Original Article

Perioperative management and postoperative outcome of patients undergoing cytoreduction surgery with hyperthermic intraperitoneal chemotherapy

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ABSTRACT

Background and Aims: The existence of cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) as a multidisciplinary approach for peritoneal cancer gains acceptance in many countries including Saudi Arabia. The aim of our study is to describe the perioperative management of patients who received CRS/HIPEC and to report their outcomes and complications at our tertiary centre. **Methods:** The preoperative characteristics, surgical variables, perioperative management, postoperative course and outcomes of 38 CRS/HIPEC patients were prospectively collected and analysed. **Results:** The mean age of our patients was 52 years, and 23 (60.5%) of them were females. The overall postoperative mortality was 42.1%. Univariate analyses of risk factors for deaths after HIPEC demonstrated that low preoperative (haemoglobin, potassium, calcium and albumin), high (tumour marker (CA19.9), intraoperative transfusion of human plasma protein (HPP), colloids, postoperative activated partial thromboplastin time and bacterial infections were potential risk factors for patient's mortality. Multivariate analysis of those variables demonstrated that low preoperative calcium [hazard ratio (HR) = 0.116; 95% confidence interval (CI) = 0.033–0.407; $P = 0.001$], high intraoperative HPP transfusion (HR = 1.004; 95% CI = 1.001–1.003; $P = 0.012$) and presence of postoperative bacterial infection (HR = 5.987; 95% CI = 1.009–35.54; $P = 0.049$) were independent predictors of patient's death. Seventy morbidities happened after HIPEC; only bacterial infection independently predicted postoperative mortality. **Conclusion:** To improve postoperative outcome of CRS/HIPEC, optimisation of transfusion, temperature, electrolytes and using broader-spectrum prophylaxis to manage postoperative infections should be warranted.

Key words: Cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, morbidity, mortality

INTRODUCTION

Previously, peritoneal carcinoma (PC) was considered a lethal disease with a poor prognosis and a high mortality rate. At the beginning, the procedure of cytoreduction surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) was not popular because of its high cost[1] and high rates of associated potentially life-threatening complications.

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Recently, CRS and HIPEC offers a promising hope for selected subjects and provides a chance for improved survival or disease-free status to those patients.[2-4] Surgical complications are the commonest causes of morbidity in these complex procedures, with incidence ranging from 12% to 56%, including intestinal obstruction, bleeding and anastomotic leak. Moreover, other morbidities are frequent including pulmonary embolism, venous thrombosis, leukopenia, thrombocytopenia, hepatotoxicity or nephrotoxicity.[5] According to a Turkish report, patients with PC were at high risk of infections after CRS/HIPEC procedure.[6] A study from China revealed improved patient survival after CRS/HIPEC.[7]

In Netherlands, they found that the disease-specific survival was 12.6 months in the control group; however, it achieved 22.2 months in HIPEC group ($P = 0.028$). The overall 5-year survival was 45% for HIPEC subjects.[8]

A French group has analysed their patients' morbidity and mortality,[9] and then further performed multicenter study which revealed overall median survival around 34 months.[10] Kusamura *et al.* in Italy analysed the HIPEC major morbidity which was estimated to be 12%; however, their operative mortality rate was 0.9%.[11] HIPEC is considered a real challenge to the anaesthetist in regarding massive fluid shifts, temperature fluctuation, coagulation derangement and renal injury. The objective of our study is to describe our growing experience in the area of CRS/HIPEC with special reference to perioperative management and postoperative outcome.

METHODS

After obtaining the approval from the local institutional review board (IRB) ethical committee of King Abdullah Medical city, (IRB no. 15-186/dated 14-02-2012) registered at the National BioMedical Ethics Committee, King Abdulaziz City for Science and Technology (Registration no. H-02-K-001) in accordance with the Declaration of Helsinki, informed consent was obtained from all patients. We prospectively observed 38 cases with peritoneal malignancy as a sequelae of colorectal cancer who underwent surgical management with CRS and HIPEC.

