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ORIGINAL ARTICLE

Preliminary security investigation and short-time follow-up of intraoperative intraperitoneal chemotherapy with lobaplatin for advanced colorectal cancer

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Abstract

Objective The aim of this study was to conduct a security assessment of intraoperative intraperitoneal chemotherapy using lobaplatin for advanced colorectal cancer.

Methods From February 2015 to February 2016, 143 patients with colorectal cancer who underwent surgery in our department were selected prospectively. All patients were randomly screened and enrolled into the intraperitoneal chemotherapy (IPC) (74 cases) and control (69 cases) groups, depending on the distribution of cases in the random table. In the trial group, patients were administered 40 mg lobaplatin by intraperitoneal implantation intraoperatively, together with intravenous chemotherapy post-operatively using a typical FOLFOX strategy with oxaliplatin, fluorouracil, and leucovorin. In the control group, only FOLFOX was administered. Bowel function recovery time, adverse reactions and complications, and pre- and post-chemotherapy laboratory examinations were compared. In addition, a 5-year-long follow-up was performed.

Results Recovery times of bowel function were 73.5 ± 9.7 h and 74.8 ± 10.3 h respectively, and the difference was not significant ($P > 0.05$). Wound fat liquefaction was observed in five cases in both groups (6.8% *vs*. 7.2%, $P > 0.05$). The outcomes of nausea and vomiting (57 cases, 77.0% *vs*. 50 cases, 72.5%), constipation (43 cases, 58.1% *vs*. 36 cases, 52.2%), and diarrhea (5 cases, 6.8% *vs*. 5 cases, 7.2%) were not statistically significant (all $P > 0.05$). Indices of white blood cell count, blood platelet count, and hepatorenal function were not significantly different (all $P>0.05$) neither post-operatively nor post-chemotherapy. The 5-year survival rate was not significantly different between the groups (58.1% *vs*. 56.5%, $P > 0.05$).

Conclusion Intraoperative chemotherapy with lobaplatin for advanced colorectal cancer is safe and tolerable.

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Key words: intraoperative intraperitoneal chemotherapy; lobaplatin; colorectal cancer

Chemotherapy can be divided into systemic and loco-regional therapies, based on the method of administration. Intraperitoneal chemotherapy (IPC) is a local application that has received increasing attention at home and abroad for advanced gastrointestinal malignancies [1-3]. The theoretical rationale of IPC was first described in 1978, which demonstrated that intraperitoneal administration of chemotherapeutic drugs for ovarian cancer led to a higher drug concentration and longer half-life in the peritoneal cavity than intravenous administration [4]. Intraperitoneal chemotherapy presents an exciting consequence in the field of gynecological oncology as it promotes both progression-free survival and overall survival in advanced ovarian malignant tumors [5]. Due to this delightful condition, the National Comprehensive Cancer Network (NCCN) guidelines now recommend IPC for patients with stage III epithelial ovarian cancer after optimal debulking surgery [6]. Intraperitoneal administration of antitumor drugs is also performed in gastrointestinal oncology, and IPC for gastric and

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rectal cancers has been researched in full swing [7, 8]. IPC can expose free tumor cells or residual tumor tissue to therapeutic drugs directly and immediately, which would not only enhance the anti-cancer efficiency but also relieve the systemic adverse reactions due to the peritoneum-plasma barrier [9]. Currently, a few drugs commonly used in IPC primarily include cyclophosphamide, platinum, mitomycin, and fluorouracil sustained-release preparations [10] for abdominal malignant tumors. Lobaplatin is one of the third-generation platinum drugs, which is used in gynecologic and thoracic tumors by serous-cavity injection in lung cancers and oophoromas, but few investigations have been conducted on gastrointestinal carcinomas. The efficacy of this treatment is not known. Hence, security assessment data are limited. This study was mainly aimed at observing the safety of intraoperative IPC with lobaplatin in advanced colorectal cancer, and the 5-year survival rate was also observed to speculate whether this strategy plays a role in improving survival time.

