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ORIGINAL ARTICLE

Efficacy and safety of berberine in the prophylactic treatment of acute radiation proctitis in postoperative patients with cervical cancer: a randomized controlled study*

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Abstract

Objective The aiom of this study was to study the efficacy and safety of berberine as a prophylactic treatment of acute radiation proctitis in postoperative patients with cervical cancer.

Methods A total of 120 postoperative patients with cervical cancer were enrolled between July 2016 and October 2019, and randomly divided into a treatment group (berberine 300 mg three times a day, $n = 60$) and a control group (receiving vitamin C tablets, 100 mg three times a day; $n = 60$) using the random number table method. All patients received pelvic intensity-modulated radiation therapy (IMRT) and concurrent sensitizing chemotherapy weekly. The difference in the percentage of irradiation volume to the rectum and small intestine as well as the incidence, onset time, severity, and duration of acute radiation proctitis and cystitis during radiotherapy were compared between the two groups. The completion rate, completion time, number of chemotherapy sessions, and quality of life during radiotherapy were also compared.

Results There were no statistical differences in age, FIGO stage, pathological type, complications, high-risk factors, and rectum and small intestine irradiation dose distribution (V_{20}, V_{30}, V_{40}, and V_{50}) between the two groups ($P > 0.05$). No acute radiation proctitis of grade 3 or above occurred in the two groups. There was no significant difference in the incidence of acute radiation cystitis, grade 2 acute radiation proctitis, completion rate of IMRT, and frequency of sensitization chemotherapy between the two groups. After prophylactic treatment with berberine, the incidence of grade 1 acute radiation proctitis, occurrence of grade 1 radiation proctitis, and completion time of radiotherapy in the treatment group were significantly lower than those in the control group ($P < 0.05$). The SF-36 score of the treatment group after radiotherapy was 67.53 ± 4.21, which was significantly better than that of the control group (64.90 ± 6.32; $P < 0.05$). The incidence of grade 3-4 neutropenia in the treatment group was 10% and lower than that in the control group (31.7%, $P = 0.003$). No adverse reactions related to berberine were observed.

Conclusion Prophylactic prescription with oral berberine can reduce the incidence, onset time, and duration of grade 1 acute radiation proctitis, and improve the quality of life of postoperative patients with cervical cancer receiving concurrent chemoradiotherapy.

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Key words: berberine; adjvuant therapy; cervical cancer; intensity-modulated radiation therapy (IMRT); acute radiation proctitis

Cervical cancer is a major public health problem worldwide that seriously threatens women's health. The incidence of cervical cancer in young women is still rising [1]. Cervical cancer was the eighth leading cause of cancer death in China in 2015, accounting for 2.83% of the total new malignant tumors and 3.96% of deaths [2]. Adjuvant concurrent chemoradiotherapy has been proven to improve the progression-free survival and overall survival of patients with early-stage cervical cancer (stage IB to stage IIA) with poor prognosis (positive margin, positive lymph node, or para-uterine involvement) after radical hysterectomy [3–4]. Radiation proctitis, with

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symptoms of nausea, vomiting, diarrhea, pain, bleeding, weight loss, and intestinal fistula, is the most frequent complication of radiotherapy for cervical cancer [5]. Acute radiation proctitis usually occurs within 3 months after radiotherapy, and its incidence is as high as 50%–75% [5–6]. Common risk factors for acute radiation proctitis include previous abdominal surgery history, low body mass index, cardiovascular disease, diabetes, advanced age, female sex, and smoking history [6]. However, there are only a few preventive strategies for acute radiation proctitis, including the drug, amifostine, and physical intervention [7].

Berberine is an isoquinoline alkaloid isolated from plants that has been used as an antidiarrheal, antiarrhythmic, and anti-inflammatory agent [8]. Studies have shown that berberine can regulate the expression and secretion of tumor necrosis factor-α and interleukin-10, and plays an important role in inhibiting radiation-induced intestinal injury and improving survival, thus serving as an effective treatment strategy for radiation-induced intestinal injury [9]. The purpose of this study was to explore the clinical efficacy and safety of berberine as a preventive treatment of acute radiation proctitis caused by intensity-modulated radiation therapy (IMRT) in postoperative patients with cervical cancer.

