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ORIGINAL ARTICLE

The short-term effect analysis of intraoperative intraperitoneal perfusion chemotherapy with lobaplatin for colorectal cancer

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Summary

Purpose: *To explore the safety and feasibility of intraoperative, intraperitoneal perfusion chemotherapy with lobaplatin for colorectal cancer (CRC).*

Methods: *From November 1, 2016 to January 15, 2017, a total of 100 patients with CRC in Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College, who had undergone radical surgery, were randomized into two groups as follows: the lobaplatin group (50 patients) and the control group (50 patients). The time of recovery of postoperative intestinal functions, hematotoxicity, hepatic-renal toxicity, and postoperative complications were observed and analyzed, with the goal of exploring the safety and feasibility of the drug administration.*

Results: *The time to first gas exhaust in lobaplatin and the control group was 3.08 days and 3.20 days, respectively (p=0.392). The time of defecation in lobaplatin and the control group was 4.38 days and 4.50 days, respectively (p=0.524). There was no statistically significant difference between them in terms of the time of gas exhaust and defecation. One case with intra-abdominal hemorrhage, 1 case with anastomotic leakage, 3 cases with incision complication, 1 case with adhesive intestinal obstruction, and 1 case with pulmonary infection occurred in lobaplatin group compared to 1 case with anastomotic bleeding, 1 case with anastomotic leakage, 2 cases with incision complication, 2 cases with adhesive intestinal obstruction, 2 cases with pulmonary infection, and 1 case with lymphatic fistulas occurred in control group. There was no statistically significant difference between the groups in terms of the total incidence of postoperative complications (p=0.790). No statistically significant difference was observed between the groups in terms of leukocyte and platelet levels on the first, third, and fifth postoperative day. There was also no statistically significant difference in terms of platelet level 2 weeks after surgery. Both the lobaplatin and control group had 2 cases with postoperative abnormal hepatic-renal function. A total of 6 cases in the lobaplatin group and 7 cases in the control group developed gastrointestinal reactions, showing no statistically significant difference (p=0.766).*

Conclusion: *Intraoperative intraperitoneal perfusion chemotherapy with lobaplatin showed no effect on short-term recovery in patients with CRC.*

Key words: *colorectal carcinoma, intraoperative chemotherapy, intraperitoneal chemotherapy, lobaplatin, operation*

Introduction

One of the most commonly diagnosed cancers in China is colorectal carcinoma (CRC), with 376,000 new cases and 191,000 deaths in 2015 [1]. Despite the enormous progress in the diagnosis and treatment of CRC over the past 20 years, metastasis remains the main reason for the poor disease prognosis [2]. Although liver is the most likely site for metastasis, lung and intraperitoneal metasta-

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sis are also common. Intraperitoneal metastasis is found in 7-15% of patients at first surgery [3,4], occurring in 4-19% of patients who initially underwent radical surgery. Some studies [5,6] have found that high-risk factors for postoperative intraperitoneal metastasis include the right colon cancer, tumor invasion of more than half circle of bowel, poorly-differentiated cancer, invasion of serosa or beyond serosa, presence of lymph node metastasis, and preoperative CEA level ≥10 ng / mL.

As an important method [7,8] for the treatment and prevention of colorectal intraperitoneal metastasis, attention has been increasingly focused on intraperitoneal chemotherapy in domestic and foreign clinical authors. Lobaplatin is a third generation platinum derivative. Compared with other traditional platinum drugs, lobaplatin has relatively lighter gastrointestinal reactions and inhibitory effects on leukocytes, with lower toxic side reactions, as well as having certain inhibitory effects on platelets. Nevertheless, it can inhibit the metastasis of CRC cells, similar to oxaliplatin [9]. Nowadays, it is applied in the treatment for advanced colorectal carcinoma [10-13]; however, its role in the intraperitoneal chemotherapy of CRC is unclarified. This study intended to explore the safety and feasibility of intraoperative intraperitoneal perfusion chemotherapy with lobaplatin, which is given to prevent postoperative intraperitoneal metastasis of CRC.

