloTracVigileo® Edwards Lifesciences S.L. 4.0) is applied for some patients.[34] Intraoperative fluid management maintains urine output at 0.5 ml/kg/h. During the postoperative period in PACU and ICU, monitoring vital signs, maintaining normothermia, using ventilation if patients on a ventilator and administering regional anesthesia continue, and fluid therapy is adjusted to maintain adequate tissue perfusion to obtain a neutral or preferably negative fluid management balance. CRS+HIPEC patients are assessed and managed daily by the surgical teams. In the case of postoperative complications (e.g. acute respiratory failure), the physicians from corresponding specialties are consulted. Postoperative complications are assessed and graded based on the Clavien-Dindo classification system.[36] The Clavien–Dindo classification is a standardized system for the registration of postoperative complications and the detailed definition is shown in Table 5. When patients have postoperative Infectious complications, the culture from the urine, blood, and central catheters tips are taken for testing. The clinical

laboratory service conducts lab tests (e.g., complete blood count, basic chemistry panel, coagulation panel, and arterial blood gas) on physicians' orders during the perioperative period for clinical management.

Statistical Analysis

All statistical analyses were performed using SPSS statistics 18.0 (SPSS Inc, Chicago, IL). Normally distributed data were recorded as mean ± SD, and non-normal variables as the median and interquartile range (IQR). Missing values in the dataset were excluded. The Pearson or Spearman's rho correlation test was used to assess correlations among variables. Statistical significance was set at 5% (i.e., $p < 0.05$).

Results

Our cohort included 189 patients with a mean age of 55.52 years (± 12.44) and median age of 57 years, of which 60% were male. The majority (i.e., 79%) of patients exhibited an American Society of Anesthesiologists (ASA) physical status classification score of 3. Most patients had limited medical history besides cancers. For example, 33% of patients were treated for hypertension, but only 2% had a history of coronary artery disease. Surgical team pre-screened patients' physical condition before scheduling surgeries since the healthy patients had better clinical outcomes from CRS+HIPEC surgery.[37] The tumor origin was distributed as follows: colorectal 29%, ovarian 14%, appendix 37%, mesothelioma 15%, gastrointestinal 3% and other 2%. Table 1 summarizes the demographic information and medical history of the patients.

Table 2 summarizes general information about the CRS+HIPEC surgeries in this hospital. The total anesthesia time for these operations ranged from 4.63–19.03 hours. All 189 patients had undergone completed CRS+HIPEC surgery. The median value of the peritoneal cancer index (PCI) before operations was 15 and ranged 2–36. PCI is used to assess the extent of peritoneal cancer throughout the peritoneal cavity. It has a range from 0 to 39 with 0 indicates no peritoneal cancer.[5] Figure 1 shows the distribution of PCI in this study. The completeness of cytoreduction (CC) ranged 0–2 in 96% of the patients if we excluded 30 cases with missing CC, which showed most patients had a completed tumor debulking. HIPEC was administered with closed abdomen technique for all cases. For regional anesthesia, bilateral paravertebral blocks were used for 93% of patients in this study. Although bilateral paravertebral blocks aimed for postoperative pain management, they were placed before surgery and used among 50% of the patients for intraoperative pain management with 7-10 ml/hour local anesthetic infused to each side of the paravertebral space. 48% of

patients were discharged from the OR intubated, 12% were extubated in the OR and transported to the ICU, and 40% were extubated in the OR and transported to the post-anesthesia care unit (PACU) and then to the ICU. The median length of ICU stay was 2 days, with a range of 1-70 days. When ICU patients were stable, they were transferred to the oncological floor for further recovery. The median length of hospital stay was 13 days, with a range of 6–97 days. No intraoperative mortality was recorded, but one patient died during the postoperative hospital stay. Figure 1 also shows the distributions of the length of hospital and ICU stays.