Materials and methods

Patient characteristics

Postoperative cervical cancer patients with high-risk factors who received pelvic IMRT between July 2016 and October 2019 at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology were enrolled in this study. All patients signed an informed consent form. The inclusion criteria were as follows: patients categorized as stage IB to IIA cervical cancer according to the guideline of the International Federation of Gynecology and Obstetrics (FIGO), those diagnosed with cervical adenocarcinoma via postoperative pathology, without radiotherapy, patients aged 20–70 years, and those who recovered well from radical operation of cervical cancer within 3 months. The exclusion criteria were as follows: patients with KPS score < 80, defecation ≥ 3 times a day, patients with gastroduodenal ulcer, chronic gastroenteritis, cholecystitis, diabetes, history of inflammatory bowel disease, severe damage to vital organ function, allergy to the experimental drug, hemolytic anemia, secondary primary cancer, and expected poor compliance.

Patients were randomly divided into treatment and control groups using the random number table method. They received pelvic radiotherapy and weekly synchronous sensitization chemotherapy. The baseline characteristics of patients were listed in Table 1.

Treatment plan

A total of 100 and 120 postoperative cervical cancer patients with high-risk factors were randomly divided into the treatment and control groups, respectively, and received pelvic radiotherapy and weekly synchronous sensitization chemotherapy based on the random number table method.

Treatment group (n = 60): all patients received 300 mg of prophylactic berberine (dosage: 0.1 g × 100 tablets; Shenyang No.1 Pharmaceutical Co., Ltd., China) orally three times a day before radiotherapy. Control group (n = 60): all patients received prophylactic treatment with 100 mg vitamin C tablets (dosage: 0.1 g × 100 tablets; Guangdong South China Pharmaceutical Group Co., Ltd., China) as a placebo three times a day.

Postoperative patients with cervical cancer were received IMRT and concurrent sensitization chemotherapy, and IMRT comprised a total PTV D48 of 48.6 Gy in a fraction of 1.8 Gy five fractions a week. The target delineation of IMRT in postoperative cervical cancer was based on the Consensus Guidelines for Clinical Target Delimitation published by Small, W in 2008 [4, 10], and the target delineation of normal tissues referred to the Consensus Atlas of Radiation Therapy Oncology Group published by GAY H [4, 11]. Synchronous sensitization chemotherapy was performed once weekly using an intravenous drip of cisplatin 30 mg/m^2 (dosage: 20 mg/piece; Nanjing Pharmaceutical Factory Co., Ltd., China). Upon contraindications or intolerance to chemotherapy, sensitization chemotherapy was terminated within the week.

Patients with grade 3 or higher acute proctitis or other adverse reactions related to radiotherapy (according to the RTOG/EORTC) were suspended from radiotherapy [11]. If the adverse reactions returned to grade 2 or below, radiotherapy was continued. The time of occurrence, duration, and grade of gastrointestinal reactions were recorded. The quality of life score (the MOS 36-item short-form health survey) was completed before and after radiotherapy.

Endpoints and evaluations

Primary endpoints

(a) Incidence, onset time, severity, and duration of acute radiation proctitis and cystitis

The common symptoms of acute radiation proctitis included nausea, vomiting, diarrhea, pain, hemorrhage, weight loss, and intestinal fistula. Acute radiation proctitis usually occurs within 3 months of radiotherapy. Radiation cystitis was characterized by painless hematuria, mild frequent micturition, or dysuria. In accordance with the RTOG/EORTC, the symptoms and severity of radiation proctitis and cystitis were recorded every day within 3 months after radiotherapy, and the duration of

adverse reactions was the sum of adverse reaction time at all levels. The incidence of radiation proctitis and cystitis of different grades was defined as the number of patients with radiation proctitis and cystitis divided by the total number of patients. The occurrence time of radiation proctitis and cystitis of different grades was the number of days when the corresponding symptoms first appeared within 3 months after receiving radiotherapy. By comparing the primary endpoints between the two groups, the clinical efficacy of the treatment against acute radiation proctitis and cystitis was evaluated. The blood parameters and liver and kidney function of patients were monitored weekly.

