Special Article

Society of Onco-Anaesthesia and Perioperative Care consensus guidelines for perioperative management of patients for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC)

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ABSTRACT

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) for primary peritoneal malignancies or peritoneal spread of malignant neoplasm is being done at many centres worldwide. Perioperative management is challenging with varied haemodynamic and temperature instabilities, and the literature is scarce in many aspects of its perioperative management. There is a need to have coalition of the existing evidence and experts' consensus opinion for better perioperative management. The purpose of this consensus practice guideline is to provide consensus for best practice pattern based on the best available evidence by the expert committee of the Society of Onco-Anaesthesia and Perioperative Care comprising perioperative physicians for better perioperative management of patients of CRS-HIPEC.

Key words: Consensus, cytoreduction surgical procedures, hyperthermia, induced, peritoneal neoplasms, peritoneum

INTRODUCTION

Primary peritoneal malignancy and malignant neoplasms of gastrointestinal and gynaecological origin with peritoneal metastases have a poor prognosis. Traditionally, these types of malignancies were considered incurable conditions suitable for palliation. Dr. Paul Sugarbaker showed that surgical removal of visible tumour for peritoneal mesothelioma combined with locoregional heated chemotherapeutic

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drugs improved the quality of life and survival of these patients.[1] Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) for peritoneal malignancies is now done at many centres; however, there is no document for best clinical practice related to it. In addition, the literature is scarce in many aspects related to the perioperative management of CRS-HIPEC. There is immediate need to have coalition of the existing evidence and experts' consensus opinion for better perioperative management.

CRS-HIPEC is a complex surgery and perioperative management depends on many factors including patient's preoperative health status, disease load, surgical factors, intraoperative events and chemotherapeutic drug/drugs used for HIPEC. HIPEC is a highly concentrated, heated chemotherapy treatment that is delivered directly in the abdomen after CRS. CRS-HIPEC with or without systemic chemotherapy has developed over time as an effective multimodal treatment option for selected patients with peritoneal surface malignancies. The technique involves macroscopic resection of disease burden and metastases, followed by infusion of chemotherapy heated to 41°C–43°C into the peritoneal cavity by a special pump.[2] The efficacy of HIPEC depends on a number of patient's related, clinical and treatment parameters including class of drug, concentrations of drug used, carrier solution, volume of the perfusate, temperature of the perfusate, treatment duration and the technique of delivery.[3,4] There is still high variability of HIPEC treatment worldwide based on the primary disease and institutional protocol.

The purpose of this document is to provide best evidence available and consensus for best clinical practice among perioperative physicians (anaesthesiologists, intensivists, surgeons, oncologists and pain physicians) and best practice pattern for optimal perioperative management of CRS-HIPEC.

METHODOLOGY

This consensus practice guideline document was prepared by the expert committee of the Society of Onco-Anaesthesia and Perioperative Care (SOAPC). The expert panel included onco-anaesthesiologists, onco-surgeons, intensivists and pain physicians, with inputs from physiotherapists, dietician and oncologists working in the field of peritoneal malignancies and with sufficient experience in perioperative management of such patients. This statement represents the current practice pattern and consensus based on the review of the literature for the best available evidence, individual experience in perioperative management of CRS-HIPEC patients, inputs from a survey done in India and some centres of England and United States within a reference group.

The expert committee was divided in nine subcommittees (with two experts each) and were assigned a subtopic related to the document. The experts of each subcommittee also interacted with other subcommittees for suggestions and consulted other clinicians as well working in this field during the literature review. Each group searched the existing literature from various search engines including PubMed, Medline, Cochrane Database, Google Scholar and OVID. The search included randomised controlled trials, observational studies, retrospective studies, review articles, case reports and correspondences published in English language until August 2019. The bibliography of the searched manuscripts was also reviewed for any missing relevant articles missed in initial search and such manuscripts were individually searched from literature. Each expert formulated questions on the subtopic allotted and evidence was collected accordingly.

After the collation of evidence from published literature, the experts made a survey questionnaire for the questions for which sufficient literature was not available or was inconclusive. This questionnaire was discussed in a meeting with all the experts of all the subcommittees. After validating the questionnaire among members of core committee, the final validated questionnaire was distributed to more than 60 anaesthesiologists, intensivist, onco-surgeon and pain physicians who were actively and regularly involved in management of CRS-HIPEC.

After the results of the first survey were analysed, the questionnaire was redistributed to the members of core committee for a total of three rounds for making consensus as per DELPHI method.[5] Consensus was defined[6] as 'Strong Consensus' for 90% or more agreement, 'Consensus' for 75%–90% agreement, 'Majority Agreement' for 50%–75% agreement and 'No Consensus' for less than 50% agreement after three rounds of discussion on the questionnaire between the members of experts' committee. The proposed consensus statement was then presented by select members of the expert panel in the 'HIPEC Consensus

Guidelines Session' in SOAPC annual conference, on September 21st 2019 at Hyderabad, India, for wider discussion and debate. All members of the SOAPC and delegates attending the conference were requested to provide their comments either during the meeting or later through e-mail to the first author of this consensus guideline. The proposed recommendations were then further revised by the expert panel to accommodate some of these suggestions. The resulting consensus guideline document was officially adopted by members of experts' committee. When it was possible to make an evidence-based recommendation, the term 'we recommend' is used. For other practice guidelines, the degree of consensus is mentioned. The consensus recommendations are mentioned after each section/subsection but readers are also advised to go through the entire text and not only the consensus recommendations.