Table 3 summarizes the intraoperative fluid management for CRS+HIPEC surgeries. The median amount of crystalloid administered was 7,600 ml, with a range of 1,500–34,000 ml. The average rate of administration was 8 ml/kg/h. Meanwhile, 5% albumin was administered at a median value of 1,000 ml, with a range of 100–5,000 ml. Although hetastarch was used for some of the CRS+HIPEC surgeries before 2012, it was then discontinued in this hospital due to the side effects (e.g., coagulopathy, pruritus, as well as nephrotoxicity, acute renal failure and increased mortality) reported worldwide.[38-40] The combined average rate of crystalloid and colloid administration was 9 ml/kg/h, with a range of 6–15 ml/kg/h. The median amount of blood loss was 500 ml, with a range of 50–3,000 ml. Fifty-two patients required packed blood cell transfusions, and 11 patients required fresh frozen plasma. Moreover, platelet and cryoprecipitate were required by four patients and one patient, respectively. Intraoperative urine outputs were 185–5,610 ml. Five patients had ascites drained from the intra-abdominal space, and 37 patients exhibited gastrointestinal drain output from the nasogastric or orogastric tubes.

Table 4 summarizes the intraoperative medication management for CRS+HIPEC surgeries. A similar anesthetic protocol was applied in 100% of the cases. Fentanyl was the most often used opioid for intraoperative pain management, and 99% of the patients were administrated fentanyl, with a median dosage of 500 mcg. Hydromorphone and morphine, administered to 129 patients and 3 patients respectively, were also used for intraoperative pain management because they provided longer pain control than fentanyl. Rocuronium was the primary muscle relaxation medication used, with 100% patients given a median dosage of 208.5 mg. Phenylephrine was administered to 164 patients to treat intraoperative hypotension, which was typical for CRS+HIPEC surgeries. Because patients lost electrolytes from draining and blood loss during CRS+HIPEC surgeries, several types of electrolytes were administrated intraoperatively. For example, calcium was the primary electrolyte administered, with a median dosage of CaCl of 1,000 mg.

Using the Clavien-Dindo classification,[36] 51 out of 189 (27%) patients had no postoperative complication, and 138 (73%) had at least one postoperative complication. The 140 complicated patients had the following postop complication grades: 32 patients (17%) had grade I, 51 (27%) had grade II, 34 (18%) had grade III and 20 (11%) had grade IV. The postop mortality rate (grade V) was 0.5 %. Major complications were always presented in grades III and above. All patients with grade III required surgical intervention and the patient with grade IV, who required ICU management. The definitions and results of Clavien-Dindo classification for our study are shown in Table 5.

138 out of 189 patients presented postoperative complications after this long and invasive surgery, and the most common (35%) complication was atelectasis. Three out of top five postoperative complications (see Table 6) were related to pulmonary system- 35% of patients having atelectasis, 31% of patients exhibiting hypoxemia, and 21% of patients having pleural effusion. These pulmonary complications caused postoperative acute respiratory failure among 13% of patients who needed ventilation support. The incidences of postoperative pain were high (34%) even though the nerve blocks were applied for the majority of patients. Postoperative anemia was common (24%) due to the intraoperative blood loss and hemodilution. 21% of patients had gastrointestinal dysfunctions (e.g., fistula, ileus, anastomotic leak and severe nausea and vomiting); some of them needed total parenteral nutrition (TPN) during the hospital stay. We also reported 12 cases of postoperative pulmonary embolism (PE) and 11 cases of deep venous thrombosis (DVT) in this study despite patients being routinely on venous thromboembolism (VTE) prophylaxis. For treatment of thromboembolism, anticoagulation such as low molecular weight heparin was used. Cardiac and renal complications did not differ in a statistically significant fashion from other major abdominal surgeries. Acute renal failure was diagnosed in eight patients—for two of them were clearly related to the usage of cisplatin for HIPEC per diagnosis. Table 6 summarizes the postoperative complications for CRS+HIPEC. Only the postoperative complications taking place on more than 10 patients were shown in this study since we want to show the typical postoperative complications related CRS+HIPEC surgeries.

