

Clinical Effect Observation of Bushen-Jianpi-Jiedu Formula and Its Combination with Cinobufacini on Postoperative Colorectal Cancer

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Abstract Objective: To observe the clinical efficacy of Bushen-Jianpi-Jiedu formula (BSJPJD), Cinobufacini injection (CIN) and their combination (COM) on the postoperative colorectal cancer (CRC) patients. Methods: A total of 100 postoperative CRC cases were enrolled and randomized to the groups of CIN (35 cases), BSJPJD (41 cases) and COM (24 cases). The clinical effects on progression-free survival (PFS), Traditional Chinese Medicine (TCM) syndrome, quality of life, immune function as well as side effects were evaluated in each group. Results: the BSJPJD group and COM group had the highest PFS rates at the 3 and 6 months, respectively ($P < 0.05$). The improvement rate on TCM syndrome was higher in BSJPJD group and COM group than that in CIN group ($P < 0.05$). CIN treatment increased the CD4⁺ T cell proportion ($P < 0.05$). COM group has higher diarrhea incidence than CIN group ($P < 0.05$). Conclusion: BSJPJD prolonged the PFS of CRC patients at 3 months. CIN could better modulate the immunity. COM group prolonged the survival of CRC patients at 6 months, but may cause diarrhea.

Keywords Bushen-Jianpi-Jiedu Formula, Cinobufacini, Clinical observation, Colorectal cancer

1. Introduction

Colorectal cancer (CRC) is one of the common malignant tumors in clinical practice, and new cases of CRC are rising annually [1,2]. Clinically, surgery is the treatment of choice for CRC, but about 50% of CRC patients develop metastasis within 2 years after radical surgery. The 5-year survival rate of patients with non-metastatic CRC is higher than 75%, while the 5-year survival rate of patients with metastatic CRC is only 10%, and clinical studies have shown that more than 90% of CRC patients die from metastasis [3-5]. Therefore, the prevention of CRC metastasis is of great significance to improve the survival rate of CRC patients in China.

In recent years, research into anti-tumor drugs has made notable progress, encompassing the design, synthesis, characterization, and biological activity assessment of various compounds. It also includes exploring new synthetic methods (such as microwave-assisted synthesis) and discovering

compounds with unique structures (like fan-shaped and sperm-like amphiphilic heterocyclic compounds). This underscores the pursuit of structural diversity and functional specificity in modern chemical synthesis and drug development [6-13]. However, these studies fall short in evaluating compound safety-critical indicators like toxicity and side effects are not adequately addressed, impeding the translation of drugs from lab to clinic. Furthermore, the lack of in vivo validation makes it hard to fully capture the real efficacy of these compounds in living organisms and leaves them ill-equipped to tackle the highly complex mechanisms underlying tumorigenesis and progression.

Traditional Chinese medicine (TCM) -based adjuvant therapy can improve complications such as intestinal obstruction in postoperative CRC patients, improve patients' immunity, and prevent their recurrence and metastasis [14]. Systematic evaluation and Meta-analysis showed that Jianpi formula can improve the survival quality of postoperative CRC patients, reduce the toxic side effects such as leukopenia, platelet lowering, nausea and vomiting induced by chemotherapeutic drugs [15]. Modified Si-Jun-Zi Decoction can improve the clinical efficacy of chemotherapy in postoperative CRC patients, reduce their adverse reactions, and improve their quality of life [16]. Modified Xiangsha-Liujunzi Decoction can reduce the recurrence rate and

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metastasis rate of postoperative CRC patients and prolong the survival period of patients [17]. Modified Shen-Ling-Baizhu San combined with mannan peptide significantly improved the immune function and clinical symptoms of patients after postoperative chemotherapy for CRC [18].

BSJPD is a clinically formula in the Department of Oncology, Shuguang Hospital of the Shanghai University of Traditional Chinese Medicine. It is suitable for the prevention and treatment of recurrence and metastasis in postoperative cancers including CRC under the guidance of TCM theory. Cinobufacini injection (CIN) is more effective against advanced malignant tumors of the digestive system [19]. Therefore, this study observed the effects of BSJPD, CIN and its combination on disease progression-free survival (PFS) and quality of life, immune function and adverse reactions in postoperative CRC patients.

2. Materials and Methods

2.1. Clinical Information of Enrolled CRC Patients

The study was conducted from March 2014 to February 2018, and a total of 100 postoperative CRC patients were enrolled from Shuguang Hospital, Shanghai University of Traditional Chinese Medicine. All experimental protocols complied with the Guidelines for Ethical Review of Drug Clinical Trials, the Declaration of Helsinki, and the International Ethical Guidelines for Biomedical Research Involving Human Beings (CIOMS: 2002). The project was reviewed and approved by the Ethics Committee of Shuguang Hospital (NO. 2014-345-41-01). Postoperative CRC patients were divided into the CIN treatment group, the BSJPD group, and the combination treatment (COM) group randomly.

