Clinical Analysis of Gut Barrier Dysfunction in Patients with Advanced Colorectal Cancer Undergoing Cytoreductive Surgery and HIPEC

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Research Article

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Abstract

Introduction: Hyperthermic intraperitoneal chemotherapy combined with cytoreductive surgery is a preferred treatment option for advanced colorectal cancer patients. However, little is known whether the HIPEC can cause the damage of gut barrier function.

Methods: A total of 123 patients underwent surgical resection for advanced CRC. Sixty-five patients were treated HIPEC after cytoreductive surgery whereas 58 patients underwent surgery only. Gut barrier function were evaluated using the expression of serum DAO/D-Ia/ET on D1/D5/D10 after surgery. Both groups were compared for patient characteristics, perioperative data and gut barrier function. Moreover, rats received intraperitoneal injection of retetrexed to observe possible changes of colonic structure under optical microscope.

Results: Both groups were comparable with respect to general patient characteristics and post-operative complications. The HIPEC+CRS group was associated with a higher postoperative serum level of DAO/D-Ia on D1/D5 ($p < 0.05$) and ET on D5 after surgery ($p < 0.05$) than that of the surgery only group. Ten days after surgery showed no statistical difference between the 2 groups ($p > 0.05$). A large area structure disorder, epithelial necrosis, glandular deformation and a large number of lymphocytes infiltration was found in the lamina propria in animals received intraperitoneal injection of retetrexed.

Conclusion: In this study, CRS combined with HIPEC does have but only an irreversible impact on gut barrier for advanced CRC patients.

Introduction

Colorectal cancer (CRC) is a common digestive tract tumor in China, and is ranked fourth and fifth in tumor morbidity and mortality, respectively[1]. Although CRC radical resection is a preferred solution, local recurrence and distant metastases are sometimes unavoidable [2]. Lymph node metastasis, hematogenous dissemination and local implantation, are the main causes of death for CRC patients. In the condition of advanced CRC, the exutive malignant cell will become free cancer cells which can induce abdominal cavity implantation and directly correctly with poor prognosis. Recently, the hyperthermic intraperitoneal chemotherapy(HIPEC) was widely reported used in the treatment for advanced CRC[3, 4]. HIPEC is a high selective local chemotherapy with the advantages of cooperativeness hyperthermia and chemotherapy, limited body toxicity side effect as the presence of "plasma-peritoneal barrier", maintained a high drug concentration and large area effect in abdominal and pelvic cavity

For patients with advanced colorectal cancer, radical resection with HIPEC is a safe procedure with a predictable longer survival rate outcome. It is, however, not entirely free of complications. Gastrointestinal reaction and myelosuppression are not uncommon and can be quite problematic. Most surgeons contend that during HIPEC, bowel mucosa injury caused by chemotherapeutics and temperature damage is a relative contraindication for its use. Patients may develop nausea, vomiting, diarrhea, severe mucosal necrosis, bleeding, resulting in the discontinuation of HIPEC and break clinical efficacy.

Few cohort studies have been published on the topic about the relationship between HIPEC and gut barrier. The aim of the present study was to describe the outcomes of intestinal function, in one 3a hospital, of patients with advanced CRC, with a special focus on gut barrier.

Materials And Methods

Patient Selection and Design

According to the HIPEC treatment or not at WHZXY, patients were all located into two groups. Patients received only surgical resection (Group 1). Patients received HIPEC after surgery (Group 2). From January 2017 to December 2019, 123 advanced CRC patients were admitted to the central hospital of Wuhan, Tongji medical college of Huazhong University of Science and Technology. Clinical data from patients who underwent HIPEC were recorded. All preoperative and postoperative data were reviewed by using institutional surgical database involved in this research. The clinical pathologic data, outcomes after surgery were shown in Table 1. The preoperative and postoperative gut barrier related data were shown in Table 2.

Table 1
General information and surgical results

Variables	CRS + HIPEC	CRS	<i>p</i>
	(n = 65)	(n = 58)	
Age(years)	65.9 ± 10.32	62.7 ± 12.69	0.730*
Gender(male/female)	31/34	34/24	0.363†
Time of CRS(min)	254.9 ± 90.67	226.2 ± 101.89	0.100*
Blood loss(ml)	258.7 ± 91.3	210.5 ± 63.4	0.056*
Complications	10/65	13/58	0.318†
Anastomotic fistula	3	2	
Anastomotic bleeding	1	2	
Pneumonia	4	5	
Intestinal obstruction	2	4	
Time to sips of water(d)	4(3–5)	4(3–6)	0.676‡
Time to liquid diet(d)	8(6–9)	8(6–10)	0.883‡
Postoperative stay(d)	13.9 ± 2.69	14.1 ± 3.44	0.833*
Data are presented as number of patients (%) or mean ± SD or median (range), as appropriate..			
* Student t-test †Chi-square test ‡ Mann-Whitney U test			

