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EFFECT OF ACUPUNCTURE ON PERIPHERAL BLOOD LYMPHOCYTE SUBSETS IN PATIENTS WITH CANCER-RELATED FATIGUE

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Abstract: Objective: To study the effect of acupuncture on peripheral blood lymphocyte subsets in patients with cancer-related fatigue(CRF). **Methods:** A total of 80 patients with CRF were randomized into an observation group and a control group, and finally 67 patients completed this trial(36 cases in the observation group, 31 cases in the control group). Patients in the control group were treated with conventional chemo radio therapy and symptomatic treatment, while no particular anti-fatigue intervention was adopted. On the basis of treatment in the control group, acupuncture was applied at Baihui(GV 20), Guanyuan(CV 4), Qihai(CV 6), Fengchi(GB 20), Zusanli(ST 36), Sanyinjiao(SP 6) in the observation group, once a day, 5 times as one course, with 2 days interval between each course, totally 4 courses were required. Before and after treatment,the peripheral blood lymphocyte subsets in patients with CRF were monitored by flow cytometry (FC). **Results:** After acupuncture, the levels of CD3+, CD4+,CD19+ and the ratio of CD4+/CD8 + of the observation group increased significantly (P<0.05).However, the levels of CD8+,CD16+CD56+ of the observation group decreased significantly (P<0.05).In the control group, the levels of CD3+,CD4+ were decreased significantly due to radiotherapy or chemotherapy (P<0.05). But the level of CD16+CD56+ increased significantly (P<0.05).After acupuncture, the levels of CD3+,CD4+,CD19+ and the ratio of CD4+/CD8 + of the observation group was significantly higher than these of the control group (P<0.05).However, the level of CD16+CD56+ of the observation group was significantly lower than that of the control group (P<0.05). **Conclusion:** Acupuncture can increase the levels of CD3+, CD4+,CD19+ and the ratio of CD4+/CD8 + and decrease the level of CD8+,CD16+CD56+,which indicated that acupuncture can improve the immune function of CRF patients.

Keywords: Cancer related fatigue(CRF); Acupuncture; lymphocyte subsets

1. INTRODUCTION

Cancer related fatigue (CRF) is a common symptom that seriously affects the daily life of cancer patients[1]. The national comprehensive cancer network of the United States defines CRF as a painful, persistent and subjective feeling of fatigue, accompanied by physical, emotional and cognitive fatigue, which is related to cancer or its treatment, but not related to recent activities, and has affected the daily life of cancer patients[2]. Research shows that about 50% - 90% of cancer patients have different degrees of CRF[3,4]. All CRF patients have different degrees of immune dysfunction[5]. Previous studies showed that acupuncture can improve depression, fatigue, weakness, headache and other related symptoms of CRF patients. Acupuncture also can reduce anxiety and depression, enhance patients' perception of social and family support and improve patients' confidence. Our previous research results also confirmed that acupuncture can reduce the abnormally elevated inflammatory cytokines, such as IL-6 and TNF, IL-6, sTNF-R1[6]. Lymphocytes are the most important immune cells in human body, but the effect of acupuncture on peripheral blood lymphocyte subsets in patients with CRF is not clear. The objective of this study is to research the effect of acupuncture on peripheral blood lymphocyte subsets in patients with CRF, and then to clarify the effect of acupuncture on immune function.

2. CLINICAL DATA

Between July 2016 and December 2018, a total of 80 CRF patients were recruited, all of whom were from the inpatient department of oncology department and the outpatient of acupuncture department of the first affiliated hospital of Jinan University. The diagnostic criteria of CRF refer to the ICD-10[7]. All cases were randomly divided into the observation group and the control group. This project was registered in China Clinical Trial Registration Center (Registration No. chictr-ior-17013560) and approved by the medical ethics committee of the first affiliated hospital of Jinan University (No. 2015 [024]).

3. METHODS

3.1 The control group

Routine radiotherapy and chemotherapy were carried out,

and routine symptomatic treatment was carried out for the cancer itself or various symptoms due to its treatment, but special anti fatigue treatment was not adopted for CRF.

