

Effect of perioperative variables on postoperative outcome after cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: retrospective analysis in a tertiary cancer center

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Abstract

Introduction: Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) have emerged as the treatment of choice for peritoneal carcinomatosis. There is limited literature on the postoperative complications after CRS and HIPEC from the developing world.

Aim: Our study aims to find out the incidence of postoperative complications after CRS and HIPEC and retrospectively analyzed the association of various perioperative anaesthetic factors with these complications.

Methodology: Records of patients >18 years who underwent CRS and HIPEC in our institute from September 2018 to July 2023 were collected and data was analyzed retrospectively. Demographic details, details about extent of resection and intraoperative anesthetic events were collected. Incidence of pulmonary and cardiac complications, liver failure and renal failure were analyzed. Patients were followed up retrospectively to assess the 30day mortality. Postoperative complications were graded according to Clavien Dindo grading.

Result: Cardiac complications were the most common postoperative complication followed by pulmonary then renal complications. There is also significant association between pulmonary complications and duration of surgery, transfusion of crystalloids and fresh frozen plasma. Duration of surgery, amount of blood loss, transfusion of Fresh Frozen Plasma (FFP) and platelets, intraoperative metabolic acidosis and Peritoneal Carcer Index (PCI) score were significantly associated with the development of postoperative cardiac complications. In our study, 30-day mortality was 4.7% (2/43).

Conclusion: Pulmonary and cardiac complications were the two common morbidities in the postoperative period following CRS and HIPEC. Duration of surgery, transfusion of FFPs, intraoperative acidosis and PCI scoring of the disease are the major predictors of postoperative cardiac and pulmonary complications. Incidence of complications are quite high according to Clavien Dindo grading.

Key Words: CRS, HIPEC, cancer, chemotherapy, PCI

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INTRODUCTION

Organ based malignancies especially that of gastrointestinal tract and ovaries can have widespread metastatic dissemination throughout the abdominal cavity and pelvis. Cytoreductive surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) have emerged as the treatment of choice for these peritoneal carcinomatosis [1, 2].

Cytoreductive surgery involves removal of the peritoneum almost completely, macroscopic tumor removal, multiple visceral organ resection followed by multiple intestinal anastomosis in some cases. This is followed by HIPEC which involves perfusion of abdominal cavity with heated chemotherapy [1, 3]. This surgery involves significant fluid shift because of the extensive resection, blood and fluid loss, transfusion of blood products and fluids, pharmacological vasodilatation due to neuraxial block and anesthetic drugs, vasodilatation due to systemic inflammation and hyperthermic insult. This contributes to hypotension and metabolic alterations in the perioperative period which can predispose to various postoperative complications [1, 3]. There is limited literature on the postoperative complications after CRS and HIPEC from the developing world.

Hence our study aims to find out the incidence of postoperative complications after CRS and HIPEC and retrospectively analyzed the association of various perioperative anesthetic factors with these complications.

MATERIAL AND METHOD

This study was performed according to World medical association declaration of Helsinki. After obtaining approval from institutional review board, records of

patients >18 years who underwent CRS and HIPEC in our institute from September 2018 to October 2023 were collected and data was analyzed retrospectively. Patients who underwent staged procedures, emergency re-exploration and those with incomplete medical records were excluded. Demographic details like age, sex, ASA status, comorbidities, height and weight of the patient were recorded. Details were collected about the primary disease and PCI scoring. Extent of surgical resection was analyzed in terms of total peritonectomy, multiorgan resection, diaphragmatic and liver resection. Intraoperative variables like duration of surgery, amount of blood loss, transfusion of crystalloids, colloids, packed red cells, FFP and platelets, chemotherapy drug used, occurrence of intraoperative hypotension and acidosis were recorded. Incidence of pulmonary and cardiac complications, liver failure and renal failure were analyzed. Patients were followed up retrospectively to assess the 30-day mortality. Postoperative complications were graded according to Clavien Dindo grading.

Association of various anesthetic factors with cardiac, pulmonary, renal and liver related complications, 30-day mortality and Clavien Dindo grading were analyzed.