Methods

Study design

This study was a prospective, randomized controlled phase II clinical study, which was approved (Approval No.: 16-147/122) and implemented by the Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, in compliance with Helsinki Declaration and Good Clinical Practice (GCP).

From November 1, 2016 to January 15, 2017, a total of 100 patients with CRC in Cancer Hospital, Chinese Academy of Medical Science and Peking Union Medical College, who had undergone radical surgery, were randomly divided into 2 groups as follows: the study group (50 patients) and the control group (50 patients). All of the patients enrolled in the study signed written informed consent.

Inclusion criteria: 1) Pathologically diagnosed colorectal adenocarcinoma; 2) Age between 18-70 years; 3) No present distant metastasis in chest and abdominal computed tomography (CT); 4) Tumor invasion of more than half circle of bowel; 5) Clinical stage T3, T4, or N(+) tumor; 6) Distance between the tumor and anal verge ≥10 cm in colonoscopy.

Exclusion criteria: 1) Multiple primary CRCs; 2) Uncontrolled diabetes mellitus; 3) Previous history of other cancers; 4) Any previous history of immune system diseases, connective tissue diseases, or hematological system diseases; 5) Having received preoperative neoadjuvant radiotherapy or chemotherapy; 6) Presence of anemia, leukopenia, thrombocytopenia, or hypoproteinemia; 7) Liver and kidney dysfunction.

Study method

The patients with CRC enrolled in the study were treated with regular laparoscopic surgery or open surgery. After the removal of tumor, 1000 mL distilled water were used for peritoneal lavage, which was then absorbed completely. Peritoneal drainage tube was placed in the operation area. The abdominal incision or laparoscopic puncture hole was closed layer by layer in the control group according to routine operation procedures and the operation ended. The abdominal incision or laparoscopic puncture hole was closed layer by layer in the study group and then 60 mg lobaplatin (Hainan Changan International Pharmaceutical Co., ltd. Haikou, China) was dissolved in 500 mL of 5% water solution glucose and was injected via the drainage tube. The drainage tube was clamped to prevent the lavage fluid from flowing out. After the operation, the drainage tube was opened 5 hrs later to guide the fluid perfusion. The only difference between the groups was that the control group did not receive lobaplatin.

Leukocyte and platelet levels were measured on the first, third, and fifth postoperative day, whereas liver and kidney functions were measured on the first and fifth postoperative day. The platelet level was also measured at the second week after surgery. Indicators such as bleeding, anastomosis leakage, incision healing condition, pelvic abdominal abscess, the state of intestinal function recovery, the rate of unexpected re-operation, and the duration of hospitalization were observed and registered.

Follow-up

During hospitalization, the surgeon observed each patient's recovery state. Follow-up was performed by telephone in outpatients to evaluate the state of patient at the second and the fourth week after surgery. The subsequent adjuvant therapy regimen was prepared in accordance to the postoperative pathology.

Statistics

SPSS 19.0 software (IBM, Armonk, NY, USA) was used to analyze the clinical data of patients in both groups. Quantitative variables are presented as mean and standard deviations and were compared with the Student t-test, and qualitative variables were compared with x^2 test. P values less than 0.05 were considered as statistically significant.

Results

General data

A total of 100 patients were enrolled in this study, with 50 of them undergoing intraoperative intraperitoneal perfusion chemotherapy with lobaplatin (study group) versus 50 patients not receiving intraoperative chemotherapy (control group).

Up to February 14th, 2017, no case was lost to follow-up for assessment. The general information of patients is summarized in Table 1.

Date of operation and postoperative pathological staging

All patients underwent radical resection and one-stage anastomosis, without any preventive ileostomy, colostomy, simple exploratory operation, or simple intestinal colostomy. Two patients in the study group were converted into open surgery due to serious intra-peritoneal adhesions, compared with one patient in the control group, who was converted into open surgery due to invasion of the tumor to the lateral abdominal wall. In the study group, liver metastasis was observed in two patients and peritoneal metastasis was found in one patient. The operation-related data and postoperative pathology of patients are shown in Table 2.

