Proceedings of Anticancer Research 2018, 2(1): 1-8

BIO-BYWORD SCIENTIFIC PUBLISHING PTY LTD

Proceedings of Anticancer Research

Therapeutic Effect of the Combination of Xiaoaiping Injection and Chemotherapy on Advanced Esophageal Cancer and Coagulation Function

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ARTICLE INFO

Article history:

Published online: 31st Jan, 2018

Key words:

Esophageal cancer

Middle and advanced stage

Xiaoaiping injection

Chemotherapy

Coagulation function

ABSTRACT

Objective To observe the therapeutic effect of the combination of Xiaoaiping injection and chemotherapy on advanced esophageal cancer and coagulation function. **Methods** 100 patients with advanced esophageal carcer were randomly divided into control group and observation group, and each group had 50 cases. The control group was treated with TP chemotherapy, and the observation group, on the basis of the control group's treatment, was treated with the Xiaoaiping injection, and treatment effects, Karnofsky, adverse drug reactions and INR changes before and after the treatment of the two groups were observed. **Results** After 2 periods of treatment, the local control rate of solid tumor, Karnofsky score, and stability in the observation group were significantly higher than those in the control group ($p<0.05$); and the plasma prothrombin time (PT), activated partial coagulation activity time (APTT) and thrombin time (TT) were significantly lower in the observation group than in the control group ($p<0.05$), and Fibrinogen (FIB) was significantly higher than the control group ($p<0.05$); and there was no statistically significant difference in the incidence of adverse reactions between the two groups ($p>0.05$). Conclusion: The therapeutic effect of the combination of Xiaoaiping Injection and chemotherapy on advanced esophageal cancer is obvious, and it can effectively improve the coagulation

function, improve the quality of life, and be safe and reliable, so it's worth popularizing and application.

0 Introduction

Esophageal cancer is one of the common malignant tumors of digestive tract, and it has high mortality and poor prognosis, and 5-year survival rate is below 10%[1]. Due to the lack of vigilance, most patients with esophageal cancer is in the late stage when they come to doctors, and most patients have been transferred, so 60% patients diagnosed in hospitals have lost the opportunity for surgical treatment. Therefore, chemotherapy has become an important means to prolong the survival time and improve the quality of life of patients with advanced esophageal cancer, but the side effects of chemotherapy are obvious. For the patients with poor physique and low immune function, the tolerance is poor, which severely limits their clinical application. Therefore, it has become a hot topic to explore a therapeutic regimen with both good clinical efficacy and high safety. Traditional medicine in the motherland think the reasons of occurance of esophageal cancer are deficiency-excess mixing, deficiency in origin and excess in superficiality, or deficiency in health[2], so treatments like clearing heat and detoxicating, resolving phlegm and softening hard masses are needed to be given. In order to improve the curative effect of advanced esophageal cancer and study its mechanism, this study has observed the curative effect and the effect on coagulation function of the treatment of middle and late stage esophageal carcinoma with the combination of chemotherapy and cancer. The report is as follows.

1 Clinical Materials

1.1 General Materials

From December 2014 to December 2016, 100 patients with middle and advanced esophageal carcinoma in our hospital were picked, and they all meet diagnosis standards related to this disease in *The Standard of Diagnosis and Treatment of Common Malignant Tumors in China* [3]: The general condition is good, Karnofsky score ⩾ 60 points, the estimated survival period is more than 3 months; haven't accepted other anticancer therapy in 1 month; the patient's family have signed informed consent. Pacients with other serious primary disease in cardiovascular, liver, kidney, hematopoietic system, mental patients, women who are in breastfeeding, gestation or preparing for pregnancy, patients have obstruction and can not take Chinese medicine, patients who are allergic to a variety of drugs are all excluded. 100 patients were divided into control group and observation group according to random digital method, each group has 40 cases, and the age, sex, clinical stage, pathological type, body mass index and other general data in two groups are not statistically significant ($p>0.05$), so they have comparability. See table 1.

Groups	cases	Gender		Pathology (case)		Age (years old)	BMI (kg/m^2)	clinical stage	
		male	female	SCC	adenocarcinoma			Period Ⅲ	Period Ⅳ

The observation group	40	20	20	25	15	50.25±3.71	25.88±2.91	25	15
The control group	40	22	18	23	17	50.11±3.65	26.01±2.67	23	17
χ^2/t		0.060		0.202		1.523	0.373	0.202	
P		0.807		0.802		0.122	0.708	0.802	

Table 1. Comparison of general materials of two groups

1.2 Treatment

The control group was given TP chemotherapy regimen: 135 mg/m^2 Taxol (Beijing Concord Pharmaceutical Factory, NMPN(national medicine permission number): H10980068) was dissolved into 500ml 0.9% sodium chloride solution, use intravenous drip in the first day for 4h; 25mg/m^2 cisplatin (Qilu Pharmaceutical Co., Ltd., the NMPN: H37021362), use intravenous drip from day 1 to day 4. The observation group, on the basis of the treatment for the control group, was given 60ml/times Xiaoaiping injection (Nanjing Shenghe Pharmaceutical Co., Ltd. production, the NMPN: Z20025868), add 500ml 5% glucose injection and dilute it, use intravenous drip for 1 time daily. Both groups were treated for 21 days as 1 cycle, and therapeutic effects were compared after using two consecutive cycles.