Our study was performed in the duration between March 2012 and May 2015. The preoperative investigations included pathological characteristics of the tumour, haemoglobin (Hb) (g/dL), total leucocyte count (white blood cells) ($\times 10^9$/L) and platelets (PLT) ($\times 10^9$/L); coagulation profile; international normalised ratio (INR) levels, prothrombin time (PT) (s) and activated partial thromboplastin time (APTT) (s); renal function tests – blood urea nitrogen (mg/dL) and creatinine (CRE) (mg/dL); liver function tests – total bilirubin (mg/dL), aspartate transaminase (IU/L), alanine transaminase (IU/L), albumin (ALB) g/dL. Temperature and arterial blood gas parameters such as pH, HCO_3, $PaCO_2$, PaO_2, and lactate were recorded.

All patients received thoracic epidural anaesthesia, as a standard of care, combined with general anaesthesia. Coagulation profile was usually optimised preoperatively. If it was difficult to be optimised, the epidural decision was cancelled and the patient was excluded from our study. Epidural anaesthesia was administered, using Touhy needle 16 gauge after anatomical identification of the space at the level of T8–T9 or T9–T10. A test dose of lidocaine 1% was given; 10–15 mL bolus dose of bupivacaine 0.5% was given followed by maintenance infusion in a range of 6–10 mL/h using a mixture of 0.25% bupivacaine and 2 μg fentanyl per mL. We maintained haemodynamic stability using titrated vasopressors. We have inserted invasive arterial blood pressure monitor usually under local anaesthesia however, central venous pressure monitoring was done after induction of general anaesthesia. At the time of this study, we did not have non-invasive cardiac output monitor in our institute. General anaesthesia induction was done using intravenous (IV) propofol 2–3 mg/kg, fentanyl 1–2 μg/kg and rocuronium 0.6–0.9 mg/kg, and the tracheal intubation was facilitated by regular endotracheal tube and confirmed by $ETCO_2$ and auscultation. FiO_2 was 100% at the start and then decreased to 50%–60%; controlled mechanical ventilation was done using volume-controlled ventilation or pressure-controlled ventilation. Maintenance was done by sevoflurane, rocuronium, fentanyl and paracetamol administration.

The surgical technique for HIPEC consumed 90 min for every patient as a standard protocol.[12]

Insulin was not used prophylactically. If the patients received chemotherapy with dextrose-containing solution during HIPEC, insulin was given to prevent hyperglycaemia.[13] If blood glucose was above 11 mmol/L, the insulin regimen was initiated. Insulin intravenous (IV) infusion was administered at a range of 2–5 U/h, bolus dose (5–10 U) IV to control intraoperative blood glucose.

Maintenance of body temperature was done using an IV hotline, warming blanket, Bair Hugger® blanket, at a maximum setting of 43°C together with blood/fluid warmers from the start of surgery till half an hour before starting HIPEC. Cooling of the patient was started using temperature control adult blanket (Stockert-Code 80939, Munchen, Germany). Other physical applications were used as cold fluid IV infusion and ice enclosed into insulating bags wrapped with cotton to avoid skin injury applied at the axillae and around head and neck. Patient's cooling was continued till 15 min before the end of the HIPEC procedure at which re-warming was started.

We usually performed a coagulation sample, which included complete blood count (CBC), PT, INR, APTT, and fibrinogen level, which was done in all patients before and after HIPEC. Our fluid management was done using optimal strategy with a combination of colloids and crystalloids. The target endpoints were sufficient urine output and maintaining the lactate level after using goal-directed fluid therapy. We aimed for at least 0.5 mL/kg/h urine output during CRS phase, 4 mL/kg/h during HIPEC and 1–2 mL/kg/h in post-HIPEC phase. The diuretic was used only after ensuing normovolaemia and maintenance of renal perfusion.[14,15] Replacement of fluid loss was maintained with crystalloids (ringer lactate, normal saline), colloids (hydroxyethyl starch), human plasma protein (HPP), blood products, packed red blood corpuscles, fresh frozen plasma (FFP), PLTs and cryoprecipitate. The end point for fluid resuscitation was to restore haemodynamics, urine output and lactate level with upper limit of central venous pressure optimisation.