Discussion

Although the incidence of PC remains similar in the previous 20 years, the treatment strategies have advanced to improve patient outcomes.[41] The recent meta-analysis study demonstrated CRS+HIPEC surgery dramatically increased the survival time of PC patients and became a common technique of the surgical

oncologist.[42] Indeed, CRS+HIPEC is being used with increasing frequency worldwide as therapeutic considerations, as CRS+HIPEC is better understood and recognized.[42] However, the benefits of this approach must be evaluated in terms of the risks involved. CRS+HIPEC surgery used to associate with a high rate of perioperative mortality and morbidity.[43] Our results from 7 years of data with this procedure showed that while the percentage of perioperative mortality was relatively low (0.5%), 29% of patients experienced Clavien–Dindo grade III or higher complications. Because CRS+HIPEC surgery differs from other major abdominal surgeries in surgical techniques and anesthesia management, it poses many challenges for nurses doing perianesthesia cares.[44,45] In this study, we used the perioperative data to discuss the characteristics of perianesthesia care for CRS+HIPEC surgery. The whole perioperative period is divided into three phases for discussion: preoperative phase (from *admission* to *the time anesthesia providers taking patients from preoperative care unit*), intraoperative phase (from *the time anesthesia providers taking patients from preoperative care unit* to *the time anesthesia providers transferring patients to PACU or ICU*), and postoperative phase (from *the time anesthesia providers transferring patients to PACU or ICU* to *the time patient discharged from the hospital*).

Preoperative Preparation

Patient selection is the key for the success of CRS+HIPEC surgery.[37] Patients with minimal tumor and disease burden had associated with favorable survival outcomes and less complications.[44 46] Patient selection is determined by surgeons during a series of office visits, laboratory tests, cardiac and pulmonary function exams. Our study showed the patients in this study had mild medical history and only 2% of patients had coronary artery disease or myocardial infarction. Patients will have chlorhexidine gluconate bath the night before surgery as other patients for open abdominal surgeries. All CRS+HIPEC patients are admitted in the morning of the surgical day at our hospital. Any change on patient's physical and mental condition needs to be assessed and evaluated in the morning of surgery by healthcare team. 89% of the patients had their anesthesia start before 7:30 a.m. in the designated OR in this study. The collaborative care provided by preoperative nurses, the surgical team, and the anesthesia team begins right after admission. Upon presentation to the preoperative care unit, physical evaluation, and consent signatures by anesthesia and surgical teams are coordinated by preoperative nurses. Multiple clinicians from anesthesia and surgical teams will assess patients. Simultaneously, preoperative nurses finish patient education, preoperative medication

administration, and collect lab samples. All patients, unless having contraindications, are administered antiemetic and anticoagulation medications by preoperative nurses. Our study reported the complication rate for postoperative nausea and vomiting (5%) and VTE (12%). The mean anesthesia time was 10.47 hours with the range 4.63–19.03 hours in our study. Previous studies reported similar operative time.[47-49] Preoperative nurses educate patients and families about the duration of the procedure and the location they will meet again since knowledge about procedures reduces preoperative anxiety for patients and families. [50] A less anxious patient is desired from the medical viewpoint. Therefore, education during preoperative period plays a critical role in reducing the anxieties of patients and their families. As Table 6 indicates the postoperative complications, including atelectasis, post-surgical pain, ileus, and infections, CRS+HIPEC patients also benefit from early educations about the following topics in the preoperative phase: (1) the use of incentive spirometer to prevent atelectasis and pneumonia; (2) pain control with infusion local anesthesia pump or pain medication; (3) early ambulation to prevent VTE, stimulate bowel movement and prevent pneumonia; (4) possible wound care and ostomy care after the surgery.