SURGICAL FACTORS

CRS-HIPEC is a complex procedure with morbidity and mortality rates reported between 20%–40% and 3%, respectively.[7] Over the years, there has been a reduction in the morbidity of CRS-HIPEC which has been attributed to better patient selection, standardisation of surgical technique, systematic surgical training and increasing surgical experience. The Peritoneal Carcinomatosis Index (PCI) provides a quantitative assessment of the extent of disease within the peritoneal cavity [Figure 1]. The PCI is an independent predictor of both morbidity and survival. If the PCI is more than 17–20 in a patient with colorectal metastases, CRS-HIPEC should not be offered. No benefit was seen with HIPEC in patients with PCI >12 in gastric cancers and PCI >8 in recurrent ovarian cancer. Although there is no such cut-off for PCI in mesothelioma or pseudomyxoma peritonei (PMP), a higher PCI is a predictor of poorer long-term outcome.[8-10] It has suggested that for conditions where there is no cut-off for PCI, CRS-HIPEC is contraindicated if complete cytoreduction cannot be achieved.[9,10] Some sporadic case series suggest an extended indication of CRS-HIPEC with pelvic exenteration for rectal cancers.[11]

PREOPERATIVE ASSESSMENT AND OPTIMISATION

Preoperative optimisation of CRS-HIPEC patients should be individualised and depends on patients' age, body mass index, comorbid diseases, functional status, disease burden, presence or absence of malnutrition (low albumin) and presence or absence of preoperative anaemia.

Preoperative hypoalbuminaemia can be used both as an independent predictor of major postoperative complications and as a prognostic parameter.[12] Perioperative nutrition is a must for major cancer surgeries, and enteral nutrition started preoperatively is the method of choice.[13] In malnourished patients, preoperative sip feed enteral nutrition and in patients with severe metabolic risk, in whom enteral nutrition cannot provide adequate energy, preoperative parenteral nutrition is recommended.[14]

Preoperative malnutrition is prevalent in more than 30% patients undergoing CRS-HIPEC and is associated with increased length of stay in hospital and higher

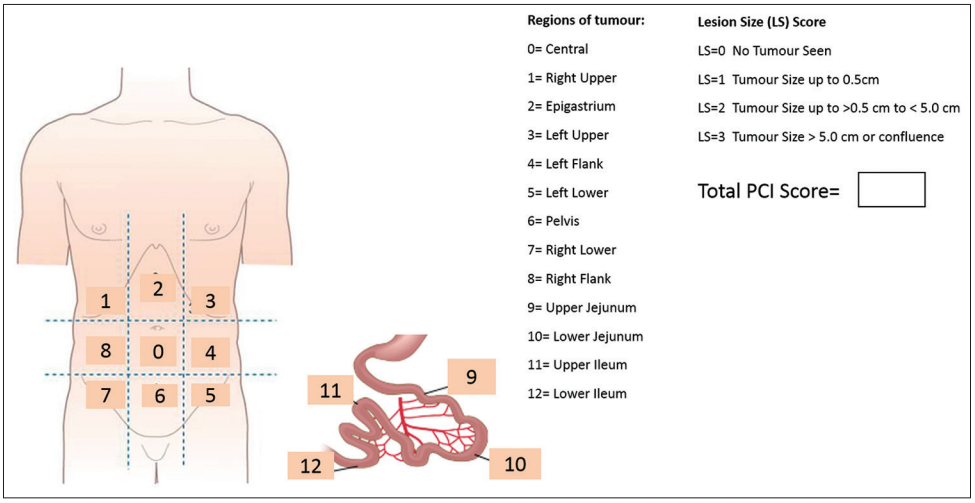

Figure 1: Sugarbaker's Peritoneal Carcinomatosis Index scoring

infectious complications in the postoperative period.[15] There is a need for preoperative nutrition assessment and support if needed.[16] Current guidelines are sparse in directing nutrition practice in this patient group. General cancer nutrition guidelines recommend routine preoperative nutrition assessment and 1–2 weeks of oral nutritional optimisation and support prior to surgery in nutritional compromised patients to decrease morbidity.[17,18] The role of perioperative immune nutrition in major cancer surgeries is controversial; few studies showed benefit,[19] whereas others showed no advantages.[20]

Assessment of the functional status in these patients is vital. In addition to routine blood testing, the patient should be screened and optimised according to the preexisting comorbidities. A 12-lead electrocardiogram and a baseline two-dimensional echocardiogram are usually enough. Dynamic cardiac testing can be done using either exercise testing or dobutamine stress echocardiography in patients with limited cardiac reserve or in conditions where functional capacity cannot be assessed.[21] Preoperative anaemia is common, and it is associated with increased morbidity and requires massive blood transfusion.[22] Correction of anaemia should be started as soon as decision for surgery is made.[23]

CRS-HIPEC is associated with increased incidence of postoperative pulmonary complications. The factors contributing to this are prolonged operative time, diaphragmatic splinting, lithotomy position, preoperative pleural effusion, ascites or presence of preoperative compromised pulmonary functions. Preoperative incentive spirometry and respiratory muscle training and continuation in postoperative period help prevent postoperative pulmonary complications. These patients should undergo regular chest physiotherapy under the supervision of a physiotherapist.[24] Consensus recommendations are summarised in Table 1.

CHEMOTHERAPY

The rationale for HIPEC is to maximise the exposure of local tissues to high concentrations of chemotherapeutic agents (20–1000 times greater than plasma levels) with minimal effects on normal tissue.[25] The most commonly used drugs for intraperitoneal (IP) administration are mitomycin-C and the platinum-based drugs, cisplatin, carboplatin, and oxaliplatin which have synergistic effect with heat. The less commonly used are doxorubicin, docetaxel, paclitaxel, 5-fluorouracil and irinotecan [Table 2].[4] Bidirectional intraoperative chemotherapy involves concomitant administration of intraoperative intravenous and IP chemotherapy, aiming to create a bidirectional diffusion gradient through the cancer cells.

The ideal carrier solution should improve exposure of the peritoneal surface, have slow clearance from the peritoneum, maintain high intraperitoneal volume and not have any adverse effects on the peritoneal membranes.[26] Currently, isotonic saline or dextrose-based peritoneal solutions are recommended with most centres using 1.5% dextrose isotonic peritoneal dialysis solutions.[27] Oxaliplatin was given in 5% dextrose-based water solution as previously it was thought that chloride ions degrade oxaliplatin into less cytotoxic metabolites. However, it is demonstrated that chloride-containing solutions can be safely used with oxaliplatin and in fact it increases its cytotoxicity.[27] The systemic absorption of 5% dextrose solutions can lead to severe hyperglycaemia and hyponatremia.