Materials and methods

Patients

A total of 143 colorectal cancer patients (Table 1) undergoing surgical operations were enrolled in this study between February 2015 and February 2016 in the Department of Gastrointestinal Surgery, the Affiliated Hospital, Southwest Medical University. After signing informed consent, they were randomly allocated into an experimental group of 74 patients and a control group of 69 patients, according to the case distribution random table. This study was approved by the Ethics Committee of our hospital. Tumor stage classification was performed according to the 8th edition of the AJCC Cancer Staging Manual [11]. The inclusion criteria were as follows:

(1) The patients had not undergone abdominal surgery before, and did not have diabetes, hyperthyroidism, hypothyroidism, post-operative hypokalemia, or any other diseases that could affect gastrointestinal function.

(2) Tumors affected or penetrated the serous membrane layer and could undergo radical or palliative resection.

(3) Blood indicators met the basic requirement for chemotherapy: white blood cell count (WBC) > 3.0×10^9/L, blood platelet count (PLT) > 100×10^9/L, hemoglobin (Hb) > 100 g/L, and indices of hepato-renal function, such as alanine aminotransferase (ALT), aspartate transaminase (AST), and creatinine (Cr.) were normal.

(4) The age range was from 55 to 80 years.

Table 1 The general materials of this 143 patients, [*n* (%)]

	Group A	Group B	*P* value
No. of patients	74	69	
Gender			
Male	42 (56.8)	40 (58.0)	> 0.05
Female	32 (43.2)	29 (42.0)	
Age (years)	59.4 ± 10.8	56.9 ± 10.2	> 0.05
Site			
Colon	31 (41.9)	28 (40.6)	> 0.05
Rectum	43 (58.1)	41 (59.4)	
Stage			
III	68 (91.9)	64 (92.8)	> 0.05
IV	6 (8.1)	5 (7.2)	
Time (min)	136.8 ± 14.7	134.5 ± 15.8	> 0.05
Operation selection			
Radically	67 (90.5)	63 (91.3)	> 0.05
Palliatively	7 (9.5)	6 (8.7)	

Group A means intraperitoneal chemotherapy group, Group B means the control group

Protocol treatment

All the patients underwent surgical resection. The operations were performed by the same set of surgeons who possessed the necessary qualifications and ample experience. Various methods were carried out according to the practical situation during the operation, such as left, right-half, and transverse colon resection, low anterior resection (LAR, Dixon), abdominoperineal resection (APR, Miles) for rectal cancers, as well as Hartmann and colostomy.

In the IPC group, 40 mg lobaplatin (Hainan Changan International Pharmaceutical Co., Ltd.) was mixed with 20 mL 5% glucose at room temperature. The mixed solution was then extensively infused into the washed cavity in the IPC group. In the control group, the same quantity of room-temperature 5% glucose, with no other composition, was infused into the peritoneal cavity. In both groups, the drainage tube was fixed at the proper site of the abdominal wall and kept off for 4 to 6 h after the operation. As soon as the operated patient exhausted, defecated, and could have some liquid diet, he or she would receive systemic chemotherapy using the FOLFOX scheme with oxaliplatin (Jinghua Pharmaceutical Group Co., Ltd.), fluorouracil, and leucovorin (Jiangsu Hengrui Medicine Co., Ltd.), according to the NNCN guidelines for colorectal cancer [12].

Observation indices

Immediately after the operation, daily observations were conducted including temperature monitoring, bowel sound auscultation, exhaust and defecation inquiry, and observation of drainage condition. Early in the morning before and after intravenous chemotherapy, hematological indices, including ALT, AST, and Cr, were retested hollowly.

Statistical analysis

All data were analyzed using the professional statistical software SPSS 20.0. If the data were not normally distributed, we used the median (quarterback spacing) [M (P25, P75)] for description and using rank and inspection, we used an inspection level of α= 0.05. If the data was normally distributed, we used the mean ± standard deviation ($\bar{\chi} \pm s$) to represent the parametric test using the *t*-test and Fisher's exact probability method.