Intraoperative Management

1. Intraoperative nursing care

Before a CRS+HIPEC patient is transferred from the preoperative care unit to the OR, the circulating nurse and scrub person prepare the OR for the patient's specific surgery, considering the individual needs of the CRS+HIPEC patients. The scrub person prepares the working space to accommodate hyperthermia pumps that need to be set up in the middle of the whole surgery. The circulating nurse assists the anesthesia providers during intubation and helps anesthesia providers if the patient experiences distress after moving to the OR bed and lying flat. The circulating nurse remains vigilant and is ready to assist in the deteriorations in the patient's cardiac, respiratory, and vital sign status throughout the procedure with anesthesia providers. The median value of the peritoneal cancer index (PCI) before surgeries was 15 with a range of 2–36 in our hospital. Previous studies indicated the PCI correlated with bleeding, postoperative complications, and clinical outcomes.[51-53] Our data showed the PCI and intraoperative blood loss had a correlation coefficient of 0.55. The median amount of blood loss was 500 ml with a range of 50–3,000 ml and 52 patients had intraoperative blood production transfusion. The circulating nurse communicates with surgeons and anesthesia providers about blood loss, obtains the order for blood products, reminds blood banks to send blood products to the OR, and

checks blood products with anesthesia providers. In this hospital, a chemotherapy-certified perfusionist is the person to handle the chemotherapy drug and hyperthermia pumps directly. Any waste containing cytotoxic agents is disposed of in a rigid yellow chemotherapy bin. The perfusionist must wear chemotherapy PPE during HIPEC. The perfusionist also document the whole HIPEC process on a paper form which is scanned to save in EMR. Although it is low risk of exposure to cytotoxic agents for OR staffs during HIPEC, anyone at the surgical field is suggested to wear double gloves and appropriate chemotherapy PPE when handling waste or touching patients. Our hospital's educational program covers the intraperitoneal chemotherapy perfusion, handling cytotoxic agents, waste disposal and effects of hyperthermia on the cytotoxic agents. In some hospitals, the circulating nurse is responsible for managing the hyperthermia pumps. Therefore, the circulating nurse is required to know the specific guidelines for the safe administration of cytotoxic drugs based on the established regulations by their institutions.

2. Intraoperative hemodynamic stability

Patient's hemodynamic stability during the intraoperative period has a close relationship with recovery time and postoperative complications. Recovery time, postop complications, and postop morbidity rates are also related to the intraoperative hemodynamic stability of CRS+HIPEC.[54] We found that the hemodynamic instabilities were hypertension and tachycardia during CRS phase. During HIPEC phase, acute body hyperthermia and increased intraabdominal pressure caused hemodynamic instability,[55] which related to (1) increasing cardiac output, (2) decreasing systemic vascular resistance, (3) increasing heart rate, and (4) increasing end-tidal CO2. Anesthesia providers should monitor patient's core temperature carefully and apply ice packs, cool forced air blanket or water blanket to lower patient's temperature when needed. A hemodynamic monitor, hourly urinary output, central venous pressure monitoring, and invasive arterial blood pressure monitoring should be used. For the patients with high-risk for hemodynamic instability, Vigileo/floTrac monitors are used for close hemodynamic monitoring. Intraoperative fluid management and volume therapy are important for maintaining hemodynamic stability during CRS+HIPEC surgery. Physicians debated about a restrictive fluid approach versus liberal fluid administration had better patient outcomes and less complications for major abdominal surgery and the related research was still inconclusive.[56] In adults, fluid administration at an average rate of 9–12 ml/kg/h was recommended to maintain satisfactory urine output of 0.5 ml/kg/h or more in our study. Our hospital applied goal-directed fluid administration to CRS+HIPEC with a combination of

colloids and crystalloids with a specific therapeutic endpoint.[57] Goal-directed therapy decreases the amount of administered fluid during CRS+ HIPEC surgery.[58] Therefore, lower risk of postoperative complications and hospital stay was observed.[58] Our patients received a mean of approximately 9,500 ml of combined crystalloids and colloids during surgery, which resulted in a positive fluid balance on the day of surgery. No correlation was found between the intraoperative fluid therapy used (crystalloids, colloids, and the sum of both) and the occurrence of postoperative pulmonary complications. Vasopressors are used for maintaining patients' intraoperative hemodynamic stability and cardiac output. Phenylephrine, used for 89% of patients, was the first choice for intraoperative vasopressors in our hospital with its fast-acting, short duration, and fewer complications.