Table 1: Consensus recommendations for preoperative assessment and optimisation

Recommendation/suggestion	Level of consensus/evidence
We recommend all routine blood investigations and 12-lead electrocardiogram for all patients.	Evidence
We suggest routine preoperative resting 2D echocardiogram.	Consensus
Patients should visit perioperative physician 1-4 weeks prior to surgery for optimisation depending on time availability.	Strong consensus
We recommend that preoperative oral or enteral nutrition should be started in all malnourished patients.	Strong consensus and evidence
Preoperative oral supplemental nutrition may be considered even if patients are not malnourished.	Majority agreement
There is no role of routine perioperative immune nutrition in CRS-HIPEC patients.	Strong consensus
Preoperative physiotherapy and physical exercise should be started	Strong consensus
Respiratory exercise training	Strong consensus
Muscle training	Consensus
Aerobics	Majority agreement

2D – Two-dimensional; CRS-HIPEC – Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

Table 2: Commonly used chemotherapeutic drugs and their characteristics

Drug	Type	Dosage (mg/m² BSA)	AUC ratio	Common toxicities	Common uses
Mitomycin C	Antitumour antibiotic	10-160	23.5	Nephrotoxicity, pulmonary toxicity, myelosuppression	Appendix, PMP, colorectal, gastric, ovary
Oxaliplatin	Alkylating agent	160-460	16	Neurotoxicity, GI bleeding, nephrotoxicity, peripheral neuropathy, myelosuppression	Colorectal, appendix, gastric
Cisplatin	Alkylating agent	50-360	7.8	Nephrotoxicity	Ovary, colorectal, gastric, PMP
Carboplatin	Alkylating agent	350-800	18	Myelosuppression	Appendix, ovary
Doxorubicin	Antitumour antibiotic	15	230	Cardiotoxicity, myelosuppression	Appendix, PMP, colorectal, ovary, malignant ascites
Irinotecan	Plant alkaloid	100-400		myelotoxicity	Colorectal
Paclitaxel	Plant alkaloid	60-175	1000	Myelosuppression, peripheral neuropathy	Ovary
Docetaxel	Plant alkaloid	80	552	Myelosuppression, pulmonary toxicity	Gastric
5-Florouracil	Antimetabolite	1000	250	GI, myelosuppression, neurotoxicity	GI

AUC – Area under curve; BSA – Body surface area; GI – Gastrointestinal; PMP – Pseudomyxoma peritonei

HIPEC can be delivered by open or closed abdominal techniques. The closed abdominal method was the first technique described and still used widely. The open abdominal is usually performed by the 'Coliseum technique'. The commonly used perfusate volumes are 1.5–2 L/m² body surface area. During the HIPEC procedure, the roller pump forces the perfusate through the inflow line into the abdomen and pulls it out through the drains at the rate of 1 L/min. The heat exchanger keeps the perfusate temperature at 43°C–45°C, so that the intraperitoneal temperature is maintained at 41°C–43°C. Once full circulation of the perfusate in and out of the abdomen is achieved with a temperature of around 41.5°C, the drug is added to the primer and the timer is set to 30–90 min depending on the drug.

ANAESTHETIC TECHNIQUES AND MONITORING

The choice of anaesthesia and analgesia may affect long-term cancer outcomes after CRS-HIPEC. In animal models, volatile anaesthetic agents and opioids enhance the malignant potential of tumours by promoting invasion and proliferation of tumour cells and by immunosuppression and angiogenesis.[28,29] A recent meta-analysis showed that use of propofol-based total intravenous anaesthesia (TIVA) was associated with improved recurrence-free survival and overall survival after cancer surgeries.[30]

Induction of anaesthesia varies with the type of primary disease. Patients with large PMP and other appendiceal tumours may have a large abdomen due to ascites and disease load and there may be a risk of aspiration in these patients and may require rapid sequence intubation.[2] There are data that suggest that use of volatile anaesthetic agents and opioids decreases the recurrence-free survival and overall survival in oncologic patients.[31,32] However, a retrospective study of CRS-HIPEC for appendiceal tumours demonstrated that volatile agent with opioid anaesthesia is associated with increased progression-free survival and 5-year overall survival when compared with multimodal TIVA group.[33] The survival benefit of opioid sparing TIVA was only demonstrated in low-volume diseases and lower American Society of Anesthesiologists (ASA) physical status patients.[31,32,34] Use of nitrous oxide during CRS-HIPEC is not evaluated and many researchers and practitioners are using it routinely. Guidelines for anaesthetic management are summarised in Table 3.

MONITORING

Haemodynamic monitoring

In addition to standard monitoring such as electrocardiogram, noninvasive blood pressure, pulse oximetry, end-tidal CO_2 monitoring and core-body temperature monitoring, these patients require invasive blood pressure monitoring and sometimes central venous pressure monitoring.[35,36] Cardiac output monitoring is being used in many centres in high-volume diseases (PCI >15) or in isolated case reports.[37-39] Goal-directed therapy (GDT) in CRS-HIPEC had shown lower morbidity and postoperative length of stay with no difference in mortality.[40]

Arterial blood gas monitoring is often needed periodically throughout the surgery to assess gas exchange, electrolyte and lactate levels.[37,38] When 5% dextrose is used as a perfusate, it is essential to monitor serum sodium and 1–2 hourly blood glucose levels as hyponatraemia and hyperglycaemia can occur.[41] It is prudent to measure the serum magnesium levels during surgery especially before the HIPEC phase and also in postoperative period as hypomagnesaemia

can result from dilution secondary to fluid infusion and following administration of platinum-based perfusate.[42,43] With massive/significant blood loss and transfusion of blood and blood products, ionised calcium should be monitored and corrected.

Goal for intraoperative urine output

The incidence of acute kidney injury (AKI) after CRS-HIPEC ranges from 21.3% to 48%.[44,45] Higher age, higher BMI, use of preoperative pregabalin, platinum-based chemotherapy, major blood loss, hypertension and low intraoperative diuresis were predictors of development of AKI. The incidence of AKI was 3.7% following cisplatin-based (50 mg/m^2) HIPEC. Low intraoperative urine output, use of angiotensin II receptor antagonist and hypertension were factors associated with development of AKI.[42] Intraoperative measurement of urine output is used as a surrogate marker of renal perfusion. During HIPEC phase, maintaining optimal urine output is vital. The recommended targets for urine output during various phases are up to 0.5 mL/kg/h during CRS, 2–4 mL/kg/h during the HIPEC phase and 1–2 mL/kg/h post-HIPEC phase.[13,46,47] However, these thresholds are debatable in the context of individualised fluid therapy.