(b) Quality of life: Quality of life was assessed using the SF-36 scores before and at 1-2 weeks after radiotherapy. The scores were compared between the two groups. A lower SF-36 score indicates worse quality of life.

Secondary endpoints:

(a) Completion time, completion rate of radiotherapy, and frequency of sensitization chemotherapy. Completion time of radiotherapy: the days from receiving radiotherapy to completing radiotherapy, excluding the time of treatment suspension due to machine failure and holidays. The completion rate of radiotherapy was the proportion of patients who completed external radiotherapy. Preventive treatment with berberine was evaluated by comparing the days of radiotherapy completion, completion rate, and times of sensitization chemotherapy between the two groups.

(b) Normal tissue assessment

To evaluate the effect of irradiation volume on radiation proctitis, the percentage of irradiation volume to the small intestine and rectum was compared between the two groups. The radiation doses were 20, 30, 40, and 50 Gy.

Statistical analysis

Data were analyzed using SPSS20.0 software (SPSS Inc, USA). Measurement data are presented as mean ± standard deviation and compared between the two groups using *t*-test. Calculated data are expressed as percentages, and compared between the two groups using the chi-square test. Differences with $P < 0.05$ were considered significant [12].

Results

Characteristics of the treatment and control groups

The age, FIGO stage of cervical cancer, pathological type, complications, and postoperative high-risk factors of the two groups were compared ($P > 0.05$). The results showed no obvious difference between the two groups, as shown in Table 1.

Percentage of irradiation dose volume to organs at risk (rectum and small intestine)

The percentages of irradiation volumes V20, V30, V40, and V50 to the rectum in the treatment group were higher than those in the control group, but with no significant difference ($P > 0.05$). The percentages of irradiation volumes V30, V40, and V50 to the small intestine in the treatment group were lower than those in the control group, but without significant difference ($P > 0.05$). The percentages of irradiation volume V20 to the small intestine in the treatment group was higher than that in the control group, but the difference was not

Table 1 Baseline clinical characteristics of postoperative patients with cervical cancer

Parameter	Treatment (*n* = 60)	Control (*n* = 60)	*t*	*P*
Mean age (years)	50.17 ± 3.54	49.57 ± 3.43	1.069	0.289
Stage			0.135	0.713
IB	34 (56.7%)	32 (53.3%)		
IIA	26 (43.3%)	28 (46.7%)		
Complication				
History of abdominal surgery	2 (3.3%)	3 (5%)	0.209	0.648
Low body mass index	0	0		
Cardiovascular diseases	6 (10%)	8 (13.3%)	0.323	0.57
Diabetes	0	0		
Smoking	6 (10%)	7 (11.7%)	0.086	0.769
Histological type				
Adenocarcinoma	60 (100%)	60 (100%)		
High risk factors				
Tumor size ≥ 3cm	10 (16.7%)	8 (13.3%)	0.261	0.609
LVSI*	38 (63.3%)	40 (66.7%)	0.147	0.702
Infiltrate 1/3 of the stroma outside the cervix	10 (16.7%)	12 (20%)	0.223	0.637
Preoperative neoadjuvant chemotherapy	20 (33.3%)	28 (46.7%)	2.222	0.136

* Lymph-vascular space invasion

Table 2 Distribution of irradiation volume to the small intestine and rectum (%)

Organs at risk	Group	*n*	V_{20}	V_{30}	V_{40}	V_{50}
Small intestine	Treatment	60	79.30 ± 4.31	44.40 ± 3.25	18.20 ± 1.41	8.37 ± 1.96
	Control	60	77.83 ± 2.92	44.57 ± 2.20	18.55 ± 1.41	8.40 ± 1.85
	t		1.948	–0.323	–1.725	–0.111
	P		0.056	0.748	0.09	0.912
Rectum	Treatment	60	76.28 ± 1.64	57.47 ± 1.27	38.35 ± 1.39	4.73 ± 1.33
	Control	60	76.08 ± 1.83	57.03 ± 1.85	38.03 ± 1.48	4.63 ± 1.34
	t		0.666	1.776	1.329	0.365
	P		0.508	0.081	0.189	0.716

significant ($P > 0.05$), as shown in Table 2.