3. Respiratory status

During CRS+HIPEC, impaired tissue oxygenation and an increase in peak airway pressures were reported due to the cranial shift of the diaphragm.[59] Data from our studies indicated that the intraoperative SpO_2 dropped to 94%. Peak airway pressures increased from 17 to 21 cmH2O during HIPEC compared with values throughout cytoreductive surgery, paralleled by an increase in end-tidal carbon dioxide values from 4.4 to 4.8 kPa after initiation of HIPEC. Although pulmonary complications after CRS+HIPEC were the leading cause of postoperative complications in our hospital, we did not find relations between intraoperative respiratory status and postoperative pulmonary complications. Currently, a lung-protective strategy consisting of positive end-expiratory pressure (i.e., >6 mmg), low tidal volume (i.e., 6–8 ml/kg), and recurrent recruitment maneuvers (e.g. a sustained increase in airway pressure with the goal to open collapsed alveoli) should be considered as the respiratory compromise during high peak airway pressures.[59]

4. Intraoperative pain management

Intraoperative multimodal pain management for CRS+HIPEC surgery consists of intravenous opioid agonists, non-opioid medications and regional analgesia. Intravenous opioid agonists are the primary method for intraoperative pain control, with 100% of our patients received opioids during surgery. The majority (93%) of CRS+HIPEC patients in our study had a bilateral paravertebral block via catheters placed preoperatively. Thoracic epidural block and bilateral paravertebral block are regional anesthesia methods for postoperative pain management.[60] Our hospital uses the bilateral paravertebral block. Although the primary purpose of regional anesthesia is for postoperative pain management, 50% of patients received a continuous infusion of

local anesthetic (i.e., Lidocaine) through bilateral paravertebral block catheters during surgery to achieve better pain management. Intraoperative and postoperative regional anesthesia reduces the requirement for postoperative ventilation, and the opioid-sparing effects of an epidural result in decreased incidence of bowel dysfunction and atony.[60] Some institutions prefer epidural analgesia over the bilateral paravertebral block for perioperative pain management.[61] Arguments exist about how epidural analgesia may worsen intraoperative hypotensive episodes because of (1) its synergistic effect with hyperthermia during HIPEC in decreasing systemic vascular resistance and (2) epidural analgesia causing the sympathetic blockade in some cases. One study, however, showed that epidural analgesia might improve patient survival time after surgeries by decreasing the incidence of tumor relapse.[62]

Postoperative Management

1. Perianesthesia care in PACU and ICU

After the CRS+HIPEC is completed, patients are either extubated in the OR or ICU after physicians evaluate the duration of surgery, preoperative major cardiac or respiratory comorbidities, blood loss and transfusion, hemodynamic stability, metabolic derangement, arterial lactate toward end of surgery and any possible organ failure. Our data revealed that 52% of patients were extubated in the OR, and 48% of patients were kept intubated to ICU. Previous studies reported extubation in 66-75% of patients after CRS+HIPEC in the OR.[63-66] Our data showed the average ICU stay was 4.41 days, with 77% of patients staying in the ICU for three days or less. Several studies reported the average ICU stay was from 2.7 to 6 days.[63-65 67-69] Based on our subgroup analysis of ICU and non-ICU patients, we conclude that ASA score, PCI, blood loss during surgery, and total anesthesia time are the factors to affect the length of ICU stay. In particular, the close monitoring at PACU and ICU for CRS+HIPEC patients is necessitated by (1) surgery needs to perform multiple organ resections and excise all macroscopic cancers, (2) HIPEC (i.e., ~100 minutes), (3) the long anesthesia time (averagely more than 10 hours). Intubated patients are extubated as soon as they are awake and demonstrated strong spontaneous breathing. Although the systemic chemotherapy is not restarted immediately after CRS+HIPEC, any body fluid and blood sample from patients are considered contaminated by cytotoxic agents for 48~72 hours after CRS+HIPEC.[70] Therefore, although PACU and ICU nurses do not handle cytotoxic drugs directly, they still must know the safety guideline for cytotoxic drugs.