Debate about hydration and higher diuresis during HIPEC has many reasons. First, chemotherapy is not administered intravenously. Second, the degree of absorption and serum concentration may be variable depending on the surface area. Third, drug clearance depends on the renal blood flow and not the urine output. Fourth, while renal failure can be attributed to platinum, it is often multifactorial. Thus, maintaining euvolaemia in the perioperative period by individualising fluid therapy seems prudent.

Coagulation monitoring

Coagulopathy following CRS is multifactorial and depends on the duration of surgery, extent of resection, that is, PCI, blood loss and degree of haemodilution which in turn depends on the volume of replacement with crystalloids and colloids, transfusion of packed red cells and hypothermia. Coagulopathy peaks at 24 h and may persist up to 72 h in the postoperative period.[13] Intraoperative monitoring of coagulation parameters periodically depending on the volume of estimated blood loss is advisable. Prothrombin time (PT), activated partial thromboplastin time (aPTT) and international normalised ratio (INR) are used in most centres and thromboelastography (TEG or ROTEM) in some centres.[48] Use of point-of-care coagulation monitoring (TEG and thrombocyte function analyser multiplate) can detect complex coagulation disorders such as hyperfibrinolysis, thrombocytopathies/penia or factor XIII deficiency.[49] There is no clear evidence of timing/phase to do coagulation testing in perioperative period except preoperative period.[48,50,51] Consensus recommendations are mentioned in Table 4.

Fluid management

Fluid management is an important aspect of haemodynamic management in patients undergoing CRS-HIPEC, but it also one of the most controversial. During CRS phase, intraoperative fluid loses may reach as high as 8–12 mL/kg along with significant blood loss.[52] Adequate perioperative crystalloids and colloids are needed to ensure end-organ perfusion and maintain haemodynamic goals without causing volume overload. There is lot of heterogeneity in the literature regarding the type of intravenous fluid, that is, crystalloids and colloids, to be used in CRS-HIPEC. Use of hydroxyethyl starch (HES), although extensively used,[52,53] remains debated because of the association with AKI and need for renal replacement in critically ill patients[54,55] but not in surgical patients.[56,57]

Table 3: Consensus recommendations for anaesthetic management and monitoring

Recommendation/suggestion	Level of consensus/ evidence
Thoracic epidural analgesia should be used in all patients if not contraindicated.	Strong consensus
Intravenous induction of anaesthesia with propofol and induction dose of opioid should be done.	Strong consensus
Volatile agents (isoflurane/sevoflurane/desflurane) can be used for maintenance of anaesthesia.	Strong consensus
Inhalational anaesthesia vs TIVA can be selected based on patient's disease load, tumour grading and ASA status. Low-volume disease and lower ASA physical status patients may be given TIVA.	Strong consensus

TIVA – Total intravenous anaesthesia; ASA – American Society of Anesthesiologists

Table 4: Consensus recommendations for coagulation monitoring

Recommendation/suggestion	Level of consensus/ evidence
We recommend PT, aPTT and INR testing in the preoperative period.	Evidence, consensus
We suggest PT, aPTT and INR testing in the postoperative period.	Consensus
PT, aPTT and INR testing should be individualised in intraoperative period if blood loss is more than 50% of blood volume and after HIPEC phase.	No consensus, <50% agreement

PT – Prothrombin time; aPTT – Activated partial thromboplastin time; INR – International normalised ratio; HIPEC – Hyperthermic intraperitoneal chemotherapy

HES (130/0.4) was found to have a negative impact on the renal function in patients undergoing HIPEC, though fewer HIPEC patients received HES.[58] HES causes increased reduction in maximum amplitude on TEG and increased perioperative bleeding compared with crystalloids and albumin.[59] Balanced fluids, like Ringer's lactate and acetate-based solutions, have an electrolyte composition close to plasma, whereas isotonic normal saline has supraphysiologic chloride content which induces hyperchloremia and metabolic acidosis.[60,61] Liberal fluid administration leads to fluid overload and tissue oedema and causes abdominal, cardiac or pulmonary complications. Fluid overload has been found to be associated with an increased morbidity.[46,47] Restrictive fluid regimens have demonstrated decreased perioperative mortality in other major surgical procedures.[62-64] However, restricted fluid therapy can cause suboptimal tissue and renal perfusion in the face of extreme haemodynamic changes that occur during the phases of CRS-HIPEC.[65] In CRS-HIPEC procedures, Colantonio *et al*.[40] found that patients in the GDT group received significantly reduced volume of fluids, had lower morbidity and postoperative length of stay with no difference in mortality.

GDT with individualised therapeutic end points can be achieved using a combination of colloids, crystalloids and vasopressors. There is extensive loss of protein in the ascitic fluid and secondary to surgical dissection. Hence, albumin replacement has been shown to be beneficial in patients requiring extensive debulking and large-volume ascites drainage.[66]

Early start of vasopressors is advocated to avoid hypervolemia. Routine use of furosemide, mannitol or low doses of dopamine to prevent renal dysfunction is not recommended as it does not affect the creatinine values after CRS-HIPEC.[13,67] Diuretics may be required in selected cases wherein urine output is inadequate despite adequate intravascular fluid status, but it is prudent to avoid diuretics until the patient is euvolaemia.[68] Sodium thio-sulphate is being used for prevention of cisplatin-induced nephrotoxicity with promising results[69] but is yet to be established as standard of care. Perioperative blood transfusion policy should be like any other major surgery, and triggers for blood product transfusion should be individualised. The risk factors for massive transfusion during CRS-HIPEC are preoperative anaemia, impaired coagulation profile and high tumour burden (PCI 16 or more)[70] [Table 5].

