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Research Article

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A treatment for hypercoagulable states in gastrointestinal tumor patients by ginkgo leaf injection

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ABSTRACT

In this paper, the treatment efficacy for gastrointestinal tumor patients with hypercoagulable states by Ginkgo injection was researched. The levels of Fib, D-Dimer, PLT of gastrointestinal tumor group with 98 patients and health group was observed and analyzed by statistics methods, and 98 patients was divided into two groups by random, one is treated by Ginkgo injection as treatment group, the other is treated by low-molecular-weight heparin sodium injection as control group, and treatment effect between the two groups was observed. In the experiment, the levels of Fib, D-Dimer, PLT in gastrointestinal tumor patient group were significantly higher than health group ($P<0.05$), and they were both lower than before after the treatment in treatment group and control group. There were 3 patients had untoward effect in treatment group, and there were 21 in control group. The occurrence of skin ecchymosis and melena in treatment group was lower than control group ($P<0.05$). The experimental result shows that the Ginkgo injection is an effective and safe therapy to cure hypercoagulable states.

Key words: Ginkgo injection, gastrointestinal tumor, hypercoagulable states

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INTRODUCTION

In the recent half a century, the research on cancer becomes a very important field in medical science. Cancer is a common and frequently-occurring disease. According to the national survey on causes of the residents' death, it is the main one influencing the health of both urban and rural residents in China. Thrombosis is a common complication with cancer and is the second leading cause of death, and hypercoagulable state is the direct cause of thrombosis [1]. It may not only promote tumor recurrence, metastasis, but also a direct cause of thromboembolic disease and death in cancer patients. According to statistics, about 90% cancer patients are in hypercoagulable state, and about 4%~30% patients will have venous thromboembolism(VTE)[2]. Combining traditional Chinese medical theory and clinical manifestations of malignancy, stagnation of blood in Chinese medicine is similar to the hypercoagulable state in characteristics. Dense, sticky, agglomerate and clotted process of blood is the common pathological basis, which is the entire process throughout tumorigenesis and progression. Stagnation of blood is one of the main pathological products in tumorigenesis and progression, which associate with the pathogenesis of tumors. It provides a theoretical basis for treating cancer hypercoagulable state by Chinese medicine. Therefore, the treatment of blood stagnation can be used in anti-tumor therapy to reduce the risk of thrombosis and reduce or even prevent blood metastasis for prolonging the lives of patients and improving the quality of life. Ginkgo