Int J Clin Exp Med 2020;13(11):8889-8895
www.ijcem.com /ISSN:1940-5901/IJCEM0119346

Original Article

KangFuXinYe with epidermal growth factor on acute radiation enteritis

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Received August 1, 2020; Accepted August 17, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Objective: The present study is designed to observe the efficacy of KangFuXinYe combined with epidermal growth factor (EGF) on acute radiation enteritis. Methods: A total of 74 cases with acute radiation enteritis were divided into the observation group (n=37) and the control group (n=37) by using random number tables. The patients in the observation group were treated with KangFuXinYe and recombinant human epidermal growth factor, whereas the patients in the control group were subjected to KangFuXinYe. The main outcome measures were efficacy, efficacy under colonoscopy, transforming growth factor beta 1 in the serum, and interleukin (IL)-10. The secondary outcome measure was the quality of life (QOL). Results: The overall response rate of the observation group was higher than control group. The overall response rate of the former under colonoscopy was also higher than that of the latter. After the treatment, transforming growth factor beta 1 decreased, whereas IL-10 increased more evidently in the observation group. The 3-month QOL of the observation group was better than that of the control group in physiological function, physical role, social function, emotional role, and bodily pain. Conclusion: KangFuXinYe combined with EGF is effective in treating acute radiation enteritis, improving inflammation, promoting intestinal mucosal repair, and increasing QOL.

Keywords: Acute radiation enteritis, KangFuXinYe, epidermal growth factor, efficacy observation

Introduction

Colorectal cancer is the most common malignant tumor of the digestive system. The latest global epidemiology shows that colorectal cancer has an incidence of 8% and ranks third among all cancers [1]. The number of new patients with colorectal cancer in the United States in 2017 was 135,000 [2]. A domestic research has revealed that the incidence of colorectal cancer increased in 2015, and 191,000 deaths due to colorectal cancer were recorded [3]. Radiotherapy plays an important role in cancer treatment. Previous studies showed that more than 50% of patients, including over 70% of patients with colorectal cancer, receive radiotherapy [4]. Patients who receive radiotherapy have intestinal tissues that become one of the most common injury sites, often accompanying acute radiation enteritis (RE), because of high sensitivity to radiation [5]. The incidence of acute RE among patients undergoing radiotherapy reaches 50%-70% [6, 7]. Economical, effective, and safe methods are being actively explored to prevent and treat acute RE in clinical practice [8]. In Western medicine, no special scheme of treating RE is available other than those with poor effects associated with diminishing inflammation, relieving diarrhea, or protecting the intestinal mucosa [9, 10]. Clinical studies have revealed that KangFuXinYe has the effects of regulating inflammatory factors, relieving ulcers, and healing wounds [11]. Studies have also shown that the treatment of oral ulcer by using KangFuXinYe combined with thymopentin is significantly better than that using KangFuXinYe alone [12]. KangFuXinYe combined with antituberculosis drugs significantly relieves ulcerative intestinal tuberculosis [13]. Epidermal growth factor (EGF) regulates and promotes cell proliferation, allowing wounds to heal quickly [14]. Some studies have indicated that synthetic recombinant human epidermal growth factor (hEGF) is

highly consistent with natural products in activity and structure [15]. The combination of the two is rarely applied to treat RE in clinical practice. Thus, this research hypothesized that giving an effective retention enema by using KangFuXinYe and recombinant hEGF for patients with acute RE after they receive radiotherapy for colorectal cancer inflammation, promoting intestinal mucosal repair, and increasing the QOL. Thus, this treatment is to provide several effective treatment methods for clinical RE treatments.

Materials and methods

Clinical data

The present experiment was approved by the Ethics Committee of the First Affiliated Hospital of Harbin Medical University. Seventy four cases who suffered acute RE after receiving radiotherapy for colorectal cancer at the oncology department of the First Affiliated Hospital of Harbin Medical University from March 2017 to December 2018 were enrolled and randomly divided into two groups: the observation group and the control group, each with 37 cases. The two groups were treated with KangFuXinYe combined with recombinant hEGF or KangFuXinYe alone, respectively. All the subjects were aged 18-75 years with an average of 53.5±8.7 years and had signed the informed consents before the study was performed.

Inclusion criteria

Cases were enrolled following the listed requirements: (1) colorectal cancer was diagnosed following the *Clinical Practice Guidelines For Colorectal Cancer* promulgated by the Bureau of Medical Administration of the National Health and Family Planning Commission of the People's Republic of China in 2015 [16]; (2) the diagnostic criteria for acute RE [17]; (3) survival for more than 3 months; (4) with normal coagulation and marrow functions; (5) with normal cardiopulmonary function; (6) scored 0-2 points given by the Eastern Cooperative Oncology Group Performance Status Scale; (7) with complete clinical data.