Evaluation of endpoints

There was a significant difference in the incidence of grade 1 acute radiation proctitis between the treatment and control groups (61.7% *vs* 36.7%, $P = 0.006$); however, there was no significant difference in the incidence of grade 2 acute radiation proctitis between the two groups (11.7% *vs* 6.7%, $P = 0.342$). No acute radiation proctitis of grade 3 or above occurred in the two groups. There was no significant difference in the incidence of acute radiation cystitis between the two groups. The incidence of grade 3-4 neutropenia in the treatment group was lower than that in the control group (10% *vs* 31.7%, $P = 0.003$). Both the treatment and control groups completed radiotherapy. The radiotherapy time of the treatment group was slightly shorter than that of the control group, showing a significant difference (38.10 ± 1.17 *vs* 39.37 ± 1.59 days, $P = 0.001$). The SF-36 score after treatment was significantly higher than that of the control group (67.53 ± 4.21 *vs* 64.90 ± 6.32, $P = 0.001$). However, there was no significant difference in the frequency of completing sensitization chemotherapy between the two groups (4.20 ± 0.75 *vs* 4.10 ± 0.84, $P = 0.522$), as shown in Table 3.

The occurrence time of grade 1 radiation proctitis in the treatment group was slightly later than that in the control group (5.55 ± 1.26 *vs* 4.27 ± 1.28 days). In the treatment group, the duration of grade 1 radiation proctitis was significantly shorter (3.64 ± 0.90 *vs* 4.57 ± 0.90 days). Grade 2 radiation proctitis occurred slightly earlier in the treatment group than in the control group (10.50 ± 1.20 *vs* 9.75 ± 0.96 days). The duration of grade 2 radiation proctitis in the treatment group was relatively shorter than that in the control group (3.0 ± 0.82 *vs* 2.25 ± 0.89 days), but the difference was not significant, as shown in Table 4.

No adverse reactions related to berberine were observed in the study (as evaluated according to CTCAE4.0)

Discussion

Radiotherapy is one of the most effective treatments for pelvic tumors, and acute radiation proctitis is a major factor that seriously affects the completion rate

Table 3 Endpoints and acute adverse reactions according to concurrent chemoradiotherapy

Characteristics	Treatment group (*n* = 60)	Control group (*n* = 60)	*t*	*P*
Acute radiation proctitis				
Grade 1	22	37	7.502	0.006
Grade 2	4	7	0.901	0.342
Grade 3	0	0		
Grade 4	0	0		
Acute radiation cystitis				
Grade 1	2	4	0.702	0.402
≥ Grade 2	0	0		
Hematologic complications (Grade 3–4)				
Neutropenia	6	19	8.539	0.003
Anemia	4	9	2.157	0.142
Thrombocytopenia	4	7	0.901	0.343
SF-36 score (before radiotherapy)	67.10 ± 4.02	66.17 ± 4.47	1.609	0.113
SF-36 score (after radiotherapy)	67.53 ± 4.21	64.90 ± 6.32	3.615	0.001
Radiotherapy completion rate	100%	100%		
Radiotherapy completion time/day	38.10 ± 1.17	39.37 ± 1.59	–4.75	0.001
Number of sensitization chemotherapy	4.20 ± 0.75	4.10 ± 0.84	0.644	0.522

Table 4 Treatment course for acute radiation proctitis ($\bar{x} \pm s$)