When preoperative serum ALB was below 2.5 g/dL, ALB administration was initiated. 5% ALB (100 mL) was infused every 12 h. During haemodynamic instability, we usually started with phenylephrine infusion for preliminary support and dopamine infusion to enhance renal perfusion. In case of persistent hypotension, we used noradrenaline infusion.[16] Prophylactic antimicrobial drugs in the form of 2 g cefazolin and 500 mg IV metronidazole were infused to patients, 30 min before surgery. Antibiotic was repeated every 6 h in case of long surgery, and the treatment was continued for 3 days thereafter.

After completion of the surgical procedures, all cases were transferred to the surgical intensive care unit (ICU). The epidural infusion was started at a rate of 4–6 mL/h of 0.1% bupivacaine, with 1 μg/mL fentanyl. The patients were ventilated overnight until they were eligible for weaning. The eligibility criteria for extubation were maintenance of normothermia, haemodynamic stability and the presence of adequate tidal volumes (6–8 mL/kg/weight); as well as absence of the following signs of difficult weaning of mechanical ventilation: heart rate more than 140/min, systolic blood pressure <90 mmHg or >180 mmHg, respiratory rate more than 35/min, oxygen saturation less than 90% by pulse oximeter and symptoms such as agitation, anxiety, sweating and altered level of consciousness. Patients were provided with postoperative organ or vasopressor support with daily weight monitoring to prevent fluid overload.

Patient characteristics and routine investigations were expressed as means and standard deviations for continuous data. We used number and percentage for categorical one. Kaplan–Meier curves and log-rank tests were used to measure patient survival and progression-free survival. The risk factors for patient survival were measured by univariate followed by multivariate Cox's proportional hazard regression models with a 95% confidence interval. A statistically significant relationship was indicated by *P* value of less than 0.05. The analysis was done on Statistical Package for the Social Sciences (SPSS) software (IBM Inc., Armonk, NY, USA), version 21.

RESULTS

Patient characteristics and potential risk factors - In all, 38 patients who have undergone CRS/HIPEC procedures (March 2012–May 2015) were observed prospectively and included in this study. Age was 52 ± 13.7 years; the majority of patients were females [23 (60.5%)], American Society of Anaesthesiologists (ASA) III [23 (60.5%)] and the rest were ASA II. They had a body mass index of 26.9 ± 5.6 kg/m^2. The anaesthesia time was 695 ± 207 min, and the surgical time was 615 ± 199 min. Details of patients' characteristics, laboratory, intraoperative parameters and risk potential variables for mortality are listed in Table 1. Diabetes mellitus was diagnosed in 9 (23.7%) patients, hypertension in 6 (15.8%) patients, renal disease in 3 (7.9%) patients, liver disease in 2 (5.3%) patients and 1 patient (2.6%) had central nervous system involvement. Only four patients had raised CRE and one of them indicated renal dialysis for 2 months. During HIPEC, lactate level did not exceed 4 mmol/L.

There were no operative or 60-day mortalities; the 1-year mortality rate was 32%. The overall

