Effect of different doses of ulinastatin on cellular immunity and hepatorenal functions in patients undergoing laparoscopic colorectal-carcinoma surgery

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Abstract: The effect of different doses of ulinastatin on cellular immunity and hepatorenal functions in patients undergoing laparoscopic colorectal-carcinoma surgery was observed and analyzed. The 200 patients with laparoscopic colorectal-carcinoma surgery in our hospital were selected as research subjects and divided into 4 groups containing equal patients, namely, saline group, 0.5 x 104U/kg ulinastatin group, 1 x 104U/kg ulinastatin group, and 1.5 x 104U/kg ulinastatin group, which were denoted as group A, group B, group C and group D, respectively. The treatment effect of patients in 4groups was observed and compared. By observing the Narcotrend cerebral state index (NT index), the results showed that NT index at tracheal intubation, pneumoperitoneum beginning, pneumoperitoneum 30min, resection of tumor, end of operation in 4 groups was significantly lower than that at preoperative anesthesia (T0) ($p<0.05$); differences in hepatorenal values (AST, ALT, BUN and Cr) among 4 groups at T0 were of no statistical significance ($P > 0.05$); each index in T cell subsets in the postoperative third days (T1) was significantly lower than that at T0; indexes of T cell subgroup of group B, C and D at T1 were higher than that of group A at T1 ($p<0.05$). For 4 groups, the difference in liver and kidney function indicators at T1 and T0 was of no statistical significance, $p>0.05$. Different doses of ulinastatin have a certain effect on cellular immunity in patients undergoing laparoscopic colorectal-carcinoma surgery and do not significantly affect hepatorenal function.

Keywords: Ulinastatin, laparoscopic colorectal-carcinoma surgery, cellular immunity, hepatorenal function, effect.

INTRODUCTION

Laparoscopic radical resection of colorectal cancer has been widely used in the treatment of colorectal cancer. It has many advantages, including reducing postoperative pain, recovering intestinal function as soon as possible, less hospitalization time and fewer complications (Yuan, *et al*., 2013; Gao, *et al*., 2014). However, the application of general anesthesia during the operation, as well as the application of CO2 pneumoperitoneum, ultrasound knife and monopole electrocoagulation and other instruments, will cause physiological changes in the body and result in changes in immune function. Postoperative t-lymphocyte decreases, and the t-lymphocyte subgroup is significantly reduced, and the ratio of CD4+/CD8+ is reduced. In order to effectively reduce the problem of surgical stress response and maintain the immune function of the body, greatly reduce the postoperative complications and promote the patients' recovery to the best state, scientific anesthesia and surgery are required (Liao, *et al*., 2015; Mocellin, *et al*., 2016).

Colorectal cancer, also known as large intestinal cancer, is shown in fig. 1. The annual incidence of colorectal cancer in the world is as high as 930,000. In China, there are 130,000 to 160,000 new cases of colorectal cancer every year in China. Colorectal cancer has become one of the three major cancers in China. The morbidity is spirally increasing at a rate of 4.2%, which seriously affects the quality of life and threatens the life safety of patients. At present, one of the effective ways to treat colorectal cancer is laparoscopic radical resection (as shown in following fig. 2). Ulinastatin is a broad spectrum protein inhibitor, which can actively improve the microcirculation and increase the volume of blood perfusion. In this study, the effect of different doses of ulinastatin on cellular immunity and hepatorenal functions in patients with laparoscopic colorectal-carcinoma surgery was observed.

MATERIALS AND METHODS

General materials

200 patients who had accepted laparoscopic radical resection for colorectal cancer in First Affiliated Hospital of Jiamusi University from January 2015 to December 2017 were selected as subjects. The selected patients and relatives signed the informed consent before treatment. All the patients meet the diagnostic criteria of Internal Medicine and were confirmed by electronic colonoscopy and pathological biopsy. The image is shown in fig. 3. Patients were all first time ill, enjoyed the right to know and signed formal informed consent. The exclusion criteria includes: patients with acute gastroenteritis, ileus, hemorrhage, perforation and other emergency surgery; patients with history of abdominal surgery, severe cardiopulmonary diseases and other malignancies;

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patients with metastatic lesions, tumor fixation during surgery or invasion of surrounding tissues and organs that could not be resected (Eiber, *et al*., 2016).

