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Original Article

Does hyperthermic intraperitoneal chemotherapy influence the rate of infective complications and change the pattern of infectious agents in patients undergoing cytoreductive surgery for peritoneal carcinomatosis?

Umit Mercan[1], Ogun Ersen[1], Cemil Yuksel[2], Ali Ekrem Unal[1]

[1]Department of Surgical Oncology, Faculty of Medicine, Anakara University, Ankara, Turkey
[2]Ministry of Health Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey

Abstract

Aim: When CRS, in which complex surgical procedures are applied combined with HIPEC in which high dose cytotoxic agents are applied, many serious postoperative complications, especially infection-related complications, may develop in the patient group with peritoneal carcinomatosis whose general condition is impaired. In this study, it was aimed to investigate the effect of HIPEC application after SRC on infection rates and microbial agent spectrum alone.

Materials and Methods: Between January 2012 and January 2020, one thousand six hundreds forty eight patients diagnosed with peritoneal carcinomatosis were scanned from hospital database and two hundred thirty-five eligible patients were included in the study. Demographic and clinical data, perioperative results and culture results were analyzed by grouping the patients as HIPEC and non-HIPEC.

Results: It has been found that the incidence of surgical site infections was significantly higher in HIPEC group. (23.6%vs11.5%p=0.011). When the culture results were analyzed. The number of patients with E.coli (13.7% vs 5.7% p = 0.001), Klebsiella pneumoniae (9.9% vs 2.8% p = 0.001) and Pseudomonas aeruginosa (2.2% vs 0.9% p = 0.034) growth was significantly higher in the HIPEC group.

Conclusions: It has been found that HIPEC application not only increases the infection rates but also expands the potential pathogen spectrum. Prediction of possible pathogens responsible for postoperative infections may affect the choice of prophylactic and ultimate treatment and so the risk of developing morbidity and mortality which may result from a possible septic progression, can be minimized with an effective antimicrobial therapy.

Keywords: Carcinomatosis; cytoreductive surgery; infections

INTRODUCTION

Peritoneal carcinomatosis (PC) usually represents the terminal stage of neoplastic disease, but is considered to be an isolated peritoneal disease by surgical oncologists dealing with this condition. In the last decade, peritonectomy for peritoneal carcinomatosis started to break with the thought that PC is a terminal disease with increased cytoreductive surgery (CRS) and peroperative intraperitoneal chemotherapy approaches (1,2). The long-term survival results obtained with this procedure were satisfactory in certain patient groups (3-8).

Although it is known that the microbial agents responsible for infections that develop following conventional chemotherapy cures differ from the normal population, there is no comparative study on this condition after intraperitoneal chemotherapy. In addition to the long and complex surgical procedures applied to this group of patients prone to infection, administration of local cytotoxic agents increases the risk of general complications as well as peroperative infection rates (9).

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Corresponding Author: Umit Mercan, Department of Surgical Oncology, Faculty of Medicine, Anakara University, Ankara, Turkey
E-mail: umit.mercan@yahoo.com.tr

In a limited number of studies on postoperative infective complications in patients undergoing CRS and HIPEC, the subject was discussed over infection rates, and there is no study comparing over two separate groups (10,11). Considering the burden of aggressive cytoreduction on the patient, many factors of the CRS procedure alone can be eliminated to assess the effect of HIPEC on infective pathogens and infective complications. Generally, evaluating HIPEC and CRS procedures together directly affects the reliability of the results of such studies. The inclusion of cytoreduction into the negative universe or exclusion criteria in the patient groups included in the study will cause the results of these two procedures, which are applied together in practice, to be reflected in the study results.

In this study, the effect of combining HIPEC to CRS that is a procedure with high morbidity and infection risk on the frequency of infectious complications may be encountered in postoperative period and microbial agent diversity was investigated by comparing 2 different groups.