Items	Grade 1		Grade 2	
	Onset time (days)	Duration (days)	Onset time (days)	Duration (days)
Treatment group	5.55 ± 1.26	3.64 ± 0.90	10.50 ± 1.20	3.0 ± 0.82
Control group	4.27 ± 1.28	4.57 ± 0.90	9.75 ± 0.96	2.25 ± 0.89
P	0.001	0.001	0.304	0.188

of radiotherapy and quality of life in patients receiving pelvic radiotherapy [7]. Gastrointestinal side effects are the most important dose-limiting factor in radiotherapy for malignant tumors [13]. To date, there have been only a few preventive strategies for acute radiation proctitis, which include preventive treatment with amifostine and physical intervention [7, 12]. In 2014, the MASCC/ISOO clinical practice guidelines recommended intravenous amifostine to prevent acute radiation proctitis [13]. Amifostine has been proven to exert protective effects in acute radiation-induced intestinal mucosal injury caused by various radiation types and doses. However, its protective effect on tissues is controversial [14]. Thus, for the radiotherapy for pelvic tumors, there is a necessity to develop new protective agents to reduce the occurrence of radiation proctitis [12, 15]. Song *et al.* found that abnormal expression of proteins in the Fas and glycolysis pathways is a possible molecular mechanism of acute radiation proctitis [16]. Li *et al.* found that berberine can protect against intestinal mucosa injury caused by radiotherapy by regulating the expression and secretion of TNF-α and IL-10 [17]. Li *et al.* found through follow-up clinical research that berberine significantly reduced the incidence and severity of acute radiation proctitis, and delayed the occurrence time of acute radiation proctitis [18]. In this study, we observed no significant difference in the irradiation volume to the rectum and small intestine between the two groups. Compared with those in the control group, the incidence of grade 1 acute radiation proctitis in patients in the treatment group was significantly reduced, the occurrence time was delayed, and the duration was shortened. There was no significant difference in the incidence, occurrence time, and duration of grade 2 acute radiation proctitis in patients between the two groups. No acute radiation proctitis of grade 3 or above occurred in the two groups. Liu *et al.* reported that the emission rate of acute radiation proctitis of grade 3 and above in patients with cervical cancer after the operation was 1.02% [3]. In this study, the incidence of grade 1 acute radiation proctitis was significantly higher than that reported by Li *et al.* (the incidence in the treatment and control groups reported by Li was 9.5% and 33.3%, respectively [18]), which may be related to the higher radiotherapy dose in the treatment target area (the clinical radiotherapy dose was 48.6 Gy in our study and 36–46 Gy in Li *et al*). In addition, the irradiated volume to the rectum was relatively larger in patients with cervical cancers who underwent surgery than in those who did not. Both groups of patients completed IMRT, and the patients in the treatment group completed radiotherapy in a shorter time than those in the control group, which may be related to the occurrence of grade 3-4 neutropenia during chemoradiotherapy. There was no significant difference in the frequency of sensitization chemotherapy and the incidence of radiation cystitis between the two groups. This indicated that IMRT can be used as a safe treatment for postoperative cervical cancers with good tolerance. Moreover, the SF-36 scores in patients in the treatment group were significantly higher than those in the control group after radiotherapy. No berberine-related side effects were observed in this study. Thus, this study suggested that preventive treatment with berberine can significantly reduce the incidence of grade 1 acute radiation proctitis in postoperative patients with cervical cancer caused by IMRT, delay the occurrence time, shorten the duration of symptoms, and improve the quality of life of patients. However, for the prevention and treatment of serious radiation proctitis (≥ grade 2), it may be necessary to improve the radiotherapy plan, reduce the range of irradiation volume to organs at risk, optimize the radiotherapy methods, and use other additional drugs.

Conclusion

In conclusion, the prophylactic treatment with berberine can effectively reduce grade 1 acute radiation proctitis in postoperative patients with cervical cancer receiving concurrent chemoradiotherapy, and improve the quality of life of these patients. This treatment is therefore worthy of further verification and promotion through randomized multicenter clinical studies.

Conflicts of interest

The authors declare no potential conflicts of interest.

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