RESULTS

Our study retrospectively analyzed the results of 43 patients. Mean age of the study population was 47 years. Majority of patients were females (37/43), belonged to ASA 2 (29/43). Out of the 43 patients studied, 20 patients had one or more comorbidities and most common comorbidities were hypertension and diabetes. Ovarian carcinoma was the most common primary disease and majority of patients had a PCI score <10. Table 1 shows the demographic and preoperative data of patients undergoing CRS and HIPEC. All CRS involved total peritonectomy, majority had multi-organ resection and diaphragmatic resection, but only 14 out of 43 patients underwent liver resection.

Tab. 1. Demographic and preoperative data

Serial no.	Factors	Count
1	Age	47
2	Gender (Male: Female)	6:37

3	ASA 1/2/3	13/29/1
4	Comorbidity	
	Nil	13
	Hypertension	12
	Diabetes	12
	Thyroid	4
	IHD	4
	CVA	1
5	Primary	
	Ovary	21
	Colon	6
	Hamn	8
	Pseudomyxoma	7
	Rectum	1
6	PCI score	
	01-10	24
	10-20	8
	20-30	6
	>30	5

Majority of the surgery lasted 8-10 hours. Out of 43 patients, 18 had a blood loss of 1-2 l. Only 10 patients had a blood loss of >2 l. 32 patients required PRBC transfusion intra-operatively. Majority of patients had transfusion of 1-2 PRBCS. Only 14 patients needed FFP and 9 needed transfusion of platelets intra-operatively.

22 out of 43 patients received 10-20 crystalloids during the procedure. Out of 43 patients, 34 needed colloids and 25 of them received 1-2 units and 9 required >2 units of hydroxyl ethyl starch in the intraoperative period. Cisplatin and mitomycin were the two chemotherapy drugs used for HIPEC and 23 patients were given cisplatin and 20 were give mitomycin. Table 2 highlights the intraoperative data of the study population.

Tab. 2. Intraoperative data

SL No.	Factors	Count
1	Total Peritonectomy: Yes/No	43/0
2	Multiorgan Resection: Yes/No	41/2
3	Diaphragmatic Resection: Yes/No	36/7
4	Liver Resection: Yes/No	14/29
5	Duration of surgery	
	8 HRS	8

	8-10 HRS	27
	>10 HRS	8
6	Blood Loss	
	<1L	15
	1-2 L	18
	>2L	10
7	PRC Transfusion	
	NIL	11
	<2	18
	2-4	9
8	FFP	
	NIL	29
	<2	3
	2-4	3
9	Platelet	
	NIL	34
	<2	2
	2-4	2
10	Crystalloid	
	<10	19
	10-20	22
11	Colloid	
	NIL	9
	<2	25
	>2	9
12	Chemotherapy	
	Cisplatin	23
	Mitomycin	20
13	Intraop Hypotension	19
14	Intraop Acidosis	17

Cardiac complications were the most common postoperative complication followed by pulmonary then renal complications. Majority of patients had 5 days-10 days of postoperative stay in ICU. Out of 43 patients who underwent the procedure, 19 had grade 4a Clavien Dindo complications and two patients died within 30 days of procedure. Table 3 highlights the postoperative complications after CRS and HIPEC.

Tab. 3. Postoperative complications

Sl no	Postop complications	Count
1	Pulmonary	
	Nil	29
	Prolonged Ventilation	9
	Pleural Effusion	4
2	Renal Complications	
	NIL	33
	1	2
	2	5
3	Cardiac	
	Nil	28
	Ischemia	11
4	Arrhythmia	4
	Liver	7
5	Duration of ICU stay	
	<5 Days	7
	5-10 Days	19
6	>10 Days	17
	30 Day Mortality	2
7	Clavien Dindo Grading	
	1	1
	2	18
	3a	3
	4a	19
	5	2

We analyzed the association of preoperative and intraoperative factors with postoperative complications like pulmonary, cardiac, renal and liver-related problems, Clavien Dindo grading and 30-day mortality.