MATERIALS and METHODS

Patient Selection and Data Collection

Between January 2012 and January 2020, 1648 patients diagnosed with PC were scanned from the hospital's electronic file system and a total of 235 patients who were applied only CRS and CRS + HIPEC procedures and who were eligible for study criteria were included in the study. Demographic and clinical data, perioperative results and culture results were collected by a data collection assistant who is a surgical oncologist. Patients who did not undergo surgery and were directed to chemoradiotherapy, patients who could not be operated due to intraoperative high peritoneal cancer index (PCI), patients who could not be operated due to low performance status, patients who underwent palliative and emergent surgery, patients who have serious postoperative complications requiring surgical intervention during hospitalization or resulting in mortality (anastomosis leakage, perforation, soft tissue or visceral organ necrosis vs.), patients with preoperative leukopenia / neutropenia or immune deficiency and patients whose clinical or demographic data were not fully available were excluded from the study. Patients undergoing CRS and HIPEC called as 'HIPEC group and patients who underwent CRS alone called as 'non-HIPEC group'. Flowchart of total patient enrollment and excluded patients is summarized in Figure 1.

Preoperative performance status of the patients were determined according to the Eastern Cooperative Oncology Group (ECOG) Classification and only class I and II patients were operated (12). Disease burden was determined according to preoperative computed tomography sections and PCI obtained by intraoperative exploration and defined by Sugarbaker PH et al (13).The width of cytoreduction was categorized as CC-0, CC-1 or CC-2/3 according to CC score defined by Harmon RL et al (14). Postoperative complications were categorized according to the Modified Clavien-Dindo Classification (15).

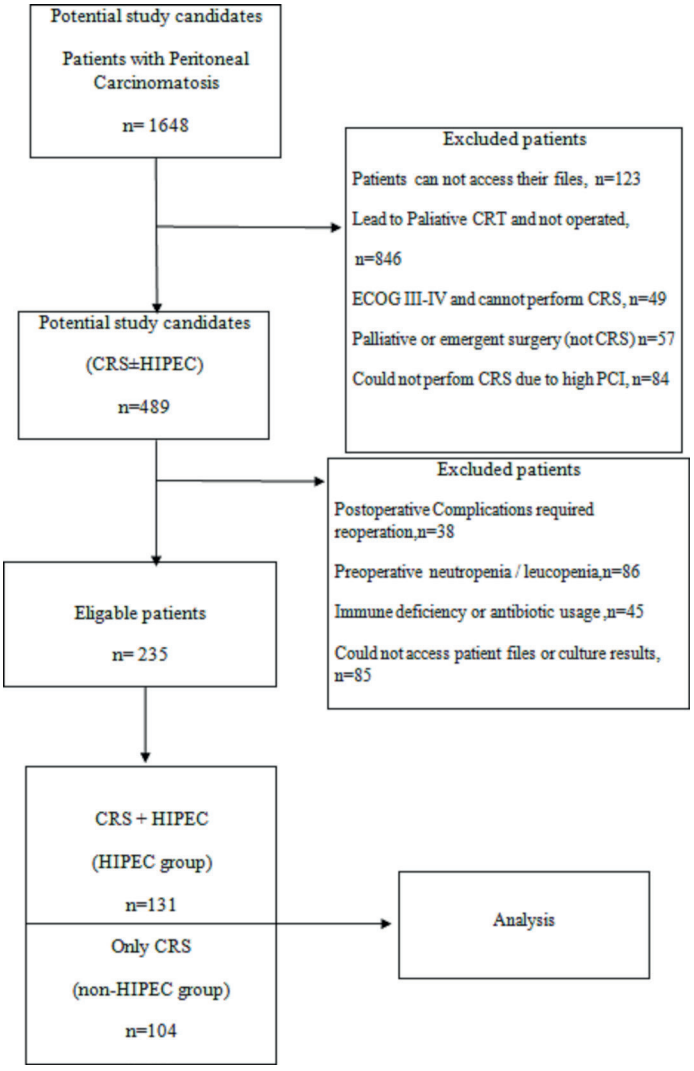

Figure 1. Flowchart of total patient enrollment and excluded patients.

This study was approved by Ethics Committee of Ankara University Faculty of Medicine.

Statistical Analysis

All numerical data are given as mean ± standard error or percentages. For statistical analysis, patients were divided into two groups as HIPEC and non-HIPEC. Histogram graphics and Kolmogrov-Smirnov test were used to determine the normal distribution of numerical data. In comparison of clinical and demographic data, perioperative results and related microbial agents isolated in related cultures, Student T-test or Man-Whitney U test were used for numerical data and X2 test or Fisher Exact Test for categorical data. P values of 0.05 and below were considered statistically significant. Statistical analysis of the study was carried out in IBM SPSS version 23.0 program.