Table 1: Potential risk factors for mortality in patients after HIPEC procedure

Variables	Mean±SD	Median (range)
Preoperative variables		
Age (years)	52±13.7	52.4 (24.5-74.9)
Gender (male/female)	15/23	
BMI	26.9±5.6	26.6 (16.4-40.4)
Preoperative hospital stay (days)	7.9±9.2	5 (2-53)
Laboratory variables		
White blood cells $\times 10^9$/L	7.1±2.7	7 (3.6-13.6)
Red blood corpuscles $\times 10^{12}$/L	4.5±3.1	4.4 (3.1-9.8)
Haemoglobulin (g/dL)	11.3±1.7	11 (8.8-15.7)
C-reactive protein (mg/L)	12.6±9.2	18 (0.2-20.9)
Coagulation factors		
INR	1.1±0.2	1.1 (0.9-1.9)
Platelet count $\times 10^9$/L	290±153	283 (55-702)
APTT (s)	34.4±8.7	33.6 (11.8-61.7)
Fibrinogen	2.2±1.4	1.7 (1.1-5.9)
Blood urea nitrogen mg/dL	11±4.4	11 (0.31-20.8)
Creatinine (mg/dL)	0.8±0.23	0.8 (0.3-1.4)
Bicarbonate (mmol/L)	26.2±3.7	26.1 (18.1-32)
Lactate dehydrogenase (U/L)	195.2±91.4	196 (19-409)
Alanine transaminase (IU/L)	41.5±31.2	31 (13-167)
Aspartate transaminase (IU/L)	30.2±30.5	20 (9-149)
Alkaline phosphatase (U/L)	131.4±99.8	104 (44-638)
Amylase (U/L)	64.9±46	54 (11-205)
Total bilirubin (mg/dL)	0.45±0.41	0.35 (0.4-2.6)
Conjugated bilirubin (mg/dL)	0.13±0.19	0.1 (0.02-1.2)
Albumin (g/dL)	3.1±0.48	3.2 (2.1-4.1)
A/G ratio	1.2±0.55	1 (0.58-2.8)
Total protein (g/dL)	6.3±1.36	6.8 (3.6-8.4)
BNP (ng/L)	74.3±38.3	74.1 (34.1-121.22)
Pro BNP pg/mL	189.4±332.7	93.2 (5.4-1002.3)
CK (U/L)	401.7±413	300.5 (15-1852)
CK-MB U/L	21±17	19.8 (0.04-68)
Lipase (U/L)	158±64.7	156 (44-365)
Random glucose (mg/dL)	154.4±75.1	129 (76-384)
HbA1C	7.8±2	7.6 (4.7-13.2)
Iron panel		
Iron (µmol/L)	39.8±54.4	21 (6-197)
Total iron-binding capacity (µg/dL)	269±140.4	285.5 (39-505)
Ferrtin (µg/L)	170.9±160.5	182 (19.6-489.1)
Tumour markers		
Alpha feto protein (ng/mL)	2.5±1.4	2.3 (0.1-4.9)
CA 125 U/mL	50.9±85.5	20.3 (4.3-347)
CA 15-3 U/mL	18±8.9	21.7 (4.8-32.7)
CA 19.9 U/mL	30.9±24.9	25.8 (1.2-100)
CEA ng/dL	42.7±112.6	3.2 (0.01-557.9)
Colloids transfusion (mL)	1417±800	1500 (500-4000)
Packed red blood cells (unit)	3.8±3.2	3 (1-14)
Fresh frozen plasma (unit)	4.3±2.5	4 (2-12)
(25% Albumin) transfusion (mL)	62.5±23.8	50 (40-100)
Human plasma protein (mL)	856±588	500 (250-3000)
Platelets (unit)	4.5±1.5	4.5 (2-6)
Blood loss (mL)	1929±1239	1750 (400-5000)
Length of ICU stay days	9.5±25.7	5 (2-150)
Anaesthesia time (min)	695±207	660 (360-1260)
Surgical time (min)	615±199	600 (280-1140)

HIPEC – Hyperthermic intraperitoneal chemotherapy; SD – Standard deviation; BMI – Body mass index; INR – International normalised ratio; APTT – Activated partial thromboplastin time; BNP – Brain natriuretic peptide; CK – Creatine kinase; CK-MB – Creatine kinase isoenzyme; HbA1C – Glycoslated haemoglobulin; ICU – Intensive care unit. Values presented as percentages median, range or (mean±SD)

postoperative mortality was 42.1%, with a mean survival time of 340.63 ± 266.85 days [Figure 1a].