2.2. Diagnostic Criteria

CRC diagnosis was confirmed by postoperative pathology according to the Guidelines for the diagnosis and comprehensive treatment of CRC liver metastases (2016) [20].

2.3. Inclusion Criteria

According to the clinical TCM syndrome and medication, postoperative CRC patients were included in this study, and the specific inclusion criteria were as follows: (1) those who had no metastatic lesions after CRC; (2) those who were identified as liver and kidney Yin deficiency, spleen and stomach Qi deficiency in TCM. The diagnostic criteria were referred to Guidelines for Clinical Research of New Traditional Chinese Medicines (Third Series). Liver-kidney Yin deficiency, spleen-stomach Qi deficiency were manifested by rib pain, lumbar and knee soreness, hot flashes and night sweats, dry mouth and throat, fatigue, nausea and more serious abdominal distension after eating, with a pale or red tongue, scanty or light moss, and a sunken and numb pulse; (3) aged 18-80 years old, male or female, with Karnofsky Score (KPS) ≥ 60 [21], and with an expected survival period of ≥ 3 months; and (4) signed an informed consent form.

2.4. Exclusion Criteria

Exclusion criteria: (1) patients with serious cardiac, renal, hematopoietic system disorders and other factors affecting drug evaluation; (2) patients with mental disorders; (3) patients with digestive tract obstruction; (4) pregnant and lactating women; (5) people who use drugs other than those specified in the program; (6) people who are allergic to the study drugs or ingredients; (7) people with poor compliance.

2.5. Treatment

CIN treatment: 20 mL of CIN were diluted into 500 mL of 5% glucose and were given intravenously once a day. The course of treatment was two weeks, after four weeks the patient rested for one day. The total duration of treatment is 3 months. BSJPD group: BSJPD formula consists of Di Huang (Radix Rehmanniae), Ba Yue Zha (Rhizoma Augustinae), Ye Pu Tao Teng (Radix et Rhizoma Dioscoreae) etc. and was supervised by Shuguang Hospital of Shanghai University of Traditional Chinese Medicine and produced by Jiangyin Tianjiang Pharmaceuticals Co Ltd (batch no.: 1611328). CRC patients took two sachets twice a day. Each sachet contained 8.95 g of herbs and was given for 30 days continuously. This study was conducted for 3 consecutive courses. The drugs were distributed by the Pharmacy Department of Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, and quality control was performed. COM group: Dosage and course of treatment were same as above.

2.6. Observation Indicators and Efficacy Evaluation

Survival observation

After the end of treatment, patients were followed up monthly until progression or death, with a follow-up date of June 31, 2018 for all patients included in the survival assessment. Patients who did not die were used as the cut-off value, which was the time of the last follow-up visit to confirm non-death. No patients were lost to follow-up. Disease progression-free survival at 3 months, 6 months, and 1 year was analyzed for postoperative CRC patients based on survival data.

Evaluation of the efficacy on TCM symptoms

Referring to the "Guidelines for Clinical Research of New Chinese Medicines" formulated by the Ministry of Health in 2002, combined with clinical practice, the criteria for TCM evidence points and TCM evidence efficacy were formulated as follows: TCM evidence points were set at 0, 1, 2, 3 according to none, light, moderate, and heavy respectively. The efficacy of TCM points: significant improvement: decrease in points $\geq 2/3$; partial improvement: $1/3 \leq$ decrease in points $< 2/3$; no improvement: decrease in points $< 1/3$.

Quality of life assessment

KPS Functional Scale: 100 points: normal, no symptoms, no abnormal signs; 90 points: normal activity with mild symptoms and abnormal signs; 80 points: normal activity with some symptoms and abnormal signs; 70 points: self-care, but unable to maintain normal life and work; 60 points:

mostly self-care with occasional need for help; 50 points: needs constant care; 40 points: unable to care for himself/herself, needs special care and help; 30 points: severely unable to care for himself/herself; 20 points: severely ill, needs hospitalization and active supportive treatment; 10 points: seriously ill, near death; 0 points: death. The lower the score, the worse the health condition [22].

Immune cell testing

Flow cytometry was used to detect the number of peripheral blood T-cell subpopulations CD3⁺, CD4⁺ and CD8⁺ as well as the number of NK cells, which were tested by the laboratory department of Shuguang Hospital.