Table 2
Comparison of gut barrier function related parameters

Variables	Time	CRS + HIPEC (n = 65)	CRS (n = 58)	<i>p</i>
DAO	Pre-surgery	6.6 ± 2.48	6.4 ± 3.34	0.682
	D1	28.9 ± 9.30	23.8 ± 9.76	0.003*
	D5	21.7 ± 6.61	17.9 ± 8.68	0.007*
	D10	7.7 ± 3.24	6.59 ± 3.17	0.069
D-Ia(g/l)	Pre-surgery	9.2 ± 4.18	9.7 ± 3.87	0.495
	D1	32.7 ± 10.72	28.4 ± 10.36	0.027*
	D5	21.4 ± 4.71	18.8 ± 6.68	0.014*
	D10	10.2 ± 3.82	9.3 ± 4.49	0.226
ET(g/l)	Pre-surgery	9.4 ± 4.24	10.3 ± 5.00	0.309
	D1	15.1 ± 4.78	13.5 ± 4.25	0.051
	D5	26.2 ± 8.38	22.8 ± 6.52	0.015*
	D10	13.7 ± 5.53	13.5 ± 5.77	0.841
Data are presented as median ± standard deviation,*represents <i>p</i> < 0.05				

The inclusion criteria included (1) advanced CRC without distant metastases (2) normal bone marrow function and no contraindication of chemotherapy (3) no history of preoperative radiotherapy and/or chemotherapy (4) Cancer has spread through the the serosa (outermost layer) of the colorectal wall.

The exclusion criteria contained (1) extensive intraperitoneal adhesions due to various causes (2) poor healing factors such as edema, ischemia and tension in the anastomosis (3) patients with intestinal obstruction ;(4) patients with significant liver and kidney dysfunction (5) severe cardiovascular diseases(6) unstable vital signs in patients and cachexia patients.

HIPEC strategy

When the infusion chemotherapy solution (raltitrexed 4mg completely dissolved in 3000 ml saline) is heated to 40°C with a HIPEC instrument(Fig. 1), open the upper end of the abdomen two times The inlet valve of the perfusion tube was injected into the abdominal cavity with the flow rate of 200–400 ml/min. After the patient adapted to the temperature, Then continued to heat, the temperature in the abdominal cavity was stabilized at 43°C through the temperature control system, and the circulation was continued for 60 minutes. According to the patient's tolerance, the perfusion flow rate was controlled at any time, and the volume of abdominal internalization solution was controlled at 2000–2500 ml. After perfusion,

about 1000–1200 ml of perfusion fluid was placed in the abdominal cavity, and the perfusion tube was connected with the drainage bag, so that the residual perfusion fluid in the abdominal cavity was released slowly, once a day for 2 times.

Alimentation protocol after colorectal surgery

After the operation, the patients received total parenteral nutrition via the central vein. TPN with a total fluid volume of 50 ml/kg/d and a temperature of 30 kcal/kg/d was required. The reasonable proportion of fat milk and glucose was in a ratio of 1:1-0.4:0.6. Protein was supplied at 1-1.2 g/(kg. d). It was necessary to add appropriate vitamins, trace elements and electrolytes to maintain the body balance of water and electrolytes. The infusion speed was controlled by a medical infusion pump to ensure the safety of transfusion within 24 h. The patients were given a continuous TPN strategy for 3 days, half of the total on day 1, and the total amount starting on day 2. All the patients received oral dietary after recovery of intestinal function.

Evaluation of intestinal barrier markers

Serum biochemical indicators, including diamine oxidase (a biomarker of intestinal barrier permeability), D-lactate (a biomarker of intestinal mucosal damage) and endotoxin (a biomarker of bacterial translocation), were measured using an enzyme-linked immunosorbent assay (ELISA) via an intestinal barrier analysis system (Diamine oxidase, Lactic acid, Bacterial Endotoxin Assay kit, JY-DLT, Beijing, China) as instructed by the manufacturer. The assay consisted of a biochemical analyzer kit reagent and terminal data analysis. The range of normal values was as follows: DAO < 10 u/L and D-lactate < 15 mg/E, and endotoxin < 20 u/L. Abnormal was defined as a single or multiple indexes are elevated.

Animal experiment

Forty Wistar rats were randomly divided into two groups. group A: blank control group (Control); group B: HIPEC model group. Day1\Day3 HIPEC group received intraperitoneal injection of retetrexed, dose of 8 mg/kg, blank control group using the same amount of normal saline intraperitoneal injection. On the fifth day, rats involved in this study were killed to observe changes in colonic structure under optical microscope.