Table 5: Consensus recommendations for fluid management and monitoring

Recommendation/suggestion	Level of consensus/ evidence
Balanced salt solutions like Ringer's lactate and acetate-based solution should be used.	Strong consensus
Albumin should be used as the colloid of choice	Strong consensus
We suggest use of noninvasive cardiac output monitoring like arterial-pressure-based cardiac output monitoring along with invasive blood pressure monitoring.	Consensus
Urine output goal of 1 mL/kg/h during CRS and reconstructive phases and 2 mL/kg/h during HIPEC phase can be considered.	Majority agreement
Urine output goal should be accomplished by use of intravenous fluids and if required diuretics based on clinical scenario.	Consensus

CRS – Cytoreductive surgery; HIPEC – Hyperthermic intraperitoneal chemotherapy

Temperature management

Normothermia maintenance is an important goal in the perioperative period in patients undergoing CRS-HIPEC.[13] Extensive CRS and HIPEC can cause wide variations in temperature.[71] Hyperthermia during the HIPEC phase results in increase in the metabolic rate, consequentially resulting in an increase in oxygen demand, heart rate, end-tidal carbon dioxide, lactatemia and worsening metabolic acidosis. These physiological alterations depend on the magnitude of the hyperthermia, which usually reaches a maximum level of 60 min after the infusion initiation. These hyperdynamic alterations reverse once the temperature normalises. The lactate levels after HIPEC should be interpreted with caution as they may not be due to hypoperfusion alone and other causes should be evaluated.[48] Hyperthermia can also cause coagulopathies, renal and liver dysfunction, neuropathies and seizures. Hyperthermia can be prevented using forced air warmers at ambient temperature, use of cold intravenous fluids <6°C and use of cooling mattress and ice packs placed in the axilla and around the head and neck prior to HIPEC. If these measures fail and core temperature continues to rise, reduction in temperature of perfusate can help. Cooling (active or passive) the patient before starting the HIPEC phase is another technique that can be used to prevent excessive rise in temperature during the HIPEC phase.[25]

Delta temperature (difference between least and highest temperatures) during CRS-HIPEC was found to be a significant predictor of intensive care unit (ICU) stay >5 days.[38] This is highest in patients with high PCI necessitating longer, aggressive resection. The sequential temperature changes exacerbate

systemic effect in addition to hypo- or hyperthermia. Hypothermia during the CRS phase is associated with cardiac morbidity, decreased humoral and cell-mediated immunity and impaired acid–base balance thus reflecting prolonged ICU stay.[72] This should be managed with forced air warming with blankets and blood/fluid warmers [Table 6].

PAIN MANAGEMENT

CRS-HIPEC requires analgesia coverage from T4 down to low lumbar dermatomal segments.[73] These patients frequently complain of chronic pain, chronic fatigue and a poor quality of life after surgery.[74,75] Intraoperative use of epidural analgesia using local anaesthetic agents with or without opioids is frequently used to decrease intraoperative systemic opioid requirement.

Some centres do not recommend or recommend cautious use of thoracic epidural analgesia as the resultant hypotension may affect the clinical determination of fluid status; also, patients may develop coagulopathy which predispose them to epidural haematoma, postoperative infections and sepsis.[50,76,77] The incidence of epidural abscess in this patient group was found to be 1:2139.[48] Clot kinetics measured by TEG indicates that epidural catheters may be safe for postoperative analgesia.[78]

The main disadvantages of primary opioid-based analgesia are increased incidence of respiratory complications and need for postoperative ventilatory support.[64] A recent retrospective review[79] of 215 CRS-HIPEC patients showed that epidural analgesia was safe to use in terms of intraoperative and postoperative haemodynamic parameters. The median duration of epidural use is 5 days and it recommends daily check of coagulation testing until the fourth postoperative day or on clinical request.[48] A study showed that only 72% of centres worldwide regularly use epidural analgesia to manage postoperative pain after CRS-HIPEC.[78] Many centres use a combination of epidural and opioid-based patient-controlled intravenous systemic analgesia (IVPCA) for postoperative pain management after CRS-HIPEC. A recent international survey has shown that only 28% of centres performing CRS-HIPEC reported postoperative pain control as excellent, despite the frequent use (69%) of combined epidural and IVPCA.[62] Other analgesic options include single or continuous paravertebral or subcostal transverses abdominis plane blockade [Table 7].

Table 6: Consensus recommendations for temperature management and monitoring

Recommendation/suggestion	Level of consensus/ evidence
We recommend monitoring of core body temperature.	Evidence
We recommend maintenance of normothermia during CRS phase.	Strong consensus and evidence
We suggest passive cooling (switching off warming devices) of patients before starting HIPEC (35°C-36°C).	Consensus
Temperature should/can be controlled during HIPEC phase by	Consensus
Use of ice packs in axilla and neck during HIPEC phase	Consensus
Use of cool air blankets during HIPEC	Majority agreement
Use of cold crystalloids at around 6°C during HIPEC phase	
We suggest keeping core body temperature below 39°C and instruct to reduce temperature of perfusate if core body temperature rises above 39°C.	Consensus

CRS – Cytoreductive surgery; HIPEC – Hyperthermic intraperitoneal chemotherapy

Table 7: Consensus recommendations for pain management

Recommendation/suggestion	Level of consensus/ evidence
A thoracic epidural catheter should be placed preoperatively if not contraindicated.	Strong consensus
We suggest intraoperative use of epidural analgesia	Strong consensus
Local anaesthetic and opioid-based epidural analgesia should be used along with intravenous paracetamol in postoperative period up to 4-5 days.	Strong consensus
IVPCA should be used long with TEA if pain relief is not adequate/all dermatomes are not covered.	Strong consensus
IVPCA should be used in patients with contraindications for placement of an epidural catheter, or discontinued epidural catheter.	Strong consensus

TEA – Thoracic epidural analgesia; IVPCA – Intravenous patient-controlled analgesia