RESULTS

While SRC + HIPEC was applied to 131 (55.7%) of 235 patients included in the study, only SRC was performed to 104 (44.3%). One hundred twenty-eight (54.4%) of the patients were male and the mean age was 56.24 ± 15.45. The most common diagnoses in the study group were colorectal cancer (31%) and appendix cancer (25.9%). There was no significant difference between the two groups in terms of clinical and demographic variables and the groups were homogeneous in this respect. Comparison of clinical and demographic data between groups is summarized in Table1.

Table 1.Comparison of clinical and demographic variables between groups of HIPEC and non-HIPEC

	Total N=235	HIPEC N=131	Non-HIPEC N=104	p value
Age	56.24±15.45	55.84±14.69	56.98±15.81	0.548
Gender (Male)	128(54.4)	70(53.4)	58(55.7)	0.350
BMI (kg/m^2)	21.12±3.57	20.44±4.72	21.78±3.16	0.468
ASA Score				
I	28(12)	15(11.4)	13(12.5)	0.625
II	123(52.3)	64(48.8)	59(56.7)	
III	84(35.7)	52(39.6)	32(30.7)	
ECOG*				
I	188(80)	105(80.1)	83(79.8)	0.835
II	47(20)	26(19.9)	21(21.2)	
Comorbid Diseases				
DM	43(18.2)	26(19.8)	17(16.3)	0.364
COPD	19(8)	10(7.6)	9(8.6)	0.746
HT or Cardiovascular Disease	123(52.3)	68(51.9)	55(52.8)	0.712
Chronic Renal Failure	21(8.9)	12(9.1)	9(8.6)	0.592
Origin of Peritoneal Carcinomatosis				
Ovarian Cancer	53(22.5)	27(20.6)	26(25)	0.614
Colorectal Cancer	73(31)	40(30.5)	33(31.7)	0.768
Gastric Cancer	8(3.4)	8(6.1)	0(0)	-
Primary Peritoneal Cancer Appendiceal Cancer	40(17)	21(16)	19(18.2)	0.651
Appendiceal Cancer	61(25.9)	35(26.7)	26(25)	0.326
Preoperative Hospital Stay	3.42±2.28	3.86±1.47	3.15±2.49	0.627

Numerical variables are given as mean±standart error and n(%). HIPEC: Heated Intraperitoneal Chemotherapy, BMI: Body Mass Index, ASA: American Society of Anesthesiology, ECOG: Eastern Cooperative Oncology Group, DM: Diabetes Mellitus, COPD: Chronic Obstructive Pulmonary Disease, HT: Hypertension. * Preoperative performace status of patients were determined according to ECOG Classification (12).

The comparison of the perioperative results between the groups is summarized in Table 2. PCI was found to be significantly higher in non-HIPEC group (10.86±4.68 vs 16.75±5.15 p = 0.001), and those who could undergo CC-2/3 cytoreduction in parallel were significantly higher in this group. Given that the HIPEC procedure had an additional 60 minutes, the operation time in the HIPEC group was significantly longer compared to the other group (220.65±48.82 vs 163.46±49.36 min. p = 0.001). Combining HIPEC with CRS did not affect the duration of hospitalization in intensive care unit,but it was seen to extend the length of hospital stay(15.16±6.57vs10.72±5.48 p = 0.032). While there was no difference between the groups in terms of incidence of serious postoperative complications, when postoperative infective complications were evaluated within themselves, it was found that HIPEC application after CRS significantly increased the incidence of surgical site infections (23.6% vs 11.5% p = 0.011). Patients who needed antibiotic therapy for 14 days or more due to any infective complications were significantly higher in the HIPEC group (29.7%vs16.3% p=0.014). The number of patients who were unable to tolerate oral intake due to various conditions such as postoperative complications, delayed gastric emptying or anorexia and therefore given total parenteral nutrition for 7 days or more was significantly higher in the HIPEC group (51.9% vs 31.7% p = 0.029).

When the culture results of the patients with infective complications were examined, the most common pathogen isolated from wound, drain content and urine cultures was Escherichia coli; from blood cultures was Candida albicans and from sputum cultures was Acinetobacter baumannii (Table 3). When the number of patients with positive culture results according to the isolated microbial agents was compared between the two groups, the number of patients with E.coli (13.7% vs 5.7% p = 0.001), Klebsiella pneumoniae (9.9% vs 2.8% p = 0.001) and Pseudomonas aeruginosa (2.2% vs 0.9% p = 0.034) growth was significantly higher in the HIPEC group (Table 4).