14 patients developed pulmonary complications postoperatively. Prolonged ventilation was the most common complication (9/14). 7 patients developed pneumonia and 4 had pleural effusion postoperatively. Occurrence of postoperative pulmonary complications was significantly high in those who underwent liver resection during CRS. There is also significant association between pulmonary complications and duration of surgery, transfusion of crystalloids and FFP.

Out of the 36 patients who underwent diaphragmatic resection, only 13 developed pulmonary complications postoperatively and it showed that there is no significant association between pulmonary complications and diaphragmatic resection. There is statistically significant association between pulmonary complications and intraoperative acidosis. Pulmonary complications were high in those who had intraoperative hypotension, but the association was not significant. Postoperative pulmonary complications were significantly associated with the PCI score of the disease. Majority of the patients with the PCI score >10 developed pulmonary complications in the postoperative period.

Out of the 43 patients studied, 10 patients developed acute renal failure in the postoperative period. Acute renal failure was diagnosed based on the AKIN criteria. Even though the incidence of acute renal failure was high in those who received colloids, PRC and in patients who had intraoperative hypotension, association was not statistically significant. Out of the 10 patients who developed postoperative renal complications, 7 received cisplatin and only 3 received mitomycin, but the association of acute renal failure with the type of chemotherapy used was not statistically significant.

Fifteen patients developed cardiac complications postoperatively. 11 had ischemic symptoms and four patients had rhythm abnormalities. Duration of surgery, amount of blood loss, transfusion of FFP and platelets, intraoperative metabolic acidosis and PCI score were significantly associated with the development of postoperative cardiac complications. Although majority of patients who developed cardiac complications had intraoperative hypotension, the association was not statistically significant.

Out of 7 patients who developed postoperative acute liver failure, 6 patients recovered. One patient progressed to have decompensated liver failure and died on 26th postoperative day. Although occurrence of liver related complications were high in those patients with multi-organ resection, diaphragmatic resection, in those with intraoperative hypotension/acidosis and in

patients with higher PCI score, there was no statistically significant association.

Using the Clavien Dindo classification, one patient had grade 1 complication, 18 patients had grade 2 complications and 19 had grade 4a complications. PCI score had statistically significant association with Clavien Dindo grading of complications.

In our study, 30-day mortality was 4.7% (2/43). One patient had acute liver failure which decompensated and resulted in multi organ dysfunction and death. Other patient died due to sepsis. Primary disease, duration of surgery and transfusion of FFP showed statistically significant association with 30-day mortality.

DISCUSSION

Data of 43 patients who underwent CRS and HIPEC over last 5 years in our center was retrospectively analyzed. We calculated the incidence of postoperative complications. Our study showed that various preoperative and intraoperative factors have significant influence on patient outcome.

Majority of patients in our study were females. This was similar to Kajdi et al who studied 57 patients out of which 34 were females [2].

Most common primary disease in our study population was ovarian carcinoma. Lopez et al also found that majority of their patients (49.3%) had ovarian tumor [3]. But carcinoma appendix was the most common primary disease according to Kajdi et al [2]. Because of the immuno-compromised state, comorbidities are very common in cancer patients. Hypertension and diabetes were the most common comorbidities in our study group. IHD, hypothyroidism, CKD and CVA were also commonly found in these patients in previous studies [4-8].

Because of the extensive resection, vasodilatation due to neuraxial block and hyperthermic chemotherapy, there is large fluid shift and extensive bleeding during these procedures. Crystalloids, colloids and blood products are administered to maintain adequate tissue perfusion pressure and urine output without causing fluid overload. Patients with low cardiac reserve may not tolerate large volume transfusion and they

may need judicious early use of vasopressors and inotropes [1].

In our study, majority of patients received 10 to 20 crystalloids, 1 to 2 colloids and 1 to 2 units of packed red blood cells. Previous studies also demonstrated large volume transfusion of crystalloids and blood products intra-operatively.