2. Postoperative complications

The gastrointestinal tract and respiratory system are most affected by CRS+HIPEC surgery. CRS+HIPEC surgery is a major abdominal surgery with multiple organ resection and tumor debulking. The postoperative complications on the gastrointestinal tract include Ileus, anastomotic leak, enteric fistula, and severe nausea and vomiting. The perianesthesia care includes encouraging ambulance, identifying patients with complications, nutrition support, and administering TPN. Nurses have critical roles in the above interventions. Several studies reported that atelectasis and pleural effusion were the two major respiratory complications after CRS+HIPEC,[71,72] and we found the incidence of atelectasis and pleural effusion were 35% and 21%, respectively. Moreover, we found hypoxia and acute respiratory insufficient/failure among 31% and 13% patients, respectively. After extubating patients, it is important for PACU, ICU or oncological unit nurses to encourage patients to use the incentive spirometer. Using the incentive spirometer reduces postoperative atelectasis and pneumonia, especially for the lengthy surgeries like CRS+HIPEC.[68 73] Pleural effusion causes acute respiratory insufficiency/failure. Some patients recover from pleural effusion without any treatment, but surgeons need to place a pleural drainage tube when clinically indicated. Although (1) the reasons of postoperative pleural effusion and (2) the timing of applying subsequent pleural drainage tube need more investigations, all perianesthesia nurses involving CRS+HIPEC shall be ready for managing pleural drainage tubes for CRS+HIPEC patients.[74]

CRS+HIPEC patients are predisposed to develop postoperative VTE. Previous studies reported incidence for VTE varied between 5.6%-13.5%.[75,76] The result from our study indicated 6% of patients had PE, and 6% of patients had DVT after surgeries. Postoperative DVT of the lower limbs is often asymptomatic. Fatal PE is the first clinical manifestation of postoperative VTE. Routine and systematic VTE prophylaxis in high-risk patients is the strategy of choice to reduce the burden of VTE after surgery. Nurses will follow VTE prophylaxis protocol, which includes mobilization, graduated compression stockings, intermittent pneumatic compression devices, venous foot pumps, and medications.

30-day readmission rate is another vital patient outcome related to postoperative complications. Previous studies found 30-day readmission rates after CRS+HIPEC range between 11% and 19%.[72 77] Because most of our patients were not local and returned their home state after discharge, we did not have these results for further investigation.

3. Postoperative pain management

Pain control is crucial in promoting faster recovery from CRS+HIPEC. Severe pain decreases inspiratory effort and tidal volume, where good postoperative pain management optimizes respiratory system management. Postoperative pain for CRS+HIPEC is treated by a multimodal pain management plan including multiple medications and techniques.[78] Bilateral paravertebral blocks, which has fewer contraindications than epidural anesthesia, are being utilized frequently for these patients for both intraoperative anesthesia and postoperative analgesia. [79] Our data showed 34% of patients still complained acute postoperative pain with multimodal pain management including paravertebral blocks. Determining optimal postoperative pain management methods still requires subsequent studies. PACU and ICU nurses will assess and document patients' pain level with the 0–10 pain scale. Moreover, the regional anesthesia site shall be checked and assessed, and the dose of medication needs to be documented every shift. A CRS+HIPEC patient receives opioids through intravenous catheters if regional anesthesia cannot achieve adequate pain control. When a patient can tolerate clear liquid diets, oral analgesia is used for pain management. Nurses need to ensure that the patient knows not only the name and dosage of oral analgesia but also how often it is requested. In addition, nurses should assess and document patient's pain level and know the symptoms and treatments of opioid overdose.