Exclusion criteria

Cases that met the following criteria were excluded: (1) with metastatic or recurrent colorectal cancer; (2) accompanied with serious lung and heart conditions; (3) complication with any other primary malignant tumors; (4) coagulation or marrow dysfunction; (5) hepatorenal insufficiency; (6) previous history of complications with any other intestinal diseases, such as inflammatory bowel diseases, ischemic bowel diseases, or ulcerative colitis; (7) patients who could not cooperate.

Methods

The observation group was treated with retention enema using 30 mL of KangFuXinYe (Hu'nan Kelun Pharmaceutical Co., Ltd., China) and 30 mL of recombinant hEGF solution for external use only (concentration: 2,000 IU/mL; Shenzhen Watsin Genetech Co., Ltd., China) plus 100 mL of 0.9% normal saline (NS) solution (concentration: 40 mL) half an hour after dinner. All the patients were instructed to urinate and defecate before they underwent retention enema and to stay in bed for 2 h after they received retention enema. The enema liquid was retained for 4 h before elimination. The procedure was conducted once a day for 2 weeks, which constituted one course.

Retention enema was also given to the control group by using 100 mL of KangFuXinYe solution (concentration: 30 mL) containing 70 mL of 0.9% NS half an hour after dinner. All the patients were asked to perform the task as directed above.

Efficacy evaluation

Efficacy was evaluated in accordance with the relevant standards developed by Fan S et al., and efficacy was ranked at different levels: cured, excellent, effective and ineffective [18]. The overall response rate = (the number of cases cured and with excellent or effective effects)/the number of cases.

The efficacy of treating acute RE under colonoscopy was evaluated by ranking the efficacy at different levels: cured, effective, and ineffective [17]. The overall response rate = (the number of cases cured and with effective effects)/the number of cases.

Determination of transforming growth factor (TGF) beta and interleukin (IL)-10: The TGF beta 1 in the serum was determined through an

Table 1. General information and baseline information

Item	Observation group (n=37)	Control group (n=37)	χ^2/t	P
Gender (male:female)	17:20	15:22	0.220	0.639
Age	62.9±4.8	64.3±5.8	1.070	0.288
Differentiation grade (cases)			0.319	0.852
Highly differentiated	7	9		
Moderately differentiated	16	15		
Poorly differentiated	14	13		
PF	74.19±3.18	74.32±3.17	0.183	0.855
RP	65.54±6.15	65.02±6.37	0.353	0.752
BP	32.14±4.28	32.40±3.28	0.272	0.787
GH	75.19±3.29	75.30±3.31	0.141	0.888
VT	90.22±2.86	90.05±2.84	0.245	0.807
SF	73.35±5.47	73.86±5.78	0.392	0.696
RE	66.81±9.87	67.32±9.48	0.228	0.820
MH	90.22±2.85	90.05±2.84	0.245	0.807
Scores			0.084	0.772
0-1 point	30	29		
2 points	7	8		

Note: PF: physiological function; RP: physical role; BP: bodily pain; GH: general health; VT: vitality; SF: social function; RE: emotional role; MH: mental health.

enzyme-linked immunosorbent assay (ELISA) before and after the treatment by using an ELISA kit (Shanghai Hengyuan Biological Technology Co., Ltd.). IL-10 was evaluated through radioimmunoassay by using a radioimmunoassay kit (Shanghai Xinfan Biological Technology Co., Ltd.).

Follow-up indicators: The included patients were followed up in the outpatient department once a month with the 3-month quality of life (QOL) measures recorded before and after the treatment in accordance with the 36-item short-form (SF-36), including one multi-item scale that assesses eight health concepts: general health (GH), mental health (MH), physiological function (PF), physical role (RP), social function (SF), emotional role (RE), bodily pain (BP), and vitality (VT) [19].

Statistical indicators

Statistical analysis was performed using the SPSS 17.0 software package. Continuous variables were expressed as mean ± standard deviation ($\bar{x}$ ± sd). If data were consistent with normal distribution and variance homogeneity, a paired sample t test was conducted for intragroup comparison before and after treatment, and a t test was performed for between-group comparison based on t statistic; otherwise, a signed rank test was performed on the basis of Z statistic. Categorical variables were represented in percent. Pearson's chi-squared test and Fisher's exact test were also conducted; the test statistic for an independent sample was denoted by chi-square, and statistically significant differences were obtained at $P< 0.05$.