Sixteen patients died: 13 (81.3%) had at least one episode of bacterial or fungal infection and the infection rate among non-survivors was 2.2; the predominant site of infection was surgical site infection and the most common organism was *Klebsiella pneumonia*; the details of pathogens and site of infection are shown in Figure 1b.

Haemodynamic variables, acid–base, glucose and temperature changes during HIPEC procedure are presented in Figures 2 and 3. The risk potential variables associated with postoperative mortality are listed in Table 2.

A univariate Cox's proportional hazard regression model was used to examine potential risk factors for an association with patient mortality. Univariate analysis revealed 12 potential risk factors at a statistical level of $P \leq 0.05$ [Table 2]. Preoperative mean corpuscular Hb (MCH) ($P = 0.03$), low preoperative Hb ($P = 0.043$) and hematocrit ($P = 0.021$) were significantly associated with mortality. Preoperative tumour marker (CA19.9) was also associated with a poor survival outcome ($P = 0.008$). Regarding electrolytes, both low preoperative potassium and low preoperative calcium were potential risk factors for mortality ($P = 0.005$ and $P = 0.003$, respectively). Preoperative nutrition markers, low preoperative ALB and low preoperative total protein were potential risk factors for patient's mortality ($P = 0.043$ and $P = 0.018$, respectively).

Excessive intraoperative transfusion for HPP and colloids, hydroxyethyl starch, were significant risk factors for mortality ($P = 0.049$ and $P = 0.002$, respectively). Postoperative parameters, APTT with heparin(s) and bacterial and fungal infections were significant risk factors for mortality ($P = 0.035$ and $P = 0.014$, respectively) [Table 2].

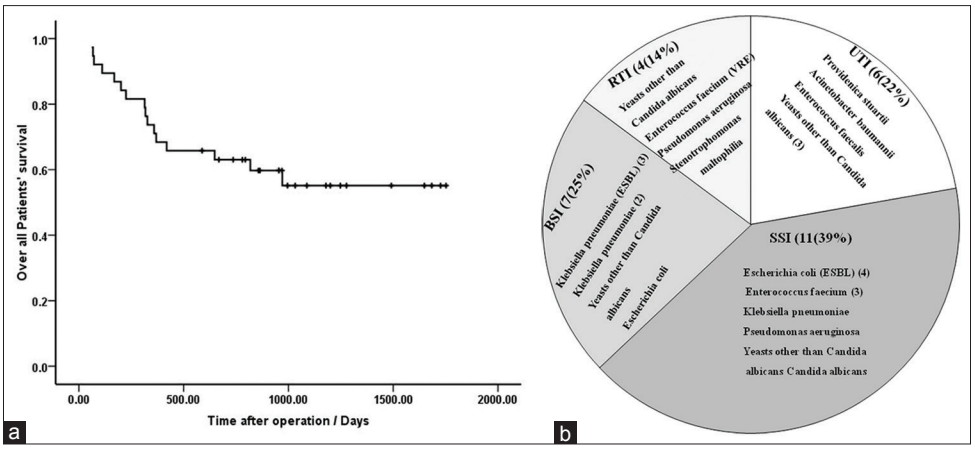

Figure 1: (a) Survival curve for patients after hyperthermic intraperitoneal chemotherapy (HIPEC) procedure. (b) Types and site of pathogens isolated from non-survivors. The most commonest site for infection was surgical site infection (SSI) followed by blood stream infection (BSI), urinary tract infection (UTI), then respiratory tract infection (RTI), ESBL: Extended-spectrum beta-lactamases; VRE: Vancomycin-resistant enterococci