POSTOPERATIVE AND INTENSIVE CARE MANAGEMENT

Tracheal extubation in the operating room (OR) or shifting the patients to ICU with endotracheal tube (ETT) *in situ* depends on the duration of surgery, preoperative major cardiac or respiratory comorbidities, blood loss and transfusion, haemodynamic stability, metabolic derangement and arterial lactate towards end of surgery or any other organ failure.[80] All or most of the patients are transferred to ICU in the immediate postoperative period (mean 93%, range 20%–100%). The ETT was removed in 42%–62% in the OR.[48] Improved patient selection, better surgical technique, better perioperative management and increasing

experience gained by high-volume centres can help in management of certain subgroup of HIPEC patients (e.g. low PCI, minimal blood loss) in a non-ICU setting.[81,82] Immediate or early extubation of the trachea, epidural analgesia, postoperative monitoring in ICU, immediate initiation of parenteral nutrition in postoperative period and stringent fluid status monitoring help in favourable postoperative outcome.[83]

Postoperative stress response involves all major organs such as cardiovascular, respiratory, coagulation, renal and endocrine system.[84,85] There can be hyperthermia-related coagulopathy leading to increased PT and INR along with low platelet counts. Hyperglycaemia is also a common finding because of physiologic stress and a hypercatabolic state. Anticipated postoperative course includes low-grade fever and moderate to severe pain. Diarrhoea can occur in the first week because of digestive hypersecretion. Leukocyte counts and platelet counts progressively decrease in the first 2 weeks followed by progressive increase. Transient severe hypophosphatemia is observed on the first 2–3 postoperative days due to renal tubulopathy related to hyperthermia. There may be transaminitis with liver function tests being elevated 2- to 3-fold during the first 4 postoperative days, probably due to extensive electrocoagulation of the liver capsule. Inflammatory markers such as C-reactive protein, interleukins and elastase increase during surgery and come back to normal within 12–24 h.

Early postoperative GDT with the help of transthoracic thermodilution technique and arterial-pressure-based cardiac output[47,86] had shown variable results. Abnormalities in coagulation profile after CRS-HIPEC surgery usually take 3-6 days to resolve. Mechanical and pharmacological deep vein thrombosis (DVT) prophylaxis should be considered as appropriate during the entire perioperative period if not contraindicated, starting from the preoperative period (low-molecular-weight heparin) through the immediate postoperative period.

Preoperative nutritional status influences the postoperative outcome in terms of length and survival in patients with cancer undergoing HIPEC.[87] A majority of the patients do not tolerate enteral feed in the first postoperative week, and hence parenteral nutrition may be initiated early and switched to enteral nutrition whenever acceptable.[88]

Postoperative complications include anastomotic leaks, sepsis, ileus, pancreatitis, fistula, pulmonary embolism, DVT and reoperation.[84] ASA class higher than 3 and surgical time more than 10 h are the significant risk factors for grades IV/V morbidity in patients with PMP.[89] Postoperative complications requiring intervention are the only significant risk factor for early recurrence other than the extent of peritoneal disease.[90] Early recurrence after CRS-HIPEC is associated with a significant reduction in overall survival.[90] Major morbidity rates range from 12% to 52% in high-volume centres. The mortality rate after CRS- HIPEC ranges from 0.9% to 5.8%.[7,91,92] Left upper quadrant peritonectomy and small bowel resection are the factors that are predicted for a poor perioperative outcome.[93] The most frequent complications are surgical site infections including intraabdominal abscess, gastric or small intestinal perforation, postoperative ileus, anastomotic leakage, urinary disturbance, intestinal fistula and postoperative bleeding[91] [Table 8].

PAEDIATRIC CRS-HIPEC

CRS-HIPEC in children has been performed in peritoneal tumours of various origins including desmoplastic round cell tumour, rhabdomyosarcoma and colorectal cancer.[94] Apart from age-based variations, the anaesthetic management of children undergoing CRS-HIPEC is similar to that in adults. Monitoring guidelines and practice are the same as an adult patient except that the arterial-pressure-based cardiac output monitoring is typically not used. A central venous catheter may or may not be required. In a retrospective study of children and adolescents who had undergone CRS-HIPEC, fluid administration at an average rate of 9 mL/kg/h was required to maintain urine output.[95] In the absence of contraindications, an epidural catheter is usually placed. Similar to CRS-HIPEC in adults, there is a risk for major blood loss during CRS-HIPEC in children.[96,97] In general, an intraoperative haemoglobin value of less than 10 g/dL is usually a trigger for discussion about blood transfusion. Transfusion rates of up to 80% have been reported.[96]

HYPERTHERMIC INTRATHORACIC OR THORACOABDOMINAL CHEMOTHERAPY

Pleural malignancies may be of different origin such as malignant pleural mesothelioma, advanced thymoma with pleural dissemination or spread from

Table 8: Consensus recommendations for postoperative and intensive care management

Recommendation/suggestion	Level of consensus/evidence
Do not routinely extubate the trachea on operating table.	Evidence
Tracheal extubation in the operating room should be attempted in low-volume (low PCI) cases.	Evidence and consensus
We suggest that patients with unstable haemodynamics should be transferred to ICU with endotracheal tube *in situ*.	Consensus
Patients with massive blood loss, high arterial lactate and diaphragmatic striping may be considered for transferred to ICU with endotracheal tube *in situ*.	Majority agreement
Decision of transferring patient to ICU with endotracheal tube *in situ* or with after tracheal extubation in patients who undergone prolonged (>10 h) surgery, presence of preoperative bad pulmonary functions and major cardiac or non-cardiac comorbidities should be individualised.	No consensus, <50% agreement
Postoperative fluid therapy should be based on	
Mean arterial pressure, heart rate and urine output guided fluid therapy	Consensus
Arterial lactate-guided fluid therapy	Majority agreement
We recommend use of early enteral nutrition or parenteral nutrition in patient who cannot tolerate enteral nutrition.	Strong consensus and evidence