Results

General information and baseline information

No significant difference was observed between the two groups in age, gender, disease type, or QOL scaling ($P>0.05$) (**Table 1**).

Between-group comparison in the efficacy

The between-group comparison of the efficacy revealed that the overall response rate of the observation group was 94.59%, which was significantly higher than that of the control group (70.27%; $P<0.05$) (**Table 2** and **Figure 1**).

Between-group comparison in clinical efficacy under colonoscopy

The between-group comparison of the efficacy revealed that the overall response rate of the

Table 2. Comparison in terms of clinical efficacy

Group	Cured	Excellent	Effective	Ineffective	Overall response rate (%)
Observation group (n=37)	28 (75.68)	5 (13.52)	2 (5.40)	2 (5.40)	35 (94.59)
Control group (n=37)	20 (54.05)	5 (13.52)	1 (2.70)	11 (29.73)	26 (70.27)
χ^2		7.897			7.559
P		0.048			0.006

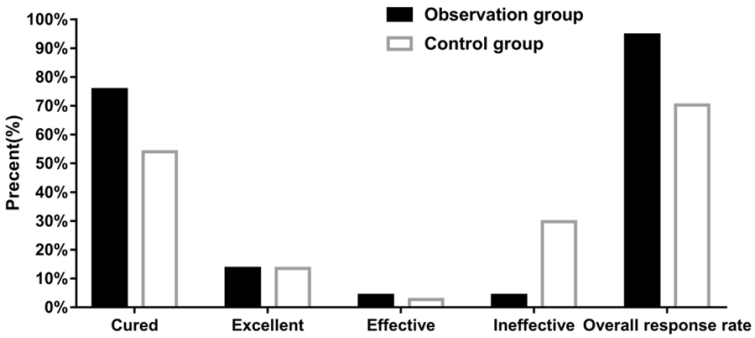

Figure 1. Comparison in terms of clinical efficacy.

Table 3. Comparison in clinical efficacy under colonoscopy

Group	Cured	Effective	Ineffective	Overall response rate (%)
Observation group (n=37)	26 (70.27)	8 (21.62)	3 (8.11)	34 (91.89)
Control group (n=37)	16 (43.24)	5 (13.52)	16 (43.24)	21 (56.76)
χ^2		11.968		11.967
P		0.003		0.001

observation group was 91.89%, which was significantly higher than that of the control group (56.76%; P<0.05) (**Table 3** and **Figure 2**).

Intragroup comparison of TGF beta 1 and IL-10 before and after the treatment

No statistical difference was observed between the two groups in TGF-β1 and IL-10 before the treatment (P>0.05). TGF-β1 was significantly declined and IL-10 was significantly increased before and after the treatment in the two groups (P<0.05). A decline and increase in the observation group overmatched that of the control group (P<0.05) (**Table 4**).

Between-group comparison of the 3-month QOL after the treatment

The 3-month QOL after treatment, specifically PF, RP, SF, RE, and BP, significantly differed between the two groups (P<0.05), suggesting that the observation group was better than the control group in terms of PF, RP, SF, RE, and BP. No significant difference was observed between the two groups in terms of GH, MH, or VT (P>0.05) (**Table 5**).

Discussion

Patients with cervical cancer after radiotherapy frequently show intestinal injuries, and the most common injury is RE with an increasing incidence [20, 21]. Patients with cervical cancer may suffer from mucosal injuries 12 weeks after radiotherapy, thereby crucially affecting their QOL and clinical prognosis [22]. KangFuXinYe is a preparation extracted from dried Periplaneta americana L., and its solution can lead to the alleviation of ulceration because it contains nutrients that not only promote the healing of ulcer, the growth of new granulation tissues from epidermal cells, and the proliferation of mucosal capillaries but also improve the circulation in the surrounding tissues [23]. Previous studies suggested that the expression of the EGF receptor in the intestinal mucosa increases significantly when EGF is applied to treat RE [24]. EGF may also cause the division and proliferation of cells and promote the mitosis of mucosal epithelial cells, thus stimulating the renewal of cells and the healing of the intestinal lining [25]. In the present research, the two drugs were combined in treating acute RE. The results showed that the observation group was significantly better than the control group in terms of the overall response rate integrating the efficacy and the efficacy under colonoscopy. The combination was synergistic in promoting intestinal mucosal recovery. This observation was consistent with the above results.