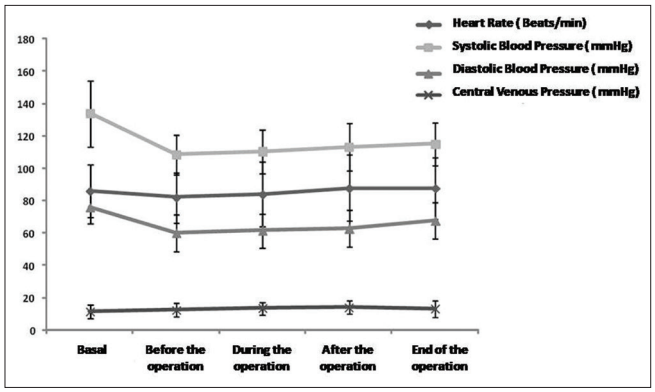

Figure 2: Haemodynamic variables during HIPEC procedure. Includes invasive systolic, diastolic blood pressures (mmHg), heart rate (beats/min) and central venous pressure (mmHg) changes during HIPEC procedure

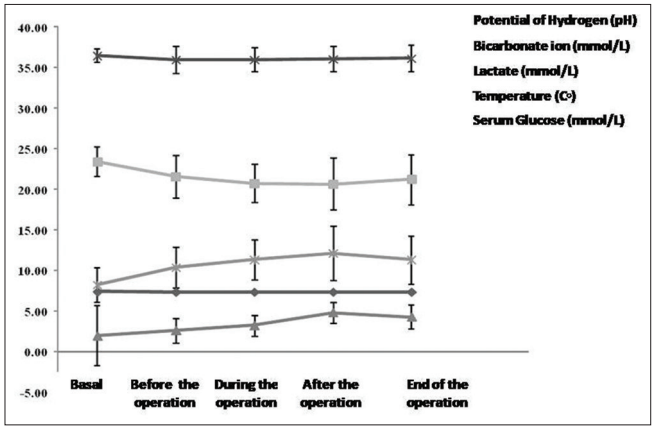

Figure 3: Acid–base, potential of hydrogen (pH), bicarbonate ion (mmol/L), lactate (mmol/L); glucose (mmol/L); temperature (C°) changes during HIPEC procedure

Those potential predictors were further examined with multivariate analysis; lower preoperative calcium [hazard ratio (HR) = 0.116; 95% confidence interval (CI) = 0.033–0.407, P = 0.001], higher intraoperative HPP transfusion volume (HR = 1.004; 95% CI = 1.001–1.003, P = 0.012) and higher postoperative bacterial infection (HR = 5.987, 95% CI = 1.009–35.54, P = 0.049) were independent risk factors for the patients' overall survival [Table 2].

Morbidities in patients after HIPEC procedure; in addition to 45 episodes of bacterial and fungal infections in 16 cases (42.1%), other complications were identified in our patients and presented in different organs. Gastrointestinal disorders included 3 cases of intestinal obstruction; 12 cases of abdominal pain; 1 case of megacolon, cholangitis, obstruction of bile duct, non-infective gasteroenteritis, colitis and fistula. Urinary tract disorders attributed to three cases of hydronephrosis, two cases of hydroureter, one case of obstructive and reflux uropathy and one case of haematuria syndrome. Cardiac disorders were presented as one case of chest pain, dyspnea and hypotension. Ovarian disorders included one case of primary ovarian failure, ovarian cyst and oligomenorrhea.

All patients were transferred to the ICU postoperatively. All the 38 cases admitted to ICU were intubated and kept on mechanical ventilation, till fulfilling criteria for weaning. All included cases received general anaesthesia in combination with epidural analgesia. Epidural analgesia was removed 48–72 h after ICU admission after full coagulation optimisation. Twenty-eight out of 38 patients required ALB infusion. Only four patients had raised CRE and one of them required renal dialysis for 2 months.