4. Postoperative hemodynamic stability

The postoperative stress response involves all major organ systems: cardiovascular, respiratory, coagulation, renal, and endocrine.[80,81] Patients also develop systemic vasodilation due to systemic inflammatory response, which causes tachycardia, hypotension and needing vasopressor support.[63] Overall, the incidences of postoperative hypotension, hypertension and tachycardia for CRS+HIPEC patients in our hospital were 10%, 8% and 6%, respectively. Our study showed 11% of CRS+HIPEC patients in our hospital needed vasopressors support after postoperative day 1. Moreover, postoperative fluid management is an important cornerstone of hemodynamic stability and organ perfusion in patients undergoing CRS+HIPEC surgery. Significant intraoperative blood loss and abdominal draining per day present a challenge for each nurse to monitor and manage hemodynamic instability.[82] Adequate perioperative fluid therapy is important to maintain hemodynamic stability and reduce the risk of chemotherapy-related postoperative renal insufficiency. On the other hand, recent studies and reviews repeatedly demonstrated a strong correlation between liberal fluid administration and the incidence of postoperative pulmonary edema.[83] Therefore, we suggest a

perioperative urine output more than 100 ml/h, which will be monitored for 3 days after surgery, to avoid over-hydration and ensure hemodynamic stability. The goal-directed fluid and hemodynamic management is recommended for preventing organ hypoperfusion, especially in the context of CRS+HIPEC surgery.[58] Physicians should adjust their fluid management plan based on patients' responses for fluid therapy. Nurses should remain vigilant of the amount of drainage, urine output, bleeding, and variable fluid intakes.

5. Discharging from hospital

In terms of recovery, the median number of hospital stay days in our study was 13 days with the range from 6 to 97 days. Most patients without postoperative complications had a hospital stay less than 8 days, a result better than that from a recent 2149-patient multi-institutional study that reported a median duration of hospitalization of 18 days (ranging from 1 to 217 days).[84] With limited available data, it is difficult to conclude the reasons of the shorter hospital stay result in our hospital than that in the study. The main reasons that cause hampered recovery in our hospital were (1) prolonged pulmonary complications and (2) repeated procedures due to gastrointestinal dysfunctions.

CRS+HIPEC patients need to meet specific criteria before being discharged from hospital. They should be able to tolerate clear liquid meals per day without complaining of nausea, vomiting or other discomforts. Patients should be able to take oral pain medication, urinate without difficulty, and ambulate independently daily. When patients meet these discharge criteria, the care team will provide patients with the discharge instructions. Instructions include a discussion of home care, pain management, and the symptoms that require medical attention. Nurses are the essential health care providers for delivery of these instructions.

Conclusion

CRS+HIPEC is a complicated surgical procedure. Recent research indicated acceptable morbidity and mortality rates.[84] CRS+HIPEC has been shown to (1) extend life among a relevant population of peritoneal carcinomatosis patients and (2) be safe in high volume surgical centers. The perianesthesia care of the patients for CRS+HIPEC is essential to improve patient outcomes. Perianesthesia care for CRS+HIPEC includes monitoring for signs and symptoms of the anticipated complications associated with CRS+HIPEC so that preventive measures can be initiated timely. Perianesthesia nursing care should focus on fluid/blood/protein losses, pain management, hemodynamic instability, and multiple postoperative

complications. It is of utmost importance to maintain or restore volume balance by aggressive substitution intravenous fluids and diuretic to meet patients' needs. Regional analgesia and non-invasive ventilation are recommended to guarantee adequate pain therapy and postoperative extubation, respectively. Hemodynamic monitoring is essential for nurses to note the real-time fluid status of the patient. Interdisciplinary clinical pathways must be developed to achieve good patient outcomes in the patients with more comorbidities for CRS+HIPEC surgeries.

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