Results

Bowel function recovery time

The recovery times of bowel function in the IPC and control group were 73.5 ± 9.7 h and 74.8 ± 10.3 h, respectively, with no significant difference ($P > 0.05$). The drainage volume was not significantly different until the tubes were pulled out (160 ± 20 mL *vs.* 150 ± 30 mL, $P > 0.05$). Tubes were pulled out after bowel function recovery and patients defecated without fistula, and the time to abandon the tubes were 96 ± 12 h post-operatively.

Complications of surgery plus IPC (Table 2)

Each group had six cases of incisional fat liquefaction (6.8% *vs.* 7.2%, $P > 0.05$), some of which developed into infection (three cases vs. two cases). These complications were controlled and cured by squeezing the incisions, taking out sutures, enlarging the incisions, debriding necrotic tissues, draining liquid, and finally placing a secondary suture. Fortunately, no IP or systemic infections occurred. Some patients in the two groups experienced abdominal distension, nausea, and vomiting (three cases vs. two cases), and the symptoms disappeared after removal of the nasogastric tube one to three days after surgery. Five patients (three cases vs. two cases) who were not exhausting and defecating five days after surgery in the two groups were considered to have bowel obstruction. One patient in the therapy group underwent exploratory laparotomy because of the invalidation of expectant treatments, which ultimately proved to be an adhesive intestinal obstruction. However, the rest were cured via non-surgical treatments and recuperated three to four days after treatment.

Side effects and adverse reactions (Table 3)

During intravenous chemotherapy in the IPC and control groups, there was occurrence of nausea and vomiting (57 cases, 77.0% *vs.* 50 cases, 72.5%), constipation (43 cases, 58.1% *vs.* 36 cases, 52.2%), and diarrhea (5 cases, 6.8% *vs.* 5 cases, 7.2%), and there was no statistical significance (all $P > 0.05$). All of these side effects vanished after chemotherapy or were cured by

Table 2 Postoperative complications, [*n* (%)]

Group	Patients (*n*)	Nausea and vomiting	Constipation	Diarrhea	Poor wound healing		Bowel obstruction	Anastomotic fistula
					Fat liquefaction	Infection		
Group A	74	57 (77.0)	43 (58.1)	5 (6.8)	5 (6.8)	3 (4.1)	3 (4.1)	0
Group B	69	50 (72.5)	36 (52.2)	5 (7.2)	5 (7.2)	2 (4.3)	2 (2.9)	0

Group A means intraperitoneal chemotherapy group, Group B means the control group

Table 3 Haematological indexes before and after IPC and IV chemotherapy

Group	*n*	WBC (× 10^9/L)	PLT (× 10^9/L)	AST (U/L)	ALT (U/L)	GR (μmol/L)
Preoperative						
Group A	74	6.56 (4.7–8.3)	137 (118–183)	22.4 (9.7–29.5)	15.8 (9.3–19.4)	67.1 ± 10.6
Group B	69	6.9 (5.4–7.9)	140 (120–197)	20.2 (11.8–28.4)	16.2 (11.3–21.7)	66.6 ± 9.8
P value		> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
Postoperative[a]						
Group A	74	9.3 (8.1–12.9)	135 (128–207)[b]	27.8 (12.8–33.1)[b]	31.1 (14.3–38.5)[b]	50.5 ± 12.4
Group B	69	9.6 (6.7–13.8)	152 (130–217)[b]	26.2 (13.4–33.6)[b]	28.2 (15.4–36.2)[b]	54.9 ± 14.6
P value		> 0.05	> 0.05	> 0.05	> 0.05	> 0.05
Post-chemotherapy						
Group A	74	5.1 (4.2–6.7)	114 (100–167)[b]	33.7 (19.7–49.8)[b]	37.8 (23.2–45.2)[b]	86.2 ± 10.6[b]
Group B	69	5.3 (3.8–6.1)	115 (104–171)[b]	35.6 (22.6–51.1)[b]	38.2 (24.5–52.1)[b]	91.4 ± 9.4[b]
P value		> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Group A means intraperitoneal chemotherapy group, Group B means the control group; [a] These data were recorded just the day before intravenous chemotherapy, that was also pre-chemotherapy; [b] Compared with preoperative data in each group internally *P* value < 0.05