Most patients were extubated on the second postoperative day, except 12 patients who needed

Table 2: Univariate and multivariate analyses with respect to overall survival in patients after HIPEC procedure

Risk factor	Univariate			Multivariate		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Preoperative MCH	1.094	(1.009-1.186)	0.03			
Preoperative haemoglobulin	0.693	(0.486-0.988)	0.043			
Preoperative HCT	0.864	(0.763-0.978)	0.021			
Preoperative CA19.9	1.03	(1.008-1.053)	0.008			
Preoperative potassium	0.147	(0.039-0.559)	0.005			
Preoperative calcium	0.246	(0.096-0.628)	0.003	0.116	(0.033-0.407)	0.001
Preoperative albumin	0.3	(0.093-0.965)	0.043			
Preoperative total protein	0.657	(0.463-0.965)	0.018			
Intraoperative human plasma protein transfusion	1.001	(1-1.002)	0.049	1.004	(1.001-1.003)	0.012
Intraoperative colloids transfusion	1.002	(1.001-1.003)	0.002			
Postoperative APTT with heparin (s)	1.036	(1.003-1.071)	0.035			
Postoperative infection	6.494	(1.471-28.673)	0.014	5.987	(1.009-35.54)	0.049

HIPEC – Hyperthermic intraperitoneal chemotherapy; HR – Hazard ratio; CI – Confidence interval; MCH – Mean corpuscular haemoglobin; HCT – Haematocrit; CA19.9 – Tumour marker; APTT – Activated partial thromboplastin time

extended periods of ventilation. The average ventilation period was 2.9 ± 3.09 (1-10) days. Postoperative pulmonary complications were mostly due to pneumonia (seven cases). Three cases were caused by acute lung injury due to systemic inflammatory response and fluid overload. One case was attributed to aspiration; one case was due to pulmonary embolism. The median length of ICU stay was 5 [9.5 ± 25.7 (2–150)] days and the overall hospital stay was 23 [37.6 ± 38.6 (10–177)] days, as shown in Table 1. Patients were followed up for a mean period of 787.8 ± 799.7 (62–1752) postoperative days. Hospital readmission with a mean of 2.9 ± 3.6 (0–14)/day was indicated in these patients.

DISCUSSION

In this study, we described the perioperative management and outcome of consecutive patients undergoing combined CRS/HIPEC at our institution. To our knowledge, the perioperative outcomes of this procedure have not been robustly reported in previous literature.

Haemodynamic stability was achieved either through optimising cardiac output with adequate intravascular volume or by augmenting the systemic vascular resistance with vasopressor drugs as described previously.[15] Diligent fluid management of these patients was a real challenge for the anaesthetist due to the optimal end-organ perfusion of vital organs.[17] We tried using optimal strategy to maintain euvolaemia, avoid volume overload and tissue oedema especially of the surgical wound. In our institute, ALB administration was guided by preoperative serum level.[18] Several studies have reported that hypoalbuminaemia has been associated with increased morbidity after HIPEC.[15,18,19] In addition, ALB replacement can benefit patients who were exposed to extensive debulking and large volume of ascites drainage.[20] Moreover, Bernardi *et al.*[21] reported that replacement of ascites with ALB reduced morbidity and death in patients with chronic liver disease.

Transfusion of FFP was guided by coagulation profiles, and transfusion of packed red blood cells was guided by clinical signs and laboratory investigations. We have shown higher colloid transfusion as an independent risk factor for patients' mortality as previously reported.[16]

The surgical procedure for CRS/HIPEC was done by surgical excision of the tumour and application of a heated and concentrated chemotherapeutic agent in the peritoneal cavity. HIPEC achieves high peritoneal concentrations with limited systemic absorption. Yet, renal dysfunction, coagulation derangements and electrolyte disturbances can happen as HIPEC squeal that demands close collaboration among surgeons, anaesthesiologists, perfusionists and nurses.[14,22]

The mechanism of heated chemotherapeutic drugs was through inhibition of DNA repair, augmentation of heat shock proteins and denaturation of proteins. Hyperthermia not only precipitates direct cytotoxic impact but also triggers immune-mediated damage to cancer cells and exposes those sick patients to both coagulation and renal dysfunctions. Therefore, perfect temperature management is crucial to reduce morbidity and mortality of those subjects by maintainace of normothermia.