Table 2. Comparison of perioperative results between the groups of HIPEC and non-HIPEC

Variables	Total N=235	HIPEC N=131	Non-HIPEC N=104	p value
PCI score*	13.24±4.92	10.86±4.68	16.75±5.15	0.001
CC score**				0.001
CC-0	101(42.9)	81(61.8)	20(19.2)	
CC-1	76(32.3)	43(32.8)	33(31.7)	
CC-2/3	58(24.6)	7(5.3)	51(49)	
Multiorgan resection (≥2)	78(33.1)	45(34.3)	33(31.7)	0.235
Splenectomy	16(6.8)	9(6.8)	7(6.7)	0.914
Urinary Reconstruction	21(8.9)	12(9.1)	9(8.6)	0.573
Operation Time (min)	198.54±43.57	220.65±48.82	163.46±49.36	0.001
Number of Patients Required Intraoperative Tx	42(17.8)	23(17.5)	19(18.2)	0.834
Blood Loss (≥1000 ml)	33(14)	18(13.7)	15(14.4)	0.724
Intraoperative Visceral Perforation	4(1.7)	2(1.5)	2(1.9)	0.336
Hospital Stay (day)	12.46±5.78	15.16±6.57	10.72±5.48	0.032
ICU stay (day)	3.28±2.52	3.67±2.18	2.98±3.02	0.104
Postoperative Complications (CD ≥ 3)***	31(13.1)	17(12.9)	14(13.4)	0.379
Infective Complications	67(28.5)	41(31.2)	26(25)	0.062
SSI	43(18.2)	31(23.6)	12(11.5)	0,011
Urinary	11(4.6)	6(4.5)	5(4.8)	0.269
Pulmonary	6(2.5)	3(2.2)	3(2.8)	0.428
Blood/Systemic	15(6.3)	8(6.1)	7(6.7)	0.536
Prolonged Antibiotic Usage (>14 days)	56(23.8)	39(29.7)	17(16.3)	0.014
Prolonged Total Parenteral Nutrition (>7 days)	101(42.9)	68(51.9)	33(31.7)	0.029

Numerical variables are given as mean±standart error and n(%). HIPEC: Heated Intraperitoneal Chemotherapy, PCI: Peritoneal Cancer Index, CC: Completeness of cytoreduction, Tx: Transfusion, ICU: Intensive Care Unit, CD: Clavien Dindo. *Disease burden were determined according to PCI (13). ** Cytoreduction width were detemined according to CC score (14). ***Postoperative complications were categorized according to Modified Clavien-Dindo Classification (15)

Table 3. Most common isolated microorganisms from related cultures of patients	
Cultures	**Microorganism (number of cultures)**
Surgical Site	
Wound	Escherichia coli (12)
Abdominal Drain Fluid	Escherichia coli (8)
Blood	Candida albicans (7)
Sputum	Acinetobacter baumannii (4)
Urine	Escherichia coli (5)

Table 4. Comparison of microbial agents isolated between the group of HIPEC and non-HIPEC

	Number of Patients			
Microorganisms Isolated	**Total (n=235)**	**HIPEC group (n=131)**	**Non-HIPEC group (n=104)**	**p value**
Escherichia coli	24(10.2)	18(13.7)	6(5.7)	0.001
Enterococcus faecalis	9(3.8)	5(3.8)	4(3.8)	0.762
Klebsiella pneumoniae	16(6.8)	13(9.9)	3(2.8)	0.001
Candida albicans	12(5.1)	6(4.5)	6(5.7)	0.391
Pseudomonas aeruginosa	4(1.7)	3(2.2)	1(0.9)	0.034
Staphylococcus spp.	9(3.8)	5(3.8)	4(3.8)	0.608
Acinetobacter baumannii	7(2.9)	4(3.1)	3(2.3)	0.473
Proteus vulgaris	2(0.8)	1(0.7)	1(0.9)	0.821

Numerical variables are given as n(%). HIPEC: Heated Intraperitoneal Chemotherapy, spp: species

DISCUSSION

It is a known fact that intravenous chemotherapeutics are predisposed to infections in cancer patients and it has been revealed in studies that different approaches may be required from standard antibiotherapy applications due to the emergence of different and special pathogens in these patients Although intraperitoneal chemotherapy is absorbed in small amounts from the peritoneum, it is possible to form a similar picture (9-16). In addition, septic shock is known to be the most important cause of mortality in patients undergoing CRS and HIPEC (17). Therefore, it is important to reveal how intraperitoneal chemotherapy is related to peroperative infectiouscomplications.