symptomatic treatment. In each group, when compared with pre-operative levels, the post-operative levels of ALT, AST, Cr, WBC, and PLT were significantly increased, and the difference was statistically significant ($P < 0.05$). However, the difference between the two groups was insignificant ($P > 0.05$).

Follow-up results (Table 4)

A few patients missed follow-up and died every year since the second year post-operatively during the 5-year follow-up period. The 1-, 3-, and 5-year survival rates were similar, but the differences were not significant (all $P > 0.05$).

Discussion

The most common reason why intestinal tumors plant, metastasize, and recur after operation is that malignant cells fall into the abdominal cavity and microscopic cancer remains in the cavity [13, 14]. Cancer cells can drop into the abdominal cavity when they invade the serosa of the intestinal tract as the adhesive force among the cells weakens. In addition, they can also come from micrometastases in the lymphatic or blood circulation system. Exfoliation and spreading of tumor cells can be intraperitoneal and transperitoneal and tend to follow the circulatory path of the peritoneal fluid. These behaviors lead to peritoneal carcinomatosis (PC) or peritoneal metastasis (PM), which is detected synchronously during primary resection in approximately 5% of patients and develops metachronously in 4%–19% of patients with colorectal cancer [15–17]. The reported incidence of PC at autopsy in patients who died from CRC ranges from 40% to 80% [15]. In peritoneal carcinomatosis from non-gynecologic malignancies, including gastric, colorectal, and pancreatic cancer, the median survival time is less than six months [18]. In China, most patients with colorectal cancer are confirmed to be at an advanced stage, which means that there might be many more free cancer cells and micrometastases existing and/or retained in the abdominal cavity. It is impossible to clear all the tumor cells, even by accepted radical resection. However, most of the cells can be eliminated by perioperative chemotherapy and rinsed repeatedly with distilled water.

IPC is a highly selective regional chemotherapy compared with systemic chemotherapy, which has the following advantages: [19–23] (1) It can improve the local drug concentration remarkably and enhance the lethal effect on residual microscopic lesions and cells directly. (2) It can strengthen local anti-cancer effects, since IP drugs are difficult to transit through the peritoneum-plasma barrier, which can also slow down the rapid entry of drugs through the peritoneum and portal system. (3) Drugs are mostly absorbed into the liver via the portal vein system, but only a small part diverts into the systemic circulation, thereby relieving systemic toxicity and reaching the maximum tolerance dose of chemotherapeutic drugs. (4) Drugs can be absorbed through the lymphatic system, which plays a positive role in microscopic metastases remaining in this system. Because of these specific characteristics, IPC has been studied as a third approach to prevent the relapse and metastasis of gastrointestinal malignancies.

Effective drugs used for IPC must have low peritoneal permeability and irritation, strong penetrating power into tumoral tissue, fast plasma ablation rate, high water solubility, and heavy molecular mass. Lobaplatin (D-19466) is a diastereomeric mixture of platinum complexes containing a stable 1, 2-bis (aminomethyl) cyclobutane ligand with lactic acid as the leaving group. Lobaplatin influences the expression of the *c-myc* gene, which is involved in oncogenesis, apoptosis, and proliferation. Lobaplatin is a third-generation platinum with a heavy molecular mass and better peritoneal permeability and irritation. Compared with cisplatin, lobaplatin is considered less toxic, more soluble, and stable in water [24–26]. It possesses the requisite factors to be a useful IP anticancer drug. In January 2003, lobaplatin was licensed to Hainan Tianwang International Pharmaceutical in China [27] and approved for use in clinical anti-tumor therapy for lung cancer, breast cancer, and chronic myelogenous leukemia by the China State Food and Drug Administration (CFDA). Before being approved clinically, lobaplatin was investigated in a series of phase I and II trials overseas [27–29]. The trials demonstrated that lobaplatin was a dose-dependent drug, and it was safer