Among 200 patients, there were 105 males and 95 females, with age ranging from 40 to 72 years old, averaging at (56.6 + 3.4) years old. The patients had grade I–II of ASA, and the body weight ranging between 52kg-75kg, with an average weight of (61.4 + 1.5) kg. The patients were randomly divided into 4 groups, each containing 50 cases: group A, group B, group C and group D. Comparing the data of 4 groups of patients, the difference was of no statistical significance (p>0.05).

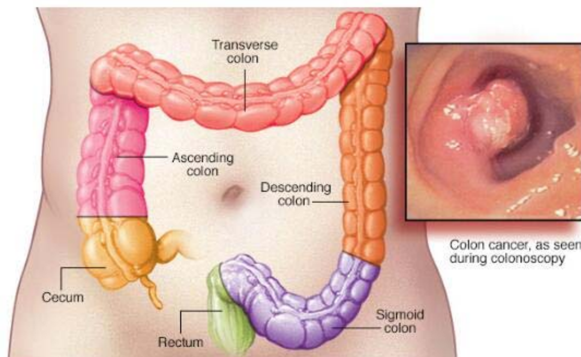

Fig. 1: Colorectal Cancer

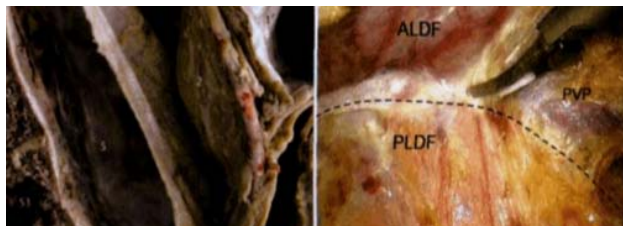

Fig. 2: Local anatomy of laparoscopic colorectal resection

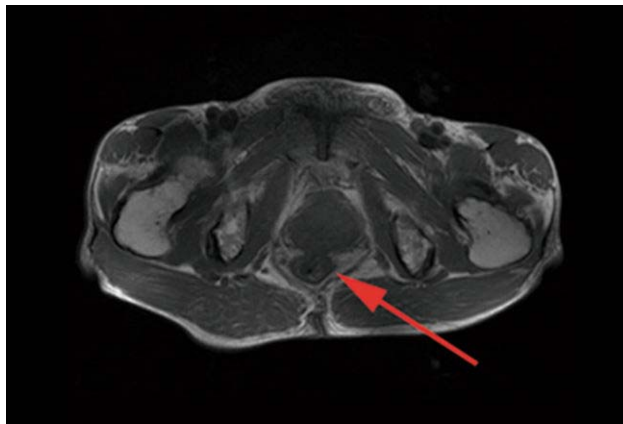

Fig. 3: Rectal tumor hinted by enhanced MRI

Methods

For all cases, the routine preparations were carried out before the operation. Before the induction of anesthesia, venous opening was conducted and different drugs were pumped into within half an hour. Group A was applied with 100 ml of saline, group B was applied with 0.5 x 104U/kgulinastatin+100ml of saline, group C was applied with 1.0 x 104U/kg ulinastatin+100ml of saline of ulinastatin and group D was applied with 1.5 x 104U/kg ulinastatin+100ml of saline. The drugs applied to anesthetics included midazolam, fentanyl, vecuronium and propofol with doses of 0.05-0.1mg/kg, 3-5μg/kg, 0.1mg/kg, and 1.5-2.0mg/kg respectively. The NT index was controlled in D2, with inhalation of sevoflurane maintained during operation.

All cases were treated by the same group of surgeons and applied with the same medication regimen after operation. The analgesic pump included sufentanil, flurbiprofen and normal saline with load capacity being 3mg and background dose being 3ml/h. The additional dose was 3ml each time. The locking time was 15 minutes and the visual analogue score was below 3 points.