3.2 The observation group

Patients in this group were treated with acupuncture. Acupoints: Baihui(CV20), Guanyuan(CV4), Qihai(CV6), Fengchi(GB20), Zusanli(ST36), Sanyinjiao(SP6). Operation: the patients laid on back.After the routine disinfection of the acupoint skin, a disposable acupuncture needle with a diameter of 0.25 mm and a length of 40 mm was inserted into the acupoint for about 15-25 mm. After the patient had the feeling of acid, numbness or distention, the even reinforcing-reducing method was carried out. The acupuncture intensity was based on the patient's tolerance. After 15 minutes, pull out the needle. Acupuncture once a day, 5 times as a course, a total of 4 courses. All acupuncture was operated by the same acupuncturist , who did not participate in the grouping of cases.

4. DETECTION OF PERIPHERAL BLOOD LYMPHOCYTE SUBSETS

Before and after intervention, 5ml of venous blood was collected at 6:30-7:30 in the morning. The peripheral blood lymphocyte subsets of serum was detected by flow cytometry, which was carried out in the Central Laboratory of the First Affiliated Hospital of Jinan University. The specific steps were carried out in strict accordance with the operating procedures.

5. STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA). The measurement data were represented as the mean values± standard deviation ($\overline{X}$ ±s).T test were used. A P value of less than 0.05 was considered to indicate statistical significance.

6. RESULTS

6.1 Comparison of general data between the two groups

During the study, 6 cases were transferred to another department or hospital due to the change of their condition (including 4 cases in the observation group and 2 cases in the control group). 7 cases were excluded for various reasons (including 4 cases in the observation group and 3 cases in the control group). A total of 67 cases were completed in this study (36 cases in the observation group and 31 cases in the control group).

In the observation group, there were 12 cases of lung cancer, 5 cases of gastric cancer, 7 cases of liver cancer, 4 cases of rectal cancer, 2 cases of breast cancer, 3 cases of cervical cancer, 1 case of pancreatic cancer and 2 cases of esophageal cancer. In the control group, there were 8 cases of lung cancer, 8 cases of liver cancer, 3 cases of gastric cancer, 2 cases of bladder cancer, 4 cases of cervical cancer, 2 cases of rectal cancer, 2 cases of breast cancer, 1 case of ovarian cancer and 1 case of lymphatic cancer.There was no significant difference in gender composition, age and course of disease between the two groups (P > 0.05). Table 1.

Table 1 Comparison of general data of CRF patients between the two groups

Group	cases	Gender		Age	Course of disease
		Male	Female	(Year)	(Month)
The observation group	36	21	15	60.19±3.32	7.31±1.74
The control group	31	20	11	59.34±4.07	7.92±1.90

6.2 Comparison of peripheral blood lymphocyte subsets between the two groups before and after acupuncture

Before acupuncture, there was no significant difference in the levels of CD3+, CD4+, CD8+, CD19+, CD16+CD56+ between the two groups (P>0.05).

After acupuncture, the levels of CD3+, CD4+, CD19+ and the ratio of CD4+/CD8 + of the observation group increased significantly (P<0.05). However, the levels of CD8+, CD16+CD56+ of the observation group decreased significantly (P<0.05).In the control group, the levels of CD3+, CD4+ were decreased significantly due to radiotherapy or chemotherapy (P<0.05). But the level of CD16+CD56+ increased significantly (P<0.05).

After acupuncture, the levels of CD3+, CD4+, CD19+ and the ratio of CD4+/CD8 + of the observation group was significantly higher than these of the control group (P<0.05). However, the levels of CD8+, CD16+CD56+ of the observation group was significantly lower than that of the control group (P<0.05). Table 2. Figure 1

Table 2 Comparison of Peripheral Blood Lymphocyte Subsets between the Two Groups

	The Observation Group（36 cases）		The Control Group（31 cases）	
	Before	After	Before	After
CD3+	66.24±14.62	71.17±16.22*#	64.49±12.38	60.73±10.64*
CD4+	38.17±9.89	45.41±8.67*#	36.21±8.17	32.22±7.96*
CD8+	27.12±6.56	24.21±7.49*	26.88±7.01	27.64±7.36
CD4+/CD8+	1.42±0.26	1.78±0.31*#	1.35±0.29	1.12±0.26
CD19+	8.72±0.89	10.35±1.41*#	8.26±0.76	7.81±0.59
CD16+CD56+	28.72±3.93	22.66±2.68*	29.89±3.54	32.72±5.23

Note: * Compared with before acupuncture, P < 0.05; # Compared with the control group, P < 0.05.