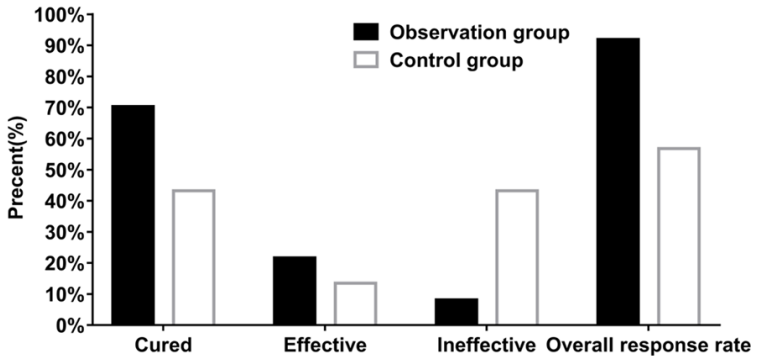

Figure 2. Comparison in terms of clinical efficacy under colonoscopy.

Table 4. Intragroup comparison of TGF-β1 and IL-10 before and after the treatment

Item	TNF-β1 (ng/L)	IL-10 (ng/L)
Before the treatment		
Observation group	28.13±4.56	8.45±3.79
Control group	27.95±4.47	8.41±3.73
t	0.154	0.038
P	0.878	0.969
After the treatment		
Observation group	14.17±2.65[a]	14.25±2.97[a]
Control group	17.11±2.69[a]	9.74±2.56[a]
t	4.269	6.287
P	<0.001	<0.001

Note: Compared with before the treatment in same group, [a]P<0.05. TNF-β1: β1-transforming growth factor beta 1; IL-10: interleukin 10.

Table 5. Comparison of the 3-month QOL after the treatment

Item	Observation group (n=37)	Control group (n=37)	t	P
PF	95.32±2.65	90.70±2.20	8.174	<0.001
RP	76.59±6.56	65.54±6.15	7.473	<0.001
BP	37.00±4.14	31.14±4.28	4.966	<0.001
GH	74.81±3.18	75.16±3.26	0.469	0.640
VT	91.27±3.50	90.22±2.86	1.418	0.160
SF	85.43±5.66	73.35±5.47	9.334	<0.001
RE	80.03±6.30	66.81±9.87	6.864	<0.001
MH	91.46±3.44	90.22±2.86	1.689	0.095

Note: PF: physiological function; RP: physical role; BP: bodily pain; GH: general health; VT: vitality; SF: social function; RE: emotional role; MH: mental heal.

Acute RE is an injury induced by the external effect of radiation, which is intestinal inflammation mediated by cytokines. Studies have shown that the expression levels of inflammatory factors, such as IL-1β, IL-6, and TGF-α, in the intestinal mucosa significantly increased 6 h after radiotherapy [26]. IL-10 induces the secretion of Th2 cytokines to participate in immunoreaction and consequently elicit anti-inflammatory effects. Previous studies suggested that IL-10 may increase the immune function of organisms, and its expression IL-10 increases after chemotherapy; however, the expression of IL-10 after radiotherapy is downregulated because of immune injuries [27]. In the present research, the two groups maintained a low IL-10 expression after they received radiotherapy. Moreover, the expression increased after KangFuXinYe combined with EGF was administered. This increase was particularly evident in the observation group. TGF-β1 participates in the occurrence and development of acute RE and plays an important role [28]. TGF-β1 may also stimulate macrophages and move fibroblasts toward the intestinal mucosa via chemotaxis, ultimately aggravating damages to the intestinal mucosa with the mass release of inflammatory cells and causing acute RE [29]. Our research also found that the expression levels of TGF-β1 in the two groups of patients who received radiotherapy remained high. However, the expression levels declined to certain extent after they were treated with KangFuXinYe combined with EGF. This decline was more pronounced in the observation group than in the control group. KangFuXinYe combined with EGF might elicit an inhibitory effect on the body's inflammatory response and promote wound healing.

With the development of science and technology, the QOL of patients after treatment has been widely explored. Many clinical studies have employed various QOL scales for evaluation; among these scales, 36-Short Form Health Survey is the most popular one [20]. The 3-month QOL of the two groups differ significantly in terms of PF, RP, SF, RE, or BP after the treatment. Nevertheless, no significant difference was found in terms of GH, MH, or VT probably because the observation group had a faster recovery and a higher efficacy than the

control group; the control group also had certain physical, mental, and social problems according to their physicians' scientific guides and instructions. These results were consistent with previous findings [22].

The small sample size in the present research should be enlarged, and the follow-up period should be extended to explore the effect of the treatment on the QOL measures of the two groups.

In conclusion, KangFuXinYe combined with EGF is effective in treating acute RE, alleviating iorth promoting in clinical practices.

Disclosure of conflict of interest

None.

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