1.3 Parameters

1.3.1 Therapeutic effects of solid tumor

The therapeutic effect is assessed according to the RECISI standard [4]. Complete remission (CR): all lesions disappeared; partial remission (PR): total reduction of focal length was decreased more than 30%; progress (PD): At least one new lesion appears or the maximum length of the lesion increases more than 20%; stable (SD): The tumor changes do not meet the above requirements. CR+PR for local control.

1.3.2 Karnofsky

Before treatment and after treatment of 2 cycles, used Karnofsky table [5] to assess the body functional status, if the score compared to the score before the treatment increased >10 means it improved, if the score increased or decreased less than 10 point means it is stable, and if the score decreased >10 means it reduced.

1.3.3 Indicators of coagulation function

Before the treatment and after 2 cycles of treatment, 5mL venous blood sample was extracted and 2mL was placed into the purple vacuum anticoagulation tube, and the ethylene diamine tetraacetic acid disodium(Na2 EDTA) was added. 3mL of sample was placed into a light blue vacuum anticoagulant tube and sodium citrate was added. The plasma prothrombin time (PT), activated partial thromboplastin time (APTT) , plasma fibrinogen (FIB) , thrombin time (TT) and other indicators were measured by automatic blood coagulation analyzer and matching reagent.

1.3.4 Adverse reaction

The adverse reaction occurred in 2 groups of patients during treatment are recorded.

1.4 Statistical method

Using SPSS17.0 software for statistical processing and comparative analysis for data obtained, and the

measurement data was indicated by mean standard deviation ($\bar{x}$ ±s), the comparison of measurement data was indicated by t test, counting data was indicated by percentage, counting data comparison was indicated by X2 test, and α=0.05 was the test level for all of them.

2 Results

2.1 Comparison of therapeutic effect of two groups of solid tumors

After 2 cycles of treatment, the local control rate of solid tumor in observation group was significantly higher than that in control group (*P*<0.05). See Table 2.

Groups	Cases	CR	PR	PD	SD	local control
observation group	50	20（40.00）	18（36.00）	10（20.00）	2（4.00）	76.00
control group	50	15（30.00）	15（30.00）	12（24.00）	8（16.00）	60.00
x^2	--	0.269	0.625	1.667	1.404	4.706
P	--	0.604	0.429	0.197	0.236	0.030

Table 2. Comparison of therapeutic effect of two groups of solid tumors [cases (%)]

2.2 Comparison of Karnofsky changes of two groups

After 2 cycles of treatment, the increase rate and stability rate of Karnofsky of the observed group was significantly higher than that of the control group (p<0.05). See table 3.

Groups	Cases	Increase	Stable	Decrease	Rate of increase and stability
Observation group	50	25（50.00）	20（40.00）	5（10.00）	45（90.00）
Control group	50	17（34.00）	16（32.00）	17（34.00）	33（66.00）
X^2		2.011	0.391	7.051	7.051
P		0.156	0.532	0.008	0.008

Table 3. Comparison of Karnofsky changes of two groups [case (%)]

2.3 Comparison of coagulation function indicators before and after treatment in two groups

There was no statistically significant difference of coagulation function indicators between the two groups before treatment (p>0.05). After 2 cycles of treatment, the average of PT, APTT and TT level was significantly decreased (p<0.05), FIB level was significantly increased (p<0.05), and the average FIB level in the observation group was significantly higher than that in the control group (p< 0.05), PT, APTT, TT level all significantly lower than the control group (p<0.05). See table 4.

Groups	Cases	PT（s）		APTT（s）		FIB（g/L）		TT(s)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group	50	11.51±1.11	10.15±0.65①	30.65±4.06	26.65±3.02①	1.54±0.38	2.25±0.44①	19.80±2.85	17.21±3.02①
Observation group	50	11.58±1.08	9.05±0.70①	30.60±4.02	24.76±2.11①	1.51±0.34	3.05±0.96①	19.85±3.10	16.05±2.80①
t		0.044	6.495	0.613	7.165	0.063	4.553	0.089	3.257
P		0.965	0.000	0.542	0.000	0.950	0.000	0.930	0.002

Table 4. Comparison of coagulation function indicators before and after treatment in two groups ($\bar{x} \pm s$)

Note: ①compared to data before the treatment, *P*<0.05

2.4 The occurrence of adverse reactions in two groups

There was no statistically significant difference in the incidence of adverse reactions between the two groups (p>0.05), and all kinds of adverse reactions occurred after discontinuation were eliminated in the patients. See table 5.