PCI – Peritoneal Carcinomatosis Index; ICU – Intensive care unit

PMP.[98] Recently, CRS along with intraoperative hyperthermic intrathoracic chemotherapy (HITHOC) perfusion has been advocated to reduce local tumour spread,[99,100] and it significantly increased the median survival, tumour-free survival rate and performance status.[101] In PMP with limited pleural extension of metastasis, thoracoabdominal approach for cytoreduction (removal of pleural metastasis) is usually performed followed by heated chemoperfusion. This procedure is called hyperthermic thoracoabdominal chemotherapy (HITAC).[37,98] Preoperative work-up and optimisation for patients scheduled for CRS and HITHOC or HITAC are the same for CRS-HIPEC. We recommend additional preoperative pulmonary function tests apart from investigations needed for CRS-HIPEC. For cardiac output monitoring, pulse pressure variation and stroke volume variation may not work because of open chest; delta SV protocol can be a better guidance of fluid status and therapy.[37] Chemotherapy in the intrathoracic cavity causes increased fluid load and may lead to increased airway pressures, increased intrathoracic pressures, mediastinal shift and decreased functional residual capacity. Extubation in the postoperative unit is preferred in view of large fluid shifts and reduction of pulmonary lung volumes after surgery. Complications of HITHOC are similar to HIPEC, but some of the complications are exclusive for HITHOC such as pulmonary emboli, chest pain, dyspnoea, bronchopleural fistula, pneumothorax, empyema and air leak.[37]

PRESSURISED INTRAPERITONEAL AEROSOLISED CHEMOTHERAPY

In pressurised intraperitoneal aerosolised chemotherapy (PIPAC), aerosol of chemotherapeutic drug is created with the help of a nebuliser which is connected to a high-pressure injector and a therapeutic capno-peritoneum is created and maintained for 30 min at a temperature of 37°C.[102] PIPAC is offered mostly in high-volume disease where complete cytoreduction is not possible. At the end of the procedure, the chemotherapy aerosol is exhausted into the OR scavenging setup through a closed system. Perioperative management of PIPAC is no different from any other gastrointestinal procedures with standard general anaesthesia. No additional haemodynamic monitoring is needed. Patients can be extubated in the OR.

Chemotherapy drugs in the aerosolised form pose potential occupational exposure to the OR personnel during PIPAC. Chemotherapy agents have several adverse effects such as hair loss, headache, acute irritation, hypersensitivity, congenital malformations in pregnant women, foetal loss, low birthweight, infertility and leukaemia.[103] A laminar flow in the OR is recommended, but when PIPAC is done with strict safety measures, even without laminar flow, PIPAC seems harmless.[104] N-95 mask with a tight seal around the nose and mouth must be worn by all OR personnel.[105] The injection and nebuliser which produce aerosol must be remote-controlled and should be controlled from outside the OR. No personnel should stay inside the OR and the patient should be monitored remotely. The whole system of capnoperitoneum must be airtight with no leaks. Severe peritoneal sclerosis post repeated PIPAC has been observed.[106] There is an elevation of CRP levels which is a sign of chemical peritonitis.[107]

ENHANCED RECOVERY AFTER SURGERY AND CRS-HIPEC

Prof. Kellet in early 1990s challenged the existing dogmas and implemented evidence-based principles/

elements in the perioperative period in colorectal surgery and demonstrated reduction in postoperative length of stay. Compliance with enhanced recovery after surgery (ERAS) elements has been favorably associated with reduced morbidity and length of stay and cost with no impact on readmission across surgical specialties.[108-110] Despite these positive results, evidence regarding ERAS in patients undergoing CRS-HIPEC procedures is lacking. The feasibility and benefits of ERAS in patients undergoing CRS-HIPEC were evaluated retrospectively before and after ERAS protocol and it was observed that the ERAS pathway was associated with significant reduction in the length of stay and early gastrointestinal recovery with no difference in morbidity and mortality.[111]

All consensus recommendations are summarised in Table 9.

Table 9: Summary of consensus recommendations

Recommendation/suggestion	Level of consensus/evidence
Preoperative assessment and management	
We recommend all routine blood investigations and 12-lead electrocardiogram for all patients.	Evidence
We suggest routine preoperative resting 2D echocardiogram.	Consensus
Patients should visit perioperative physician 1-4 weeks prior to surgery for optimisation depending on time availability.	Strong consensus
We recommend that preoperative oral or enteral nutrition should be started in all malnourished patients	Strong consensus and evidence
Preoperative oral supplemental nutrition may be considered even if patients are not malnourished.	Majority agreement
There is no role of routine perioperative immune-nutrition in CRS-HIPEC patients	Strong consensus
Preoperative physiotherapy and physical exercise should be started	Strong consensus
Respiratory exercise training	Strong consensus
Muscle training	Consensus
Aerobics	Majority agreement
Anaesthetic management and monitoring	
Thoracic epidural analgesia should be used in all patients if not contraindicated.	Strong consensus
Intravenous induction of anaesthesia with propofol and induction dose of opioid should be done	Strong consensus
Volatile agents (isoflurane/sevoflurane/desflurane) can be used for maintenance of anaesthesia.	Strong consensus
Inhalational anaesthesia vs TIVA can be selected based on patient's disease load, tumour grading and ASA status. Low-volume disease and lower ASA physical status patients may be given TIVA.	Strong consensus
Coagulation monitoring	
We recommend PT, aPTT and INR testing in the preoperative period	Evidence, consensus
We suggest PT, aPTT and INR testing in the postoperative period	Consensus
PT, aPTT and INR testing should be individualised in intraoperative period if blood loss is more than 50% of blood volume and after HIPEC phase.	No consensus, <50% agreement
We recommend PT, aPTT and INR testing in the preoperative period	Evidence, consensus
Fluid management and monitoring	
Balanced salt solutions like Ringer's lactate and acetate-based solution should be used.	Strong consensus
Albumin should be used as the colloid of choice.	Strong consensus
We suggest use of noninvasive cardiac output monitoring like arterial-pressure-based cardiac output monitoring along with invasive blood pressure monitoring.	Consensus
Urine output goal of 1 mL/kg/h during CRS and reconstructive phases and 2 mL/kg/h during HIPEC phase can be considered.	Majority agreement
Urine output goal should be accomplished by use of intravenous fluids and if required diuretics based on clinical scenario.	Consensus
Temperature management and monitoring	
We recommend monitoring of core body temperature.	Evidence
We recommend maintenance of normothermia during CRS phase.	Strong consensus and evidence
We suggest passive cooling (switching off warming devices) of patients before starting HIPEC (35°C-36°C).	Consensus
Temperature should/can be controlled during HIPEC phase by	
Use of ice packs in axilla and neck during HIPEC phase	Consensus
Use of cool air blankets during HIPEC	Consensus
Use of cold crystalloids at around 6°C during HIPEC phase	Majority agreement
We suggest keeping core body temperature below 39°C and instruct to reduce temperature of perfusate if core body temperature rises above 39°C.	Consensus

Contd...