Evaluation of adverse reactions

Hematologic and non-hematologic adverse reactions were evaluated with reference to the “Criteria for the Presentation and Classification of Acute and Subacute Toxic Side Effects” published by the World Health Organization in 1970.

2.7. Statistical Methods

SPSS 21.0 software was used for statistics. If the measured data conformed to normal distribution, the t-test was used to compare two groups. The one-way ANOVA test was used to compare three groups, and the non-parametric test was used if the data did not conform to normal distribution. The chi-square test was used for count data, and the Kaplan-Meier method was used for survival curves.

3. Results

3.1. Clinical Information of Postoperative CRC Patients

A total of 100 postoperative CRC patients were enrolled and randomly divided into 35 cases in the CIN group, 41 cases in BSJPD group, and 24 cases in the COM group. There was no statistically significant difference in age, gender, pathological stage and immune status of patients in each group ($P > 0.05$) (Table 1).

3.2. Effect on PFS of Postoperative CRC Patients

The differences in the effects of the three treatment regimens on 3-month and 6-month’s PFS of CRC patients were statistically significant ($P < 0.05$). The 3-month’s PFS of the BSJPD group was higher than that of the CIN treatment group ($P < 0.05$), and the difference was not statistically significant compared with that of the COM treatment group ($P > 0.05$). The 6-month’s PFS of the COM treatment group was higher than that of the CIN group ($P < 0.05$), and the difference was not statistically significant compared with that of the BSJPD group ($P > 0.05$), and the difference in the 1-year disease FPS of the three treatment regimens was not statistically significant ($P > 0.05$) (Table 2). The overall PFS of the COM group was higher than that of the BSJPD treatment group, and overall PFS of the BSJPD group was higher than that of the CIN group (Figure 1).

Table 1. Clinical data of postoperative patients with CRC ($\bar{x} \pm S$)

Index	CIN	BSJPD	COM	P value
Male/female (Cases)	15/20	24/17	16/8	0.888
Age (Years)	67.29 ± 9.11	60.98 ± 10.07	64.17 ± 5.90	0.088
Pathological stage				0.888
Medium-high	28	31	19	
Low	7	10	5	
Immune cells				
CD3 (%)	63.27±10.52	62.85±11.77	61.95±10.64	0.947
CD4 (%)	35.91±11.79	38.26±9.45	35.36±7.68	0.110
CD8 (%)	31.02±9.75	28.02±10.57	31.34±11.6	0.061
CD4/CD8 (%)	1.38±0.87	1.71±0.88	1.23±0.50	0.051
NK (%)	20.38±11.29	18.83±10.81	18.62±10.52	0.899

Table 2. PFS of patients after different treatment regimens (%)

Group	3 months	6 months	1 year	Average days
CIN	60.00 (21/35)	34.29(12/35)	11.43 (4/35)	112
BSJPD	90.24 (37/41)*	51.22 (21/41)	9.76 (4/41)	192
COM	83.33 (20/24)	66.67 (16/24)#	12.50 (3/24)	218

* $P < 0.05$ vs. CIN (3 months); # $P < 0.05$ vs. CIN (6 months).

Table 3. Improvement rate of TCM syndrome points after treatment (%)

Group	Significant improvement	Partial improvement	No improvement	Rate of improvement
CIN	5.71 (2/35)	22.86 (8/35)	71.43 (25/35)	28.57 (10/35)
BSJPD	9.76 (4/41)	36.59 (15/41)*	53.66 (22/41)	46.34 (19/41)
COM	33.33 (8/24)*A	29.17 (7/24)	37.50 (9/24)	62.50 (15/24)*