Observation index

The NT indexes among 4 groups at different time points were compared; venous blood of 4 groups collected before anesthesia (T0) and at the third postoperative day (T1) under the condition of limosis was examined to detect the level of C3+, CD4+, CD8+ and CD4+/ CD8+ in subgroups of T lymphocyte; aspartic transaminase (AST) and alanine aminotransferase (ALT) in liver function were examined; Urea nitrogen (BUN) and creatinine (Cr) in renal function were examined.

STATISTICAL ANALYSIS

The data were analyzed by statistical software SPSS21.0. The measurement data were expressed in the way of average number ± mean number ($\bar{x}$ ±s), with t test conducted for group comparison. The count data were expressed in the way of natural number (n) and percentage (%), and X^2 was used for group comparison. When p<0.05, the difference was of statistical significance.

RESULTS

Comparison of NT indexes at different time points

As shown in following table 1, it showed that the NT indexes at tracheal intubation, pneumoperitoneum beginning, pneumoperitoneum for 30 minutes, tumor resection and operation ending were significantly lower than that at T0 (p<0.05); the NT index when removing endotracheal tube was significantly lower than that at T0; by comparing the data among groups at the same time point, the results showed no significant difference (p>0.05).

Comparison of cellular immunity

As show in table 2, each index of T cell subgroups at T1 was significantly lower than that at T0; values of T cell

Table 1: Comparison of NT indexes at different time points ($\bar{x}$±s)

Groups	T_O	tracheal intubation	Pneumop-eritoneum beginning	Pneumo-peritoneum for 30 minutes	tumor resection	Operation ending	Removing-gendotrac-heal tube
Group A	98.02±1.06	38.70±3.21	40.41±4.52	41.29±4.39	42.35±3.55	48.56±3.90	84.58±3.20
Group B	98.09±1.11	38.19±2.31	39.05±4.26	40.26±3.58	41.29±3.20	50.28±3.64	84.56±3.20
Group C	97.60±1.20	37.88±2.49	40.69±4.36	40.42±4.57	41.80±3.30	48.90±4.23	84.36±2.88
Group D	97.68±1.23	37.35±3.26	40.114.06	40.86±4.55	41.24±3.32	49.10±4.55	83.40±2.70

Table 2: Comparison of cell immunity ($\bar{x}$±s)

Groups	Time	CD3+(%)	CD4+(%)	CD8+(%)	CD4+/CD8+
Group A	TO	74.3±6.2	41.2±6.9	27.0±6.6	1.5±0.4
	T1	52.1±10.2	27.3±8.8	24.3±5.6	1.1±0.5
Group B	TO	69.8±7.5	40.7±7.3	27.0±7.6	1.6±0.3
	T1	54.5±10.8	28.9±9.5	26.0±5.7	1.3±0.5
Group C	TO	73.6±7.5	41.2±7.7	27.5±6.6	1.6±0.2
	T1	59.0±11.0	28.6±4.6	25.7±7.3	1.2±0.7
Group D	TO	75.6±6.0	42.3±7.6	25.6±6.5	1.5±0.8
	T1	53.4±11.2	28.6±7.6	25.8±9.0	1.2±0.5

Table 3: Comparison of hepatorenal functions ($\bar{x}$±s)

Groups	Time	AST(U/L)	ALT(U/L)	BUN(mmol/L)	Cr(μmol/L)
Group A	TO	24.3±7.2	18.2±5.8	4.1±1.5	81.3±18.4
	T1	32.3±8.6	21.2±8.8	4.5±1.2	92.4±20.5
Group B	TO	25.3±7.8	17.9±7.5	4.0±1.6	80.6±21.3
	T1	31.5±7.8	20.9±5.5	4.7±1.7	90.8±22.1
Group C	TO	25.8±7.6	18.2±7.2	3.9±1.1	83.5±20.1
	T1	30.0±8.0	22.6±5.5	4.9±1.3	91.5±19.2
Group D	TO	25.4±6.2	18.3±7.4	3.8±1.5	82.5±21.6
	T1	32.4±8.8	21.6±6.3	4.8±1.4	91.8±20.3

subgroups at T1 in group B, C and D were significantly higher than that in group A, and the difference was of statistically significance.