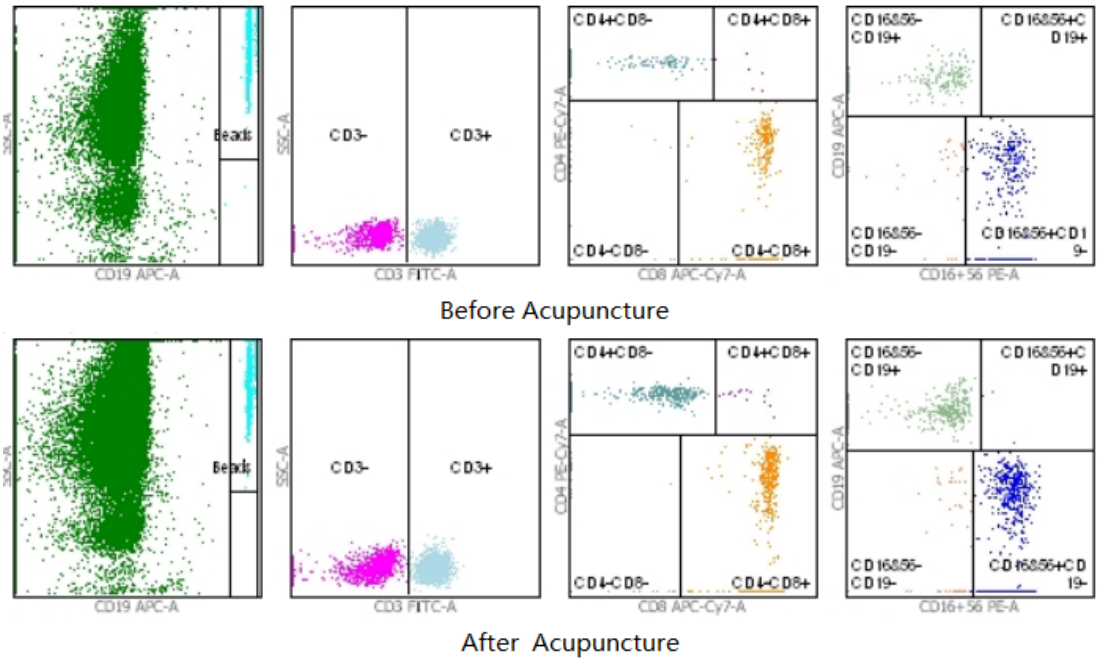

Figure 1. Comparison of Peripheral Blood Lymphocyte Subsets before and after Acupuncture

7. DISCUSSION

In a healthy human body, CD4+ and CD8+ T lymphocytes coordinate and inhibit each other, so as to ensure the normal operation of the immune system [8]. CD4+T lymphocytes play a central role in immune response. Cytokines secreted by CD4+T lymphocytes not only enhance the effectiveness of cellular immunity, but also promote the proliferation, activation and antibody production of CD19+B lymphocytes, and then assist humoral immunity to play an anti-tumor role.Therefore, when the number of CD4+ T lymphocytes in patients with malignant tumors decreases, the number of CD19+ B lymphocytes that exert humoral immune effect will also decrease. CD8+ T lymphocytes contain cytotoxic T cells, which can directly kill target cells by specifically recognizing endogenous antigens. After killing target cells, it will apoptosis rapidly, and its level in peripheral blood is unstable. In addition, CD8+ T lymphocytes are recognized as the main effector cells of anti-tumor. Studies have shown that CD8+ T lymphocytes and CD16+ CD56+ NK cells play a major role in killing tumor cells [9]. Moreover, CD8+ T lymphocytes also contain a class of inhibitory regulatory T cells, which have inhibitory activity on self reactive CD4 + T lymphocytes and can regulate the stability of the internal environment by inhibiting the immune response [10]. Therefore, the increase of CD8 + cells suggests the enhancement of immunosuppression in patients with malignant tumors, the phenomenon of tumor immune escape, and the increase of CD8 + cells in peripheral blood of patients with malignant tumors[11]. And the ratio of CD4+/CD8 + cells is one of the important indicators reflecting the functional stability of the immune system. If this ratio decreases, it indicates that the immune function of the human body has decreased[12].

The results show that acupuncture can increase the levels of CD3+, CD4+, CD19+ and the ratio of CD4+/CD8 + and decrease the level of CD8+,CD16+CD56+, which indicated that acupuncture can improve the immune function of CRF patients. The effect of acupuncture is a multi-target and multi-angle comprehensive effect, but due to objective conditions, the mechanism of acupuncture on CRF is still not comprehensive. On the other hand, due to time constraints, the follow-up study of this therapy has not been carried out, and the long-term effect of acupuncture on CRF has not be involved, which is the future research direction.

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