* $P < 0.05$ vs. CIN; ^A $P < 0.05$ vs. BSJPD

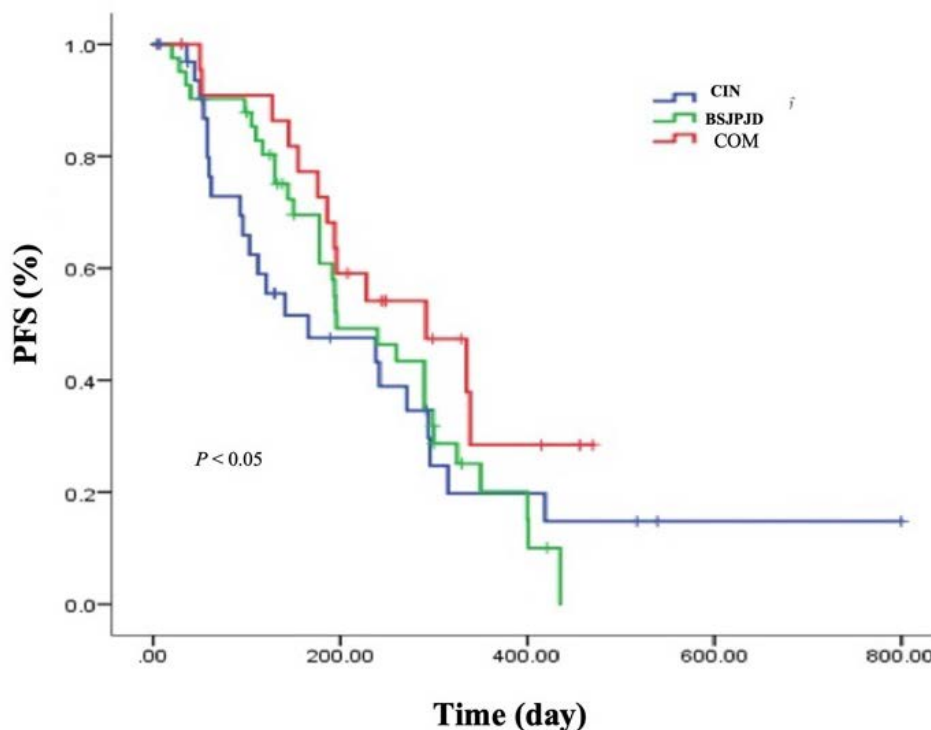


Figure 1. PFS of patients after different treatment regimens

3.3. Improvement of the TCM Symptoms in Postoperative CRC Patients

The differences in the overall distribution of the degree of improvement in TCM symptoms and the total improvement rate of the three treatment regimens were statistically significant ($P < 0.05$). The rate of significant improvement of TCM symptoms in the COM group was higher than that in the CIN group and the BSJPD group ($P < 0.05$). The rate of partial improvement in the BSJPD group was higher than that in the CIN group ($P < 0.05$). The improvement rate of TCM syndrome points in the COM group was higher than that in the CIN group ($P < 0.05$), and there was no statistically significant difference between the CIN group and the BSJPD treatment group ($P > 0.05$).

3.4. Effects on the Quality of life of CRC Patients

Table 4. KPS scores before and after treatment (Interquartile range)

Group	Pre-treatment	Post-treatment	<i>P</i> value
CIN	80, 10	90, 10	0.033
BSJPD	90, 0	90, 0	0.002
COM	80, 10	85, 10	0.058

Both the CIN group and the BSJPD treatment increased patients' KPS scores ($P < 0.05$). The difference in KPS score increase between the BSJPD group and the CIN treatment group was statistically significant, indicating that

the BSJPD improved the quality of life better than CIN ($P < 0.05$).

3.5. Effect on Immune Cell Composition of CRC Patients

There was no statistically significant difference in the proportion of CD3⁺ cells, CD8⁺ cells, NK cells and CD4⁺/CD8⁺ ratio before and after treatment with CIN, BSJPD and COM groups ($P > 0.05$). The CD4⁺ cell ratio was increased after treatment with CIN ($P < 0.05$), while the difference in CD4⁺ cell ratio was not statistically significant before and after treatment with the BSJPD and the COM groups ($P > 0.05$).

3.6. Adverse Reactions

The difference in the overall distribution of diarrhea among the three treatment regimens was statistically significant ($P < 0.05$), and the incidence of diarrhea in the COM treatment group was higher than that in the CIN group (29.17% vs. 2.86%, $P < 0.05$), suggesting that the COM group was more likely to cause diarrhea than CIN alone. The difference in the incidence of diarrhea between the CIN group and the BSJPD group was not statistically significant (2.86% vs. 14.63%, $P > 0.05$). The overall distribution of other non-hematological and hematological adverse reactions was not statistically different among the three treatment regimens ($P > 0.05$) (Table 6).

Table 5. Proportion of immune cells before and after treatment ($\bar{x} \pm S, \%$)

Immune Cells	Treatment	CIN	BSJPJD	COM
CD3 ⁺	Pre-treatment	63.27±10.52	62.85±11.77	61.95±10.64
	Post-treatment	64.96±2.40	60.41±2.28	63.02±2.24
CD4 ⁺	Pre-treatment	Pre-treatment	38.26±9.45	35.36±7.68
	Post-treatment	Post-treatment	33.88±2.53	35.85±1.73
CD8 ⁺	Pre-treatment	Pre-treatment	28.02±10.57	31.34±11.6
	Post-treatment	Post-treatment	32.29±4.02	32.93±2.16
CD4 ⁺ /CD8 ⁺	Pre-treatment	Pre-treatment	1.71±0.88	1.23±0.50
	Post-treatment	Post-treatment	1.82±0.14	1.22±0.11
NK	Pre-treatment	Pre-treatment	18.83±10.81	18.62±10.52
	Post-treatment	Post-treatment	21.12±3.25	18.62±2.41

