

Prophylactic effect of hyperthermic intraperitoneal chemotherapy in patients with high risk of developing peritoneal carcinomatosis from colorectal cancer

Mohamed I. Abdelhamid, Mohammed M. Alkilany, Osama abd Elaziz, Mohamed Abdelgawad

ABSTRACT

Aims: Hyperthermic intraperitoneal chemotherapy (HIPEC) seems to be a promising solution against development of peritoneal carcinomatosis (PC) complicating some cases of colorectal cancer (CRC). The aim of this study was to report the prophylactic effect of HIPEC against PC after radical resection of CRC. **Methods:** This prospective randomized comparative study included patients who presented to the Surgery Department of Zagazig University Hospitals with operable CRC with high risk of developing PC during the period from Januarys 2013 and June 2014. These patients were randomly divided into two groups; each one was 25 in number. One group was treated with surgery alone while the other was managed with HIPEC following surgery. Our patients were followed up till December 2016 to detect PC (mean follow-up period was 39 months). **Results:** There were statistically significant difference between both groups in which application of HIPEC following radical surgery decreases the incidence of PC recurrence ($p = 0.039$). On the other hand, postoperative complications demonstrated that cardiorespiratory complications ($p = 0.042$) and

length of hospital stay showed significant higher incidence in the HIPEC group ($p = 0.046$) whereas other complications as wound complications showed no statistically significant difference between two groups ($p = 0.15$). **Conclusion:** HIPEC has a remarkable prophylactic effect against PC recurrence and should be tried in CRC patients as long as no contraindications for this chemotherapeutic based procedure.

Keywords: Colorectal cancer, Hyperthermic intraperitoneal chemotherapy, Peritoneal carcinomatosis, Prophylactic

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INTRODUCTION

Colorectal cancer (CRC) is found to be the third most prevalent cancer [1]. Peritoneal carcinomatosis (PC) is present in approximately 5–10% of CRC patients during surgical resection. Recurrence in the form of PC complicating about 20%–50% of operated CRC patients [2, 3].

The development of peritoneal carcinomatosis begins by invasion of the tumor through the serosa or rupture

of the primary tumor within the peritoneal cavity [4]. The mechanisms of distribution of tumor cells within the peritoneal cavity are multifactorial. Briefly, these factors include gravitational pooling of cancer-cell containing fluid in the pelvis, movement of peritoneal fluid in the abdominal cavity in clockwise direction leading to sub-phrenic implantation [5].

Cytoreductive surgery (CRS) is used with hyperthermic intraperitoneal chemotherapy (HIPEC) for treatment of peritoneal metastasis (PM) complicating CRC patient [6]. Administration of chemotherapy through the peritoneal route is based on direct exposure of tumor cells to high concentration of chemotherapy with minimal systemic effect [7, 8].

The aim of this work was to report the prophylactic effect of HIPEC against development of PC after curative resection of CRC in high risk patients.

Multiple risk factors have been identified in literature as being high risk factors for developing PC (Table 1) [9].

MATERIALS AND METHODS

This prospective randomized comparative study was done at department of surgery in Zagazig University Hospitals between Januarys 2013 and June 2014. This research was approved by local ethical committee of our Faculty of Medicine, Zagazig University and Informed consent was obtained from all patients.

All patients were diagnosed as colorectal cancer by complete history taking, clinical examination and full investigations and proved histopathologically to have adenocarcinoma.

Our patients were classified into low and high risk patients for developing PC. Fifty operable high risk patients between 20 and 90 years old were included in this study and had been classified into two equal groups, the first were prepared for undergoing radical surgical resection alone; while the other for radical surgical resection followed by HIPEC.

Preoperative

Preparation of the patients was performed adopting the traditional protocol for colonic preparation beginning 48 hours preoperatively in the form of; stopping all forms of solid food and any fluid with residue to be taken

Table 1: Characteristics of high risk patients for developing peritoneal carcinomatosis [9]

- Concomitant peritoneal carcinomatosis
- Synchronous Ovarian metastasis
- Positive cytology
- Invasion of adjacent organ
- Invasion of serosa
- Perforated cancer

orally and only plain fluids were allowed to be taken and stopped just four hours preoperatively. They were giving metronidazole 500 mg and neomycin 500 mg tid, doing enema using 500 ml saline 0.9% every eight hours until having clear output and giving manitol 20% orally starting 24 hours preoperatively by a rate of 50 ml/20 min to have the full 500 ml.