Table 9: Contd...

Recommendation/suggestion	Level of consensus/evidence
Pain management	
A thoracic epidural catheter should be placed preoperatively if not contraindicated.	Strong consensus
We suggest intraoperative use of epidural analgesia.	Strong consensus
Local anaesthetic and opioid-based epidural analgesia should be used along with intravenous paracetamol in postoperative period up to 4-5 days.	Strong consensus
IVPCA should be used long with TEA if pain relief is not adequate/all dermatomes are not covered.	Strong consensus
IVPCA should be used in patients with contraindications for placement of an epidural catheter, or discontinued epidural catheter.	Strong consensus
Postoperative and intensive care monitoring	
Do not routinely extubate the trachea on operating table.	Evidence
Tracheal extubation in the operating room should be attempted in low-volume (low PCI) cases	Evidence and consensus
We suggest that patients with unstable haemodynamics should be transferred to ICU with endotracheal tube *in situ*.	Consensus
Patients with massive blood loss, high arterial lactate and diaphragmatic striping may be considered for transferred to ICU with endotracheal tube *in situ*.	Majority agreement
Decision of transferring patient to ICU with endotracheal tube *in situ* or with after tracheal extubation in patients who undergone prolonged (>10 h) surgery, presence of preoperative bad pulmonary functions and major cardiac or non-cardiac comorbidities should be individualised.	No consensus, <50% agreement
Postoperative fluid therapy should be based on	
Mean arterial pressure, heart rate and urine output guided fluid therapy	Consensus
Arterial lactate-guided fluid therapy	Majority agreement
We recommend use of early enteral nutrition or parenteral nutrition in patient who cannot tolerate enteral nutrition.	Strong consensus and evidence

2D – Two-dimensional; CRS-HIPEC – Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy; TIVA – Total intravenous anaesthesia; ASA – American Society of Anesthesiologists; PT – Prothrombin time; aPTT – Activated partial thromboplastin time; INR – International normalised ratio; TEA – Thoracic epidural analgesia; IVPCA – Intravenous patient-controlled analgesia; PCI – Peritoneal Carcinomatosis Index; ICU – Intensive care unit

DISCLAIMER AND FUTURE ASPECTS

The contents of this publication are current practice pattern and consensus guideline for perioperative management of CRS-HIPEC procedures based on the best available evidence and consensus among expert committee members at the time of development. This consensus guideline document should neither be construed nor serve as a standard of care. This consensus guideline does not represent the minimum standard of practice, nor are they a substitution for good clinical judgment. This consensus guideline needs to be used in conjunction with patient assessment and may be individualised to specific patients' needs. The clinicians are advised to keep the updated evidence in mind for best clinical management. This consensus practice guideline was developed in 2019 and may be reviewed again in 2022 or sooner, based on the availability of new evidence.

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Conflicts of interest

There are no conflicts of interest.

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Announcement

CALENDAR OF EVENTS OF ISA 2020

The cut off dates to receive applications / nominations for various Awards / competitions 2020 is as below. Please visit isaweb.in and log in with your ISA Regd. E Mail ID & Password and submit application with all documents as attachment. Mark a copy of the same by E Mail to secretaryisanhq@gmail.com. Write the name of Award applied as subject. Link will be sent to judges for evaluation. No need to send hard copy. Only ISA members are eligible to apply for any Awards / competitions. The details of Awards can be had from Hon. Secretary & also posted in www.isaweb.in

Cut Off Date	Name of Award / Competition	Application to be sent to
30 June 2020	Bhopal Award for Academic Excellence	Hon. Secretary, ISA (by log in & E Mail)
30 June 2020	Late Prof. Dr. A .P. Singhal Life Time Achievement Award	Hon. Secretary, ISA (by log in & E Mail)
30 June 2020	Rukmini Pandit Award	Hon. Secretary, ISA (by log in & E Mail)
30 June 2020	Dr. Y. G. Bhoj Raj Award	Hon. Secretary, ISA (by log in & E Mail)
30 June 2020	Mrs. Shashi & Dr. P Chandra Award	Hon. Secretary, ISA (by log in & E Mail)
30 Sept 2020	Kop's Award	Chairperson, Scientific Committee ISACON 2020 copy to Hon. Secretary, ISA (by log in & E Mail)
30 Sept 2020	ISACON Jaipur Award	Chairperson, Scientific Committee ISACON 2020 copy to Hon. Secretary, ISA (by log in & E Mail)
30 Sept 2020	Prof. Dr. Venkata Rao Oration 2020	Hon. Secretary, ISA (by log in & E Mail)
30 Sept 2020	Ish Narani Best poster Award	Chairperson, Scientific Committee ISACON 2020
30 Sept 2020	ISA Goldcon Quiz	Chairperson, Scientific Committee ISACON 2020
10 Nov 2020	Late Dr. T. N. Jha Memorial Award & Dr. K. P. Chansoriya Travel Grant	Hon. Secretary, ISA, (by log in & E Mail) copy to Chairperson Scientific Committee ISACON 2020
20 Oct 2020	Bidding Application for ISACON 2022	Hon.Secretary, ISA by log in, E Mail & hard copy
20 Oct 2020	Awards (01 Oct 2018 to 30 Sept 2020)	Hon. Secretary, ISA (by log in & E Mail)

(Report your monthly activity online every month after logging in using Branch Secretary's log in ID)

1. Best City Branch
2. Best Metro Branch
3. Best State Chapter
4. Public Awareness – Individual
5. Public Awareness – City / Metro
6. Public Awareness - State
7. Ether Day (WAD) 2020 City & State
8. Membership drive
9. Proficiency Awards

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