**P* < 0.05 vs. Pre-treatment

Table 6. Degree of post-treatment adverse effects (number of cases)

Adverse reactions	CIN					BSJPJD					COM					P value
	0	I	II	III	IV	0	I	II	III	IV	0	I	II	III	IV	
Hematology																
Leukopenia	26	6	2	1	0	32	4	3	2	0	16	4	2	2	0	0.365
Neutropenia	29	4	2	0	0	35	5	1	0	0	20	3	1	0	0	0.908
Thrombocytopenia	30	3	1	1	0	36	3	1	1	0	20	2	2	0	0	0.928
Hemoglobinopenia	25	6	3	1	0	36	3	2	0	0	21	2	1	0	0	0.081
Non-Hematologic																
Nausea/Vomiting	35	0	0	0	0	35	4	2	0	0	22	1	1	0	0	0.166
Constipation	33	2	1	0	0	38	1	2	0	0	10	2	2	0	0	0.092
Diarrhea	34	1	0	0	0	35	4	1	1	0	17	4	1	2	0	0.005
Elevated Creatinine	32	3	0	0	0	35	6	0	0	0	24	0	0	0	0	0.358
Elevated urea nitrogen	26	9	0	0	0	30	7	4	0	0	22	2	0	0	0	0.299
Elevated alanine aminotransferase	32	3	0	0	0	32	5	4	0	0	24	0	0	0	0	0.726

4. Discussion

As one of the most common malignant tumors worldwide, CRC remains a significant challenge in terms of treatment. Its high recurrence rate and marked differences in sensitivity to chemotherapy and surgery make individualized treatment difficult to implement. Additionally, the five-year survival rate for CRC is still relatively low (32%), reflecting the limitations of current treatment methods [3-5]. Research indicates that the mechanisms behind CRC development are not yet fully elucidated, which increases the difficulty of targeted therapy and leaves effective drug targets still limited.

TCM has shown significant advantages in the treatment of CRC. Extensive clinical studies have demonstrated that the integration of TCM with conventional medicine can significantly improve patient survival quality and alleviate symptoms, particularly among advanced patients [23]. Furthermore, TCM has unique advantages in enhancing patient mental health and overall quality of life, which is particularly crucial for patients with recurrent CRC [24].

The role of TCM in the prevention and treatment of CRC

has been widely reported. Bushen-Jianpi formula can improve the symptoms and quality of life of patients with liver and kidney Yin deficiency and spleen Qi deficiency after hepatocellular carcinoma surgery [25], and also inhibit the growth of subcutaneous graft tumors in nude mice with human colon cancer and prolong the survival time of rats bearing tumors [26]. A multicenter randomized controlled clinical study found that a Jianpi-Jiedu recipe significantly improved quality of life and prolonged median survival in patients with advanced CRC [27,28].

Our clinical observation on survival, quality of life, immune function and adverse reactions of postoperative CRC patients revealed BSJPJD can improve the PFS of CRC patients for 3 months, BSJPJD combined with CIN can improve the PFS for 6 months. However, there was no statistically significant difference in the 1-year survival rates among the three treatment regimens, suggesting that BSJPJD could achieve short-term clinical efficacy. The combination regimen was more effective than the BSJPJD group or CIN group, but it was prone to cause adverse reactions such as diarrhea. Therefore, the patient's status and tolerance to adverse effects should be considered when

combining the drugs. BSJPJD formula enhanced the effect of improving the quality of life better than that of CIN, which can increase CD4+ immune cells, and CD4+ T cells can initiate cytotoxic T lymphocytes through multiple pathways to exert anti-tumor effects. Therefore, the regulation of cellular immunity in postoperative CRC patients by CIN is better than that by BSJPJD formula. Therefore, BSJPJD formula and CIN exert clinical efficacy from different aspects.

In this study, we initially observed the effects of BSJPJD, CIN and its combination on survival and quality of life, immune function and adverse reactions of postoperative CRC patients. Due to the small number of enrolled cases and the occurrence of adverse reactions such as diarrhea in patients, there was a loss of cases during this study, and the results of this study need to be further verified by larger sample size. Further studies are needed to investigate the mechanism of improving PFS of postoperative CRC patients by BSJPJD, as well as the mechanism of adverse effects of combining this formula with CIN. In addition, since the efficacy of TCM is highly dependent on individual differences, it remains an important challenge to establish uniform assessment standards and operational protocols.

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