Table 4 5-year follow-up data

Time post-operatively (years)	Group A				Group B				Anastomotic fistula
	Recurrence/ Metastasis (*n*)	Loss of follow-up (*n*)	Death (*n*)	SR (%)	Recurrence/ Metastasis (*n*)	Loss of follow-up (*n*)	Death (*n*)	SR (%)	
1	0	0	0	100	0	0	0	100	> 0.05
2	3	2	4	94.6	2	2	5	92.8	> 0.05
3	14	3	7	85.1	12	3	6	84.1	> 0.05
4	7	2	9	73.0	9	3	9	71.0	> 0.05
5	10	6	11	58.1	8	5	10	56.5	> 0.05

to administer 5 days of continuous IV push or 72 h of continuous pumping every four weeks with doses ranging from 30 to 60 mg/m^2. The recommended dose was 50mg/m^2, and the maximum tolerated dose was 60 mg/m^2. These studies also revealed that the most common complication was thrombocytopenia, while nausea, vomiting, appetite loss, and leukocytopenia were less frequent.

An increasing number of tumors have been treated with lobaplatin since it was permitted in China, and abdominal cancers, such as gynecological cancers and gastrointestinal cancers, have been treated with lobaplatin. As for gastrointestinal tumors, lobaplatin is effective and has less side effects [27–33]. The reason why we chose lobaplatin as the research object was that this drug was much more stable and was verified to be effective, with fewer side effects for treating colorectal cancer in many trials both in vitro and *in vivo* [27-33].

This research was a randomized control study. The patients who were included strictly agreed with the formulated inclusion criteria, and they were randomly divided into treatment and control groups. The general clinical data had no statistical difference, so they could be comparable. The major observation items, which were also the probable complications that might be caused by IPC and systemic chemotherapy, included post-operative bowel function recovery complications such as abdominal distention, nausea, vomiting, anastomotic fistula, infection of incision, and systemic toxic reactions, (e.g., abnormalities in liver and kidney function, white blood cell count, and platelet count). The main purpose was to investigate whether patients could tolerate the toxic and side effects and whether any increase in adverse reactions would occur when IPC using lobaplatin was used at a prescribed dosage. By comparison, we found no statistical differences between the two groups with respect to intestinal function recovery time, post-operative complications, and toxic reactions of other systems. This suggests that IP lobaplatin does not cause any serious complications in patients with advanced CRC. Changes in hematologic indices in the investigation were considered to be caused by systemic chemotherapy.

These findings suggest that the technique using lobaplatin for IPC causes no serious toxic reactions and side effects and will not affect the normal recovery and systemic chemotherapy process post-operatively. However, this study did not compare the differences in various surgical procedures, especially radical and palliative resections. Although the follow-up data were recorded, there were unexpected absent cases. Therefore, the data may not be completely accurate. A better follow-up management mechanism and data-collection system are required. Because of the small sample size and the limited study items, larger multi-center randomized controlled clinical trials should be carried out to explore the optimal concentration and dose of lobaplatin on treating gastrointestinal malignant tumors that will be necessary to cause a significant change. In addition, survival time must be considered as an endpoint to determine the efficacy of the process.

Conclusion

Although it cannot improve survival time, intraoperative IPC with lobaplatin for elective surgeries is safe and tolerant, and when combined with intravenous chemotherapy, it does not increase the incidence of hepato-renal function damage or induce bone marrow suppression or other side effects.

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Conflicts of interest

The authors indicated no potential conflicts of interest.

Author contributions

All authors contributed to data acquisition, data interpretation, and reviewed and approved the final version of this manuscript.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

The study has been reviewed and approved by the ethics committee.

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