In present study, the rate of general infectious complications after mitomycin and carboplatin given intraperitoneally with CRS was 31.2%, whereas this rate was found to be 25% in the group where only CRS was applied. Studies have shown that the most common infectious complications are observed after CRS and HIPEC, the infection rates are much higher than those seen in other standard surgical procedures and vary between 10% and 36% (10,11,18). The fact that the procedure performed involves complex surgical procedures and that the target patient group has a common disease that causes immunosuppression and nutritional defect may explain these high infection rates. In addition, CRS and HIPEC are associated with postoperative hemodynamic instability, coagulopathy and metabolic changes, which is the main cause of many postoperative complications including infection (18,19).

In present study, when infectious complications were categorized, surgical site related infections were observed to be significantly more frequent in the HIPEC group. It was observed that HIPEC application did not increase the frequency of systemic infections or infections developing in areas far from the surgical site. Systemic infections were mostly observed in the patient group who received long-term total parenteral nutrition and developed serious postoperative complications. These results suggest that local cytotoxic and anti-inflammatory effects induced by the application of chemotherapeutics directly to the surgical site, unlike systemic chemotherapy, trigger the development of infection in the wound area. In contrast,

there are publications showing that HIPEC application increases central catheter-related infection rates (20). In addition, it was observed that the patients who received HIPEC treatment had a significantly longer hospital stay in parallel with the increase in the frequency of infection compared to the group treated only with CRS. There are a lot of evidence in the literature that intraperitoneal chemotherapy increases infection rates (9,10).

In many studies, the effect of CRS and HIPEC application on the development of infection has been examined, but whether the HIPEC treatment alone causes a change in the spectrum of pathogens responsible for infections has been disregarded (9,11,16). It is known that E.coli is one of the most frequently isolated pathogens due to contact with GIS flora in SSI developing after abdominal surgery (21). In present study, number of cultures and patients with E.coli growth were found to be significantly higher in patients who received HIPEC compared to the other group. Moreover, Klebsiella pneumoniae and Pseudomonas aeruginosa species, which have low probability of reproduction especially in wound and drain cultures, were also found to be more isolated in the HIPEC group. In addition, it was determined that the number of cultures with multipatogenous reproduction was higher in this group. Contrary to expectations, despite the local immunosuppressive effect of intraperitoneal chemotherapy, opportunistic pathogens such as Candida species were mostly seen to grow in blood and urine cultures, but there was no increase in the rate of growth in the wound site.

The main limitations of the study are possible selection bias due to being of a retrospective study and the limited adaptability of the results to the general population due to relatively low sample size. Moreover, the fact that the CRS procedure, which includes many complex surgical procedures including multiorgan resections, brings many risk factors that lead to the development of infection alone without HIPEC, making it difficult to attribute the results to HIPEC application. In present study, excluding patients who developed serious complications such as anastomosis leakage, organ ischemia and necrosis which may require reoperation; being of parameters that are likely to pose a risk factor for the development of infection -such as age, BMI, ASA score, comorbid diseases, and length of hospital stay in which the necessary preopeative treatments were given to take the patient in the most suitable nutritional and medical condition for the operation- were similar among the groups and being of the rate of blood loss and blood transfusion requirement in the intraoperative process and the number of patients who underwent multiorgan resection or developed organ perforation were similar among the groups enabled the comparison of two relatively homogeneous groups. For these reasons we believe that our results that should be supported by randomized prospective studies are valuable in that HIPEC administration alone increases infectious complications and changes the pathogen spectrum.

CONCLUSION

As a result, combining HIPEC with CRS procedure in which complex surgical procedures are applied to a group of patients who are more difficult to manage, significantly increases the incidence of surgical site infection. HIPEC application not only increases the infection rates but also expands the potential pathogen spectrum. Prediction of possible pathogens in the management of infections developed after SRC and HIPEC may affect the choice of prophylactic and ultimate treatment and so the risk of developing morbidity and mortality which may result from a possible septic progression, can be minimized with an effective antimicrobial therapy.

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