Common drugs used for chemotherapy during CRS/HIPEC are cisplatin, mitomycin C, doxorubicin and oxaliplatin. They are known to cause side effects like nephrotoxicity, neurotoxicity, cardiotoxicity and electrolyte disturbances. Cisplatin was the most common chemotherapeutic agent used in our study, followed by mitomycin C. This is in contrast to the study by Kajdi et al. in which they used a combination of chemotherapy drugs (doxorubicin and mitomycin) as the most common.

Pulmonary complications were the most common postoperative complications in our study group. There was significant association between occurrence of pulmonary complications and duration of surgery, transfusion of colloids and FFP, intraoperative acidosis and PCI scoring of the disease. Diaphragmatic resection had no significant association with PPCs in our study group similar to studies by Olivia Sand [5]. This is in contrast to a study by Cascales Campos et al. who identified diaphragmatic peritonectomy as the main risk factor [9]. Higher PCI, longer duration of surgery, increased estimated blood and fluid loss, increased intraoperative fluid requirement, lower Mean Arterial Pressure (MAP) and higher blood products requirement had statistically significant association with occurrence of PPCs according to studies by Balakrishnan et al. [4].

Maintaining optimal renal function and prevention of acute renal failure is crucial for reducing morbidity [10]. Known risk factors for acute renal injury are hypovolemia, hypotension, nephrotoxic drugs, and blood transfusions [11,12]. Even though occurrence of acute renal failure was high in patients with these factors, our study could not get any statistically significant association. Hemodynamic optimization (optimizing cardiac output,

tissue perfusion, and oxygenation) is highly recommended to prevent renal injury [2].

Our study showed significant association of postoperative cardiac complications with duration of surgery, amount of blood loss, transfusion of FFPs and platelets, intraoperative acidosis and PCI scoring of the disease. Duration of surgery was a significant predictor of postoperative adverse cardiac events according to Kheterpal et al. [2].

Physiological alterations associated with surgical stress and anesthesia itself may be a contributor for adverse cardiac events following major surgeries. Excessive blood loss and transfusion of blood products were also identified as risk factors for cardiac events according to Kheterpal et al. this may be because of the associated tissue hypoperfusion associated with excess blood loss. The deleterious effects of transfusion itself may also add on to it.

Our data showed that PCI scoring was a significant predictor of Clavien Dindo complications. It is likely that patients with a higher PCI need more extensive resection that would have led to increased blood loss and necessitated more fluid [1]. There was also a statistically significant and positive correlation between PCI and the day of extubating, Clavien–Dindo classification, length of ICU stays and 30-day mortality according to Raghav et al [1]. The mean PCI in their study was 15.76 ± 5.15 , with the highest for the CA colon.

30-day mortality was 4.65% according to our study. Primary disease, duration of surgery and FFP transfusion were significantly associated with 30-day mortality. In a similar study conducted by Elgendy et al, there were no operative or 60-day mortalities; the 1-year mortality rate was 32%. And the overall postoperative mortality was 42.1%. In their study, univariate analyses of risk factors demonstrated that low preoperative (hemoglobin, potassium, calcium and albumin), intraoperative transfusion of Human Plasma Protein (HPP), colloids, postoperative activated partial thromboplastin time and bacterial infections were potential risk factors for patient's mortality [6].

Our study has several limitations. Ours is a retrospective study, hence it is difficult to establish a cause effect relationship. Since this is a single Centre study, results cannot be generalized and may vary in other centers based on the expertise of the operating team and availability of facilities. Sample size analysed in the study was also small.

CONCLUSION

Pulmonary and cardiac complications were the two common morbidities in the postoperative period following CRS and HIPEC. Duration of surgery, transfusion of FFPs, intraoperative acidosis, and PCI scoring of the disease were the major predictors of postoperative cardiac and pulmonary complications. The incidence of complications was quite high according to Clavien Dindo grading. CRS with HIPEC is a very major surgery and coordinated efforts of multi-disciplinary team is required for successful patient outcome. Intensive postoperative monitoring and early detection of complications are necessary to improve morbidity and mortality.

CONFLICT OF INTEREST

Nil.

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