Postoperative complications and recovery of intestinal functions

Nasogastric tubes were removed and liquid food was allowed on the first postoperative day in all patients. Peritoneal drainage tubes were removed and semi-liquid diet was allowed after passage of gas and faces, without experiencing any anastomotic leak. There was no statistically significant difference between the groups in terms of the exhaust recovery time and defecation time, as well as in the overall incidence of postoperative complications (Table 3). In one patient with recto-sigmoid junction cancer in the study group, approximately 400 ml of dark red blood began to appear in the drainage tube after off-bed activities on the second postoperative day. In a patient with upper rectal carcinoma in the control group, approximately 500 mL of dark red clot was excreted from the anus from the first postoperative day. Both patients were discharged successfully after medical treatment including blood transfusion. One patient with sigmoid carcinoma in the study group and one patient with rectal carcinoma in the control group suffered anastomosis leakage and underwent surgery of transverse colostomy again. Both patients were discharged successfully after the operation. The remaining implications healed completely after appropriate medical treatment.

Table 1. General data of patients

Variables	*Study group (n=50)*	*Control group (n=50)*	*x^2 (t) value*	*p value*
Mean age, years±SD	58.80±12.07	57.48±11.63	0.557	0.579
Sex (cases, n)				
Male	32	31	0.043	0.836
Female	18	19		
Clinical stage cases, n				
Stage II	29	35	1.563	0.211
Stage III	21	15		

Table 2. The data of operation and postoperative pathological staging

Values	*Study group (n=50)*	*Control group (n=50)*	*x^2 (t) value*	*p value*
Operation method (cases, n)			0.706	0.401
Laparoscopic surgery	41	44		
Open surgery	9	6		
Operation time (min)				
Mean operative time of laparoscopic surgery	175.27±86.38	151.30±59.69	1.479t	0.138
Mean operative time of open surgery	162.00±48.89	186.66±52.12	-0.933t	0.368
Amount of intraoperative bleeding (ml), mean±SD				
Mean bleeding amount of laparoscopic surgery	43.95±40.72	48.30±46.65	-0.456t	0.650
Mean bleeding amount of open surgery	108.33±39.53	125.00±61.23	-0.645t	0.530
Pathological stage			2.109	0.348
Stage II	25	31		
Stage III	23	16		
Stage IV	2	3		

Chemotherapy side reactions (blood, liver, and kidney toxicity)

Preventive use of antibiotics was performed in all patients on the operation day, the first and the second postoperative day. Antibiotics were reused only in the patients with anastomosis leakage, intestinal obstruction, incision infection, lung infection, or pleural effusion. In both groups, no statistical difference was observed in terms of leukocyte and platelet count on the first, third, and fifth postoperative day, and in the platelet count at the second postoperative week. There was also no statistical difference in terms of the number of patients with postoperative abnormal liver and kidney functions. Among the groups, there was no statistically significant difference in terms of the incidence of nausea, vomiting, and diarrhea. In the study group, there was one patient with drug-related rash on the first postoperative day and the symptoms disappeared after treatment with cetirizine hydrochloride (Table 4).

Table 3. Postoperative implications and the state of intestinal function recovery

Variables	*Study group (n=50)*	*Control group (n=50)*	*x^2 (t) value*	*p value*
The state of intestinal function recovery (days), mean±SD				
Exhaust recovery time	3.08±0.70	3.20±0.70	-0.860t	0.392
Defecation recovery time	4.38±0.85	4.50±1.01	-0.639t	0.524
Drainage tube removal time	8.18±2.48	8.60±2.32	-0.873t	0.385
Postoperative duration of hospitalization (days)	9.74±4.85	10.28±2.60	-0.693t	0.490
Postoperative overall implications	8	9	0.071	0.790
Bleeding in abdominal cavity or anastomosis bleeding	1	1		
Incision infection/crack/ healing delay	4	2		
Pelvic cavity/ Abdominal cavity abscess	0	0		
Anastomosis leakage	1	1		
Intestinal obstruction	1	2		
Lung infection	1	2		
Abdominal cavity lymphatic leakage	0	1		
Cardiovascular and cerebrovascular accident	0	0		
Perioperative death	0	0		
Re-operation	1	1	0.000	1.000