The satisfactory results of CRS/HIPEC gave new hope for patients with PC, who used to be considered for poor prognosis. However, a higher rate of morbidities especially infectious complication is still considered a major cause of death, prolonged hospital stay and overall increased healthcare costs.[1,5] Our study showed that the overall mortality rate was 42.1% that was comparable to a French multicentre study which was done by Glehen *et al.*[10] in which the 3-year survival rate was 41% for patients with colorectal carcinoma and another Netherlands multi-institutional study[5] in which the 3-year survival rate was 46% for the same cancer. On the other hand, it was considered high compared with others who reported a mortality rate of 0%–12%.[9,11] This higher level could be attributed to the fact that the majority of our patients had several previous surgical and chemotherapeutic interventions and their PC is due to a colorectal carcinoma that had the lower survival rate.[5,10] Furthermore, HIPEC is a recently introduced surgical technique in our institute.

Our data demonstrated several risk factors which were associated with mortality including a higher preoperative MCH, a large intraoperative transfusion of plasma protein and colloids and higher postoperative PTT.

Lower preoperative calcium, higher intraoperative plasma protein and more postoperative infection independently predicted overall survival. We found decreased serum calcium and potassium were potential risks for mortality after HIPEC, and similar results were described previously.[23]

We observed that tumour marker, CA19.9, was related to reducing patient's survival in accordance with another study.[24] In addition, Saxena *et al.*[24] found that anaemia was associated with prolonged ICU stay and severe morbidity. We recommend using appropriate blood conservation strategies in HIPEC patients; ultimately, blood loss is expected.

In our cohort, the poor medical condition of non-survivors demonstrated by higher carcinogenic markers and high ASA score, increased the need for colloid replacement and postoperative infectious complications similar to what was found in other reports.[9,24,25]

Pain management for CRS/HIPEC is essential for patient's comfort and postoperative pulmonary function optimisation. Moreover, adequate analgesia enables these patients to participate in early pulmonary physiotherapy to prevent postoperative atelectasis. Several centres[15,26] used thoracic epidurals preoperatively for intraoperative anaesthetic management and postoperative pain control, similar to our protocol. Epidurals can reduce postoperative opioid requirements and prevent ileus via diminished sympathetic tone. HIPEC patients often receive thromboprophylaxis to prevent deep vein thrombosis In addition, these patients may develop coagulopathy after this complex procedure. Impairment of coagulation was attributed to the large volume shift and protein loss with high fluid turnover and possibly the hyperthermic chemotherapy. Since there are a lot of fluctuations in temperature, monitoring of PLT function may be beneficial. Full coagulation profile is meticulously observed. We followed the American Society of Regional Anaesthesia and Pain Medicine guidelines in safety timing during insertion and removal of the epidural catheter.[27]

The complexity of CRS/HIPEC procedures considered recently introduced in our centre. Also, the poor medical condition of non-survivors in addition to the impairment of the host defence mechanism may be reasons for associated infections.[5,9,24,25,28]

The small number of patients is one of the limitations of our study; also, it was difficult to identify recurrence in patients, and there were no major changes in the prophylactic or empirical drugs used in the study period. Our cumulative data showed that although we do not have intraoperative, 60-day mortality, we still have high mortality, morbidity rates and common incidence of infections.

CONCLUSION

Morbidity and mortality rates can be minimised not only by increasing the experience of the surgeons but also by developing a selective team to improve the overall patient outcomes. We recommend optimisation of preoperative malnutrition, anaemia, electrolytes and coagulation derangements. An antimicrobial strategy should be continually re-assessed to reduce the emergence of antimicrobial resistance.

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Conflicts of interest

There are no conflicts of interest.

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