Statistical Analyses

Statistical analyses were performed using SPSS software, version 21.0. Variables that fulfilled the criteria for normal distribution (e.g. DAO/D-la/ET) were analyzed using the Student's t test; A chi-square test was used, wherever appropriate. A difference between groups with a p value of < 0.05 was considered statistically significant

Results

No significant differences were found between groups regarding demographic or clinical characteristics (Table 1). We considered the cohort is suitable for comparing the outcomes between the Group 1 and Group 2. No mortality was found during the whole study cycles. The total anastomotic complications involved in this study were 6.5%. The common complications directly related to surgery were pneumonia (8.9%) ,ileus (4.8%) .No statistical significance was confirmed between the two groups. No differences were observed between groups with respect to anastomotic leakage directly linked to HIPEC. This created the attribution of the success (or otherwise) of the operation to the intrinsic properties of the particular chemotherapy. Moreover, there were also no serious complications such as intestinal perforation, adhesive intestinal obstruction during HIPEC on patients with advanced colorectal cancer in Group 2.Only one case in Group 2 complained of pelvic hemorrhage (cured by hemostatic drugs), indicated that HIPEC after radical resection was safe and feasible.

Gut barrier function was assessed in relation to the expression of serum level of DAO/D-Ia/ET. During the initial days after surgery, the DAO (D1: 28.9 ± 9.30 vs. 23.8 ± 9.76 $P = 0.003$, D5: 21.7 ± 6.61 vs. 17.9 ± 8.68 $P = 0.007$; Fig. 2) and D-Ia (D1: 32.7 ± 10.72 vs. 28.4 ± 10.36 $P = 0.027$, D5: 21.4 ± 4.71 vs. 18.8 ± 6.68 $P = 0.014$; Fig. 2) were found higher in the HIPEC group than that in the surgery only group. Similar outcomes were observed on D5 after surgery for ET (26.2 ± 8.38 vs. 22.8 ± 6.52 $P = 0.015$ Fig. 2). However, ten days after surgery, these differences attenuated and did not reach significance anymore (D10 DAO: $p = 0.069$; D-Ia: $p = 0.226$; ET: $p = 0.841$ Fig. 2), probably due to general improvement of the patients in the recovery of intestinal function.

For animal experiments, in the normal control group, the epithelium was intact, the glandular rules were not destroyed, and the structure was normal and distinct. The sections of HIPEC group showed large area structure disorder, epithelial necrosis, glandular deformation and a large number of lymphocytes infiltration in the lamina propria.(Fig. 3).These findings demonstrated a negative association between the impaired gut barrier and intraperitoneal chemotherapy.

Discussion

The underlying cause of poor 5-year survival for advanced CRC after radical resection is the formation of peritoneal metastases. It is mostly through two pathways. One is that tumor cells can penetrate the visceral layer of peritoneum and directly invade adjacent organs or tissues, these uncontrollable cells can become "seeds" to form peritoneal implant metastasis. This increased tumor exposure is associated with increased peritoneal metastasis morbidity. Another, and perhaps most easily overlooked cause for the formation of peritoneal metastases, is the fact that lymphatics and blood vessels located on the operative area were cut off during surgery, after that, blood or lymphatic fluid mixed with tumor cells flow into the abdominal cavity. Additionally, pull and squeeze tumor tissue often means shedding of tumor cells move through the intestinal cavity stump cells and therefore high risk for implant metastasis.

The clinical application of HIPEC was first described in 1988 by Fugimoto[5].In a word, It combined hyperthermia (heating saline) with concentration of anticancer drugs to carry out total intra-peritoneal

chemotherapy. HIPEC has revolutionized the management of patients with advanced colorectal cancer. It is in large part because of this new treatment can effectively kill the potential peritoneal free cancer cells[6]. Vic J Verwaal[7] reported that cytoreduction followed by HIPEC improves survival in patients with peritoneal carcinomatosis of colorectal origin. In another randomized multicentre trial[8], adjuvant HIPEC is assumed to reduce the risk of peritoneal carcinomatosis in patients with T4 colorectal cancer and may prolong overall survival. However, research into the chemotherapeutic drugs that have a high toxicity to rapidly dividing cells in advanced CRC has resulted in the identification of numerous organs or tissues that are also injured in HIPEC. Many of these, include intestinal epithelial cells, hematopoietic cells and lymphocytes, etc.[9].