Groups	Cases	white blood count drops	nausea	vomit	arrhythmia	adverse reactions
Observation group	50	1（2.00）	2（4.00）	1（2.00）	1（2.00）	5（10.00）
Control	50	2（4.00）	1（2.00）	2（4.00）	2（4.00）	7（14.00）

group					
X^2	0.344	0.344	0.344	0.344	0.378
P	0.558	0.558	0.558	0.558	0.538

Table 5. Comparison of occurrence of adverse reactions in two groups [case (%)]

3 Discussion

At present, the study shows that esophageal cancer patients often have abnormal coagulation function, which often manifests as abnormal changes in subclinical coagulation routine [6]. Tumor cells can not only activate coagulation factors, but also cause the destruction of vascular endothelial cells, platelet activation and fibrinolysis abnormalities, etc. [7]. Clinical statistics [8] found that in patients with esophageal cancer, the incidence of thrombosis was 15%, and autopsy found that about 50% cancer patients had different types of thrombosis. In recent years, with the increase of cancer incidence rate and mortality rate, the incidence of esophageal cancer-related thrombus increased [9], and the relationship between the abnormal changes of coagulation function and the invasion and metastasis of tumor was also paid more and more attention. In addition, evidence-based medicine has confirmed that thrombosis and tumor-related bleeding are the most common complications and causes of death in patients with advanced esophageal cancer, and the coagulation and fibrinolysis system in patients with esophageal cancer is beneficial to the growth and metastasis of tumor [10], which will undoubtedly result in lower survival rate. Therefore, it is important to adjust coagulation function in advanced esophageal cancer as soon as possibl. At present, the treatment of advanced esophageal cancer patients still lack of effective methods, and chemotherapy and radiotherapy are most common methods, but the effect of chemotherapy is not ideal, and toxic side effects are greater [11]. And chemotherapy is one of the risk factors of promoting the malignant tumor patients with high blood coagulation status, which limited its clinical application. Therefore, it is an advantage and a possible breakthrough for the study of esophageal cancer to seek the treatment method of traditional Chinese medicine or the combination of TCM treatment and to study its mechanism in depth.

There is no specific disease name for esophageal cancer in Chinese medicine, and according to its symptoms, it can be classified as "choke" category. For example, in the *On truth (Zhi Zhen Yao Da Lun),* “one will vomit if food cannot do down and pharynx is obstructed", in *Bei Ji Qian Jin Yao Fang (Prescriptions Worth a Thousand in Gold for Every Emergyency*), it said: "if one is obstructed, then he/she eats a little, and only feels obstructive in breast, and too painful to breathe." The traditional Chinese medicine thinks that it occurs on the basis of weakened body resistance, and featured qi stagnation, phlegm coagulation, and blood stasis, which belongs to deficiency in origin and excess in superficiality. A long-term invasion of the body caused Qi deficiency in the body, and disorders in blood and fluid operation, leading to other pathological changes such as qi stagnation, blood stasis, phlegm. Phlegm and blood stasis form physical block in the esophagus and become the obstruction of diet and causes of the disease [12]. In addition, the traditional Chinese medicine thinks that chemotherapy drugs are cold, bitter medicine, so the toxic side effects are mainly for chronic diseases marked by deficiency of vital energy and lowering body resistance, often manifested as deficiency of qi and blood, spleen kidney and so on, so that the body loss more healthy atmosphere. Therefore,

in the use of therapy to treat the disease, we also need to use blood circulation of stasis, heat and detoxification and other treatment. According to the above pathogenesis, the author, on the basis of the use of therapy, combined with the treatment of Xiaoaiping injection. This medicine is the sterile water solvent of the glaucescent fissistigma root, which is the root of the Fissistigma glaucescens which belongs to Anno naceae. According to the "Chinese Medicine Dictionary" records: “glaucescent fissistigma root, warm in nature, flat in taste, can come into the liver", and it has the fuction of heating and detoxificating, softening hard mass and dispersing the obstruction. In addition, modern pharmacological studies have shown that Xiaoaiping injection contains polysaccharides, alkaloids, saponins and other effective components, and has a high inhibition and killing effect [13] on tumor in digestive tract, the lungs and other parts of body, and can increase the immune function. By inhibiting esophageal cancer Ec-9706 expression, it can induce cancer cell apoptosis and inhibit tumor cell growth and DNA synthesis, while blocking the growth of tumor cells and make them stay in the G1 period, and gradually induce them to normal cells [14]. In addition, the Xiaoaiping injection can improve vascular endothelial function and coagulation function, promote hemostasis, blood coagulation process to balance and stability, and reduce the risk of thrombosis [15].

The results showed that the local control rate, the increase and stability rate of Karnofsky of the solid tumor in observation group were significantly higher than those in the control group, and the average level of PT, TT and FIB after treatment was significantly lower than that in the control group, the FIB level was significantly higher than that in the control group, and the incidence of adverse reactions between the two groups was not significant. It is suggested that the curative effect of the treatment of middle and advanced esophageal cancer with the use of Xiaoaiping injection combined with chemotherapy can effectively improve the coagulation function, improve the quality of life, and is safe and reliable. However, the sample is small, the observation time is short, and long-term follow-up to the patient has not been carried on, so the exact evidence-based data should be further observed.

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