Table 4. Chemotherapy side effects (blood, liver and kidney toxicity)

Variables	*Study group (n=50)*	*Control group (n=50)*	*x^2 (t) value*	*p value*
Leukocyte level($\times 10^9$/L)				
The first postoperative day	11.18±4.56	11.25±3.95	-0.085t	0.933
The third postoperative day	7.83±3.15	7.29±2.97	0.997t	0.321
The fifth postoperative day	7.60±3.40	7.13±2.92	0.735t	0.464
Platelet level ($\times 10^9$/L)				
The first postoperative day	195.88±66.44	214.00±88.44	-1.158t	0.250
The third postoperative day	186.42±56.80	181.88±50.89	0.421t	0.675
The fifth postoperative day	223.54±74.89	221.12±82.54	0.154t	0.878
The second postoperative week	213.84±69.76	197.40±73.69	1.146t	0.255
Postoperative liver and kidney function abnormalities	2	2	0.000	1.000
Liver function abnormality	1	2		
Kidney function abnormality	1	0		
Digestive tract reaction	6	7	0.088	0.766
Nausea and vomiting	4	3		
Diarrhea	2	3		
Allergic reaction	1	0		1.000
Neurotoxicity	0	0		1.000

Discussion

For CRC, an important reason for the treatment failure is intraperitoneal metastasis after radical surgery [14]. Currently accepted factors affecting the recurrence of CRC and intraperitoneal metastasis after radical surgery include: (1) Presence of free cancer cells in the patient's abdominal cavity right before surgery. (2) The implementation of surgical treatment which leads to shedding and implantation of cancer cells. (3) The implementation of surgical treatment that injuries the peritoneum and decreases patients' resistance, resulting in the acceleration of implantation and growth of cancer cells [15].

The early postoperative intraperitoneal chemotherapy combined with intravenous chemotherapy is currently considered as the main method to prevent postoperative intraperitoneal metastasis of CRC. Early intraperitoneal chemotherapy has many advantages as follows [16]: (1) no adhesion occurs in the abdominal cavity, hence drugs can effectively reach all the regions in the abdominal cavity and fully contact with free cancer cells. Moreover, in the early postoperative period, there are only small numbers of cancer cells in the patients' body, hence chemotherapeutic drugs can achieve better results. (2) Peritoneum is a semi-permeable membrane. The intraperitoneal substances pass through the "Peritoneum-plasma barrier" and enter into the blood vessels and lymphatics at different speeds, depending on the physical properties (i.e., size, molecular weight, concentration, fat solubility). However, due to relatively larger molecular weight, cytotoxic drugs pass slowly through the "Peritoneum-plasma barrier", thus making the intraperitoneal drug concentration higher than blood drug concentration and working for a longer time. (3) After being absorbed by the capillaries and lymphatic vessels, chemotherapeutic drugs can enter the liver via the portal vein, which may kill the cancer cells in the liver. Meanwhile, due to the first pass effect of drugs in the liver, only a small part of drugs enters the body circulation, thus causing relatively light systemic adverse reactions. Therefore, intraperitoneal chemotherapy is currently considered as a highly selectable regional chemotherapy, with light systemic adverse reactions, but lasting local effect. It is recommended to perform postoperative early intraperitoneal chemotherapy to prevent implantation of cancer cells [17,18].