Operative

The radical surgical resection was done through a midline incision allowing adequate exploration of the entire abdomen. The abdomen was firstly explored regarding the primary tumor and its relation to the surroundings and excluding the presence of synchronous lesion and liver metastasis. When the above data were confirmed and resection was determined to be done, its limits are determined according to the site of the primary tumor. As a rule, obtaining a longitudinal margin of at least 5 cm from the lesion proximally and at least 2 cm distally with a minimum of 12 lymph nodes within the mesentery is mandatory.

For the HIPEC maneuver following surgery, we used in our study doxorubicin as the chemotherapeutic agent. The dose of the drug was calculated based on the patient's body surface area as follow; doxorubicin 15 mg/m². The dose was reduced by 30% in patients above 60 years of age. The solute we used was dextrose 5% with the dose of 1.5 L/m². As the surgical procedure was going on, the stock container of the HIPEC machine was filled with the calculated amount of dextrose 5% and the digital heater was adjusted to temperature 44° and the solute is allowed to be warmed to that level but the chemotherapeutic agent was not added until then.

After completion of the surgical resection, the abdominal exploratory incision is shortened to allow just the hand of the HIPEC performer to pass through it by temporarily suturing the skin of the excess part of the wound. A thermometer is introduced in the abdomen with 2 catheter; one for the inflow of the heated chemotherapeutic solution and the other to return it back to be reheated to the targeted temperature.

The abdomen was irrigated first by the heated dextrose 5% at 41°:43° before the chemotherapy was added, then after priming the abdomen with heated dextrose the chemotherapy was added. The perfusate now with a temperature of 41°:43° within the abdomen as detected by the thermometer was maintained for 90 min, during which the perfusate was in a cycle of flowing to the patient abdomen and then back to the machine keeping the perfusate at the above temperature for the above period within the abdomen all the time of the procedure.

The performer during that time uses his hand (which was well gloved up to the elbow) to homogenously distribute the perfusate within the abdomen ensuring that the chemo. Perfusate was get in contact with all the organs and the whole peritoneal surface. After the procedure fulfilled its time, the chemo-perfusate was

washed out of the abdomen using 2 L of normal saline 0.9% then the abdomen is closed definitively with the drains in the proper sites

Postoperative

Our patients underwent routine postoperative measures (starting oral feeding and removal of drains) according to the procedure. And followed-up till December 2016 to detect PC (mean follow-up period was 39 months).

RESULTS

The total number 50 patients were included in the study. The baseline demographic criteria of patients were given in Table 2. Twenty-five patients underwent radical surgical resection alone. Twenty-five patients underwent surgical resection followed by HIPEC.

In the surgery followed- by HIPEC group 15 patients were males and 10 were females with age ranging from (36–62) and mean age (50.57), but in the surgery alone group, 14 patients were males and 11 were females, their ages ranged from (38–65) with mean age was (53.53).

Sixteen patients presented with chronic constipation (11 in HIPEC and five in surgery) followed by 14 had abdominal pain (eight in HIPEC and six in surgery) then 10 had bleeding per rectum (three in HIPEC and seven in surgery) and finally 10 had other non-specific symptoms like anemia with its symptoms, anorexia (three in HIPEC and seven in surgery).

Regarding the primary tumor site; 16 patients had right colonic mass (eight in each group), 10 patients had left colonic mass (two in HIPEC and eight in surgery), nine patients had sigmoid mass (seven in HIPEC and two in surgery) and 15 patients had rectal mass (eight in HIPEC and seven in surgery).

Regarding the preoperative serum CEA level; 14 patients had elevated level (6 in HIPEC and 8 in surgery) and 36 patients had normal CEA level.

Regarding the operative data including the limits of surgical resection and the termination of the operation by intestinal anastomosis or permanent stoma, all shown in Table 3. The histopathological examination of the resected specimen including the grading of the tumor and number of lymph node resected also given in Table 3.

Serosal invasion and Invasion of adjacent organ were the commonest risk factors in both groups; Risk factors along both groups summarized in Table 4. Concerning the postoperative complication and early post-operative mortality; the return of bowel habits ($p = 0.021$) needed longer time in HIPEC group, cardiorespiratory complications were commoner in HIPEC group and length of hospital stay was more also in HIPEC group ($p = 0.046$). While other complications showed no statistically significant difference between the two groups. All are shown in Table 5.

Long-term follow-up

The follow-up period of our cases were 30–48 months (mean follow-up period was 39 months) to detect PC recurrence. All patients were followed up by serum CEA

Table 2: Demographic data, presentation, tumor site and pre-operative serum CEA level in both groups

Demographic data, presentation, tumor site and pre-operative serum CEA level		Surgery followed by HIPEC group N(25)	Surgery alone group N(25)	p-value
Sex of patients	Male	15	14	0.774
	Female	10	11	
Mean age (years)		50.57 (36–62)	53.53 (38–65)	0.381
Patient presentations	Chronic constipation	11	5	0.125
	Abdominal pain	8	6	
	Bleeding per rectum	3	7	
	Non-specific symptoms	3	7	
Site of the primary tumor	Right colon	8	8	0.091
	Left colon	2	8	
	Sigmoid colon	7	2	
	Rectum	8	7	
Preoperative serum CEA	Elevated	6	8	0.528
	Not elevated	19	17	

Abbreviations: CEA: Carcinoembryonic Antigen, HIPEC: Hyperthermic Intraperitoneal Chemotherapy

Table 3: Operative and postoperative pathological data

Operative and postoperative data		Surgery followed by HIPEC group N(25)	Surgery alone group N(25)	P Value
Extent of resection	Right hemicolectomy	8	7	0.438
	Left hemicolectomy	2	4	
	Sigmoidectomy	7	2	
	Anterior resection	3	3	
	Abdominoperineal resec	5	7	
No of LN in resected specimen	<12	13	11	0.571
	≥12	12	14	
Grading of the tumor in post-op pathology report	II	9	6	0.354
	III	16	19	

Abbreviations: HIPEC: Hyperthermic intraperitoneal chemotherapy, LN: lymph nodes

Table 4: Risk factors along both groups

Risk factor	Surgery followed by HIPEC group N(25)	Surgery alone group N(25)	P Value
Concomitant peritoneal carcinomatosis	2	2	1
Synchronous Ovarian metastasis	1	1	1
Positive cytology	2	2	1
Invasion of adjacent organ	6	10	0.225
Invasion of serosa	12	8	0.248
Perforated cancer	2	2	1

Abbreviations: HIPEC: Hyperthermic intraperitoneal chemotherapy

Table 5: Postoperative morbidity and mortality

Postoperative follow-up and complications	Surgery followed by HIPEC group N(25)	Surgery alone group N(25)	P Value
Mean period for regaining bowel habits/day	2.5±0.5	1.3±0.9	0.021
Cardiorespiratory complications	6	1	0.042
Mean period of the length of hospital stay/day	10.3 ± 3.3	7.1 ± 1.8	0.046
Wound complications	4	1	0.157
No liver, kidney or bone marrow dysfunction nor intestinal anastomosis leakage were recorded in either groups			
Early postoperative mortality	0	0	1

Abbreviation: HIPEC: Hyperthermic Intraperitoneal Chemotherapy

every three month and enhanced pelvi-abdominal CT annually or when re elevation of CEA was done, no case of recurrence was recorded in the HIPEC group while four cases were recorded in the surgery alone group (p= 0.038); three of them had preoperatively elevated serum CEA (p= 0.015). Recurrence was occurred on 11, 12, 15 and 20 months postoperative. Recurrence was occurred in the form of appearance of peritoneal nodules (diagnosed by pelvic-abdominal CT scan) and re-elevation of CEA which was normalized after surgery if was elevated preoperatively. Long-term follow-up is recommend to evaluate up to 10 years recurrence and survival rates of those patients.

DISCUSSION

The essential fact stating that peritoneal carcinomatosis carries a dismal prognosis for CRC disease if present, synchronous PC is diagnosed at primary surgery in about 5–10% of patients undergoing CRC resection. Additionally up to 20–50% of patients undergoing curative intent CRC resection can go on to develop disease recurrence limited to the peritoneal cavity [2, 3].

Our work aimed to evaluate safety and efficacy of HIPEC procedure in prevention of PC recurrence after radical resection of CRC in high risk patients.

Following-up the patient in both groups, those had HIPEC following radical surgery compared to those had surgery alone, It was noted that bowel regained its motility more rapid in surgery alone group than surgery plus HIPEC. This may be explained by the transient hypokalemia noted in most of those had HIPEC. These findings are in agreement with those found by Hompes et al. [10] and Klaver et al. [11], but on contrary Varban et al. [12] and Kianmanesh et al. [13] reported insignificant percentage for those with prolonged ileus after HIPEC.

The cardiorespiratory complications were recorded significantly more in surgery plus HIPEC group. This significant percentage of cardiac complications in the HIPEC group could be explained by hidden underlying cardiac function borderline impairment that could not be discovered by preoperative investigation but could be retrogradely concluded upon occasion of the complication. These findings go with those obtained by Klaver et al. [11], Varia et al. [14] and Yan et al. [15] But both Glehen et al. [16] and Hompes et al. [10] reported insignificant percentage of these complications.

The cases that underwent surgery plus HIPEC stayed for a longer period in the hospital compared to those underwent surgery alone and this difference is significant and mostly it is attributed to the need of some cases for ICU admission for the sake of cardiorespiratory complications. These results was quite similar to the study made by López–Basave et al. [17] who had nearly the same duration of hospital stay as ours but in the study made by Shimizu et al. [18] the duration was considerably longer for HIPEC group.

In our study, there was no significant difference between the two groups of the study regarding occurrence of wound dehiscence. These findings were similar to Varban et al. [12]. We recorded no case of organ dysfunction mostly due to proper patient selection for application of HIPEC. Verwaal et al. published two studies [19, 20] in which he recorded none of these complications. In other studies like Glehen et al. [16] and Varban et al. [12] small percentage of the above complications were recorded. But higher percentage were recorded with Pilati et al. [21] and Shen et al. [22].

In our study no death occurred early postoperative or during follow-up period in our patients. In the study done by López–Basave et al. [17], two out of 39 patients died one due to reactionary hemorrhage four hours postoperative and the other due to massive pulmonary thromboembolism although the same researcher in earlier study [23] recorded no early postoperative mortality at all.

In our study, we followed the patients up for 2.5 years to detect PC recurrence using enhanced pelvi abdominal CT scan. We found four patients from those undergone surgery alone had recurrent PC which represented significant rate of recurrence with three of these four cases had elevated preoperative serum CEA).

On contrary none of those undergone surgery followed by HIPEC had PC recurrence after 2.5 years although six patients of this group had elevated preoperative serum CEA. This can ascertain the prophylactic effect of HIPEC against PC recurrence after radical resection of colorectal cancer even when preoperative serum CEA is elevated.

Almost all studies reported the same prophylactic effect of HIPEC following radical resection of colorectal cancer on PC recurrence provided that no synchronous PC is present at the time of primary tumor resection. In a systematic review by Honore et al. (this review for studies published between 1940 and 2011) [24] reported that surgery alone has rate of recurrence 11.6% compared to no recurrence when HIPEC is done.

CONCLUSION

Based on this study, we conclude that hyperthermic intraperitoneal chemotherapy (HIPEC) following surgery has a prophylactic effect against the peritoneal carcinomatosis recurrence and that will consequently affects patient overall survival and disease free survival positively. This procedure is considered a safe one as long as the patient is properly selected based on proper investigations and preparation; but still there is possibility of some complications to occur either systemic in the form of organ dysfunction which almost is reversible, or local complication in the form of wound dehiscence which also is correctable by improving the general healing parameters and later secondary repair.

Author Contributions

Mohamed I. Abdelhamid – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Mohammed Alkilany – Substantial contributions to conception and design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Osama Abd Elaziz – Substantial contributions to conception and design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Mohamed Abdelgawad – Substantial contributions to conception and design, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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