Comparison of hepatorenal functions

As shown in table 3, indexes of hepatorenal functions in 4 groups of patients (values of AST, ALT, BUN, Cr) showed no significant difference ($p>0.05$), without statistical significance; there was no significant difference in the indexes of hepatorenal functions of 4 groups of patients between T_1 and T_0 ($p>0.05$), without statistical significance.

DISCUSSION

In the gastrointestinal tract, colorectal cancer is a relatively common malignant tumor with a high incidence. Its early symptom is not apparent. However, in the case of a growing cancer, all sorts of typical symptom problem will occur, including defecate habit changes, hemal, diarrhoea, diarrhoea and constipation alternant, local abdominal pain and so on. When the disease progresses to an advanced stage, systemic symptoms such as anemia and weight loss will appear (Liang, *et al*., 2015; Zhao, 2017). According to relevant statistics, the incidence and fatality rate of colorectal cancer is second only to that of gastric cancer, esophageal cancer and primary liver cancer in the malignant tumors of digestive system. Therefore, it is a disease that needs effective treatment (Koshiyama, *et al*., 2017).

Laparoscopic radical resection has been widely used in treatment of colorectal cancer. It has many advantages, including reduction of postoperative pain, rapid recovery of intestinal function, less time of hospitalization and fewer complications and so on (Yan, *et al*., 2017; Wang, *et al*., 2018). However, due to the application of general anesthesia during operation, postoperative t-lymphocytes of the body will be reduced, and the t-lymphocyte subgroup will be significantly reduced, reducing the ratio of CD4+/CD8+. Therefore, scientific anesthesia and surgery should be carried out to effectively reduce the problem of surgical stress response and maintain the body's immune function, so as to reduce the postoperative

complications and promote the patients to recover to the best state as soon as possible.

Ulinastatin is a broad-spectrum protease inhibitor, which can inhibit the activity of various hydrolases at the same time, stabilize cytomembrane and lysosomal membrane, inhibit the formation of inflammatory mediators, oxygen free radicals and myocardial inhibitory factors as well as improve microcirculation and tissue perfusion. This study shows that ulinastatin has protective effect on cellular immune function during perioperative period and is associated with the improvement of the disorder of immune adhesion factors in serum.

By observing the Narcotrend cerebral state index (NT index), the results showed that NT index at tracheal intubation, pneumoperitoneum beginning, pneumoperitoneum 30min, resection of tumor, end of operation in 4 groups was significantly lower than that at preoperative anesthesia (T0) ($P<0.05$); each index in T cell subsets in the postoperative third days (T1) was significantly lower than that at T0; indexes of T cell subgroup of group B, C and D at T1 were higher than that of group A at T1 ($P<0.05$). The result of this study is consistent with that of the study by Zhao Pengcheng *et al*. (2017).

CONCLUSION

Laparoscopic radical resection of colorectal cancer has been widely used in the treatment of colorectal cancer and has many advantages. However, the application of general anesthesia during surgery will make the body produce physiological changes and immune function changes, so scientific anesthesia and surgery are of vital importance. Colorectal cancer has become one of the three major cancers in China, which seriously affects the quality of life of patients. One of the ways to treat colorectal cancer is laparoscopic radical surgery. Ulinastatin is a broad-spectrum protein-inhibiting enzyme that can actively improve microcirculation and increase blood perfusion. Moreover, it can stabilize cell membrane and lysosomal membrane, inhibit the formation of inflammatory mediators, oxygen free radicals and myocardial inhibitory factors, and improve microcirculation and tissue perfusion. In conclusion, laparoscopic colorectal surgery can exert certain inhibition on cellular immune function. Different doses of ulinastatin can improve cellular immune function after surgery, without causing negative effect on liver and kidney function. Therefore, such medical scheme can be widely used in clinical practice.

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