Lobaplatin is a new generation platinum compound. It has the same inhibitory effect on CRC cells as oxaliplatin [19]. However, excluding its sole certain inhibitory effect on platelets, its inhibitory effects on gastrointestinal system, neurological system, and hematological system are relatively lighter. Therefore, theoretically, it is more suitable to use it in the intraoperative intraperitoneal chemotherapy. Formerly, lobaplatin was applied in the intraperitoneal chemotherapy of gynecologic carcinomas [20] and less used in the intraoperative intraperitoneal chemotherapy of CRC. A previous study [21] reported that 40 mg lobaplatin was dissolved in 20 ml of 5% glucose water and sprayed on the tumor bed, revealing that lobaplatin had influences on the healing process of patient's postoperative incision and abdominal infection, as well as having effects over postoperative adhesive intestinal obstruction. However, in this study, less solvent was used to dissolve lobaplatin, thus it may not have been able to reach all the regions in the abdominal cavity. Meanwhile, this study found that intraoperative intraperitoneal chemotherapy with lobaplatin did not increase serious postoperative complications such as postoperative anastomosis leakage, and abdominal cavity and intestinal bleeding.

In the abdominal cavity of normal body, a small amount of liquid (no more than 200 ml) plays the role of lubrication on the intestinal peristalsis. In this study, 500 ml glucose water was used as solvent for lobaplatin to be injected in the peritoneal cavity; therefore the dissolved lobaplatin is more likely to reach all the gaps in the pelvic abdominal cavity. When the patient was injected 500 ml of lobaplatin solution via the drainage tube in supine position during the operation, one can observe the lobaplatin solution in the pelvic cavity, bilateral sub-phrenic, bilateral para-colic sulcus, and small bowel mesentery gaps under laparoscopic surveillance. An *in vitro* study [16] showed that under a concentration of 120 mg/l, the inhibition rate of lobaplatin on the invasion and migration capability of CRC reached up to 91.67±2.57%. Therefore, we dissolved 60 mg lobaplatin in 500 ml solvent in order to obtain a strong inhibitory effect on the possible CRC cells in the abdominal cavity, while the dose of 60 mg/patient was also far lower than the recommended dose for body surface area (50 mg/m^2), without any obvious toxic side reaction on patients.

Depending on whether it increases postoperative complications and slows down the recovery of postoperative intestinal functions, the application of intraoperative, intraperitoneal chemotherapy may be influenced. This study showed that the intraoperative intraperitoneal perfusion chemotherapy with 60 mg lobaplatin did not increase the incidence of serious complications such as postoperative anastomosis leakage and adhesive intestinal obstruction. After closing the abdominal

incision and puncture hole, injecting chemotherapy drugs into the peritoneal cavity via the drainage tube can prevent the drugs from contacting the abdominal incision, therefore the number of complications such as incision infection, incision crack and delayed wound healing did not increase. Since chemotherapy drugs pass slowly through the "peritoneal-plasma" barrier, low dose of lobaplatin enters the body circulation within five postoperative hrs, thus causing relatively lighter blood system and systemic toxic side reactions. When used in the veins, the most important adverse reaction of lobaplatin is decrease in platelet levels, which usually starts within two weeks after drug injection. In this study, there was no difference between the groups in terms of the postoperative leukocyte level, platelet level, liver and kidney functions. At the second postoperative week, no decrease in platelet level occurred in the study group and there was no difference between the two groups. Both groups of patients had the same exhaust recovery and defecation time in terms of the recovery of intestinal tract functions and duration of postoperative hospitalization. Therefore, the results showed that the intraoperative intraperitoneal perfusion chemotherapy with lobaplatin neither increased the incidence of postoperative complications nor did it affect the normal recovery of intestinal functions. Meanwhile, it has good safety and feasibility profile, without obvious toxic side reactions.

Conclusions

In summary, lobaplatin is safe and feasible for use in the intraoperative intraperitoneal perfusion chemotherapy for CRC. Moreover, theoretically, it has certain inhibitory effects on the postoperative intraperitoneal metastasis. Due to the small number of patients in this study and short follow-up time, further prospective and multi-centered clinical studies including large number of patients are needed in order to determine the optimal effects of lobaplatin in the intraoperative intraperitoneal perfusion chemotherapy for CRC.

Conflict of interests

The authors declare no conflict of interests.

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