Indeed, in most clinical trials and animal experiments, the application of HIPEC is associated with the low incidence of postoperative complications, low mortality, and better survival rate [10–12]. The present study also supports this notion. In this study, however, we want to explore whether HIPEC does cause irreversible damage on gut barrier. Theoretically, hyperthermia combined with chemotherapy usually lead to abnormal expression and redistribution of tight junction proteins in intestinal epithelial cells[13, 14]. The penetration depth of chemotherapeutic drugs can be deepened from 1 ~ 2 mm to 5mm under a high temperature of 43°C during the HIPEC process, which also can aggravate the intestinal mucosal barrier damage[15]. Few studies reported the gut barrier dysfunction related to HIPEC. Hence, we performed HIPEC after CRS and compared its influence on gut barrier with that of conventional strategy. Obviously, surgical resection can cause the gut barrier damage. The novel strategy (CRS + HIPEC) appears to bring out a higher expression of postoperative serum level of DAO, DLA except ET in patients with advanced CRC. Interestingly, no significant increased serum ET level was found in both the groups on the first day after treatment ($P > 0.05$), bowel preparation may play a key role. Absolutely, rapid bowel preparation causes short-term changes of fecal microbiota, the amount of total bacteria sharply decreased to a low level[16]. Ten days after surgery, parameters related to gut barrier tend to normal. In animal experiments, compared with the control group, the bacterial translocation of lymph nodes and liver in raltitrexed chemotherapy group increased significantly. After a observation through the optical instrument, a large area structure disorder, epithelial necrosis, glandular deformation and a large number of lymphocytes infiltration was found in the lamina propria can be found; This finding is in line with the results reported by Trepanier JS [17]. Our clinical data and animal experiment show that HIPEC can indeed increase gut permeability and lead to reversible gut barrier dysfunction.

It has been suggested that HIPEC might lead to poor results like nausea, anastomotic leakage, and intractable abdominal distention[18, 19]. In general, CRS + HIPEC appear to work well. There was no HIPEC-related mortality in this study. Further, there was no evidence of longer duration of hospitalization, high incidence of postoperative ileus or anastomotic leakage ($p > 0.05$ for all). This finding is consistent with the results reported by Van Eden[20]. There were certain limitations in our research. Firstly, the short follow up period, was a limitation to elucidate the long term adverse effects related to HIPEC and gut barrier. Secondly, advanced CRC without distant metastasis contained severe stages like IIB, IIIA, IIIB and III C. This research was failed to exclude the exactly adverse effect of HIPEC on gut barrier in different clinical

stages. Another potential interference factor is that only retetrexed is involved, other chemotherapy drugs like cisplatin combined with fluorouracil and how they work is unclear.

Conclusion

Our study highlights the gut barrier dysfunction in patients with advanced CRC received HIPEC. We saw temporal changes in most subjects and try to disparate results from animal experiments. We conclude that CRS combined with HIPEC does not have an irreversible impact on gut barrier in all subjects, although more randomized controlled clinical studies are essential to verify the influence of HIPEC on gut barrier in colorectal disease.

Declarations

Statements

Acknowledgement (optional)

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Availability of data and materials

All data generated or analysed during this study are included in this article. All data are fully available without restriction.

Statement of Ethics

The board of the Human Research Ethics Committee of the central hospital of Wuhan approved the study protocol (YB16A02) after institutional review. All patients were provided written informed consent to participate prior to surgery. Ethical approval and study protocol was given by the medical ethics committee of the central hospital of Wuhan involved in this research. All procedures performed in

this study involving human participants were conducted in accordance with Chinese ethical standards and the 2008 Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Concept and design: CW; search and collection of data: LLP and JXM; analysis of data and interpretation: CW and LLP; tables and figures: LLP; writing the manuscript and review: CW.

Consent for publication

Written informed consent was obtained from the patients for publication of this research and any accompanying images.

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Figures

Figure 1

Patient received the second hyperthermic intraperitoneal chemotherapy in inpatient ward As shown in Figure 1, four special HIPEC tubes (blue tube inlet, red tube outlet) were placed in the spleen fossa, the liver diaphragm junction, the left and right pelvic cavity respectively, and the ipsilateral tubes crossed up and down to ensure a normal internal and external circulation of chemotherapeutic infusion fluid.

Figure 2

Condition of gut barrier function for the 2 procedures at different times after operation. As shown in Figure 2, D1 and D5 after surgery, the serum level of DAO and D-la were found higher (represented by mean $\pm$ SD) in the HIPEC group than in the surgery only group ($p < 0.05$). D5 after surgery, the serum level of ET was found higher in the HIPEC group ($p < 0.05$). D10 after surgery showed no statistical difference between the 2 groups ($p > 0.05$).

Group A

Group B

Figure 3

Differ colonic morphology of rat in HIPEC model and control group As shown in Figure 3, in the normal control group, the epithelium was intact, the glandular rules were not destroyed, and the structure was normal and distinct. However, the sections of HIPEC model group showed a large area structure disorder, epithelial necrosis, glandular deformation and a large number of lymphocytes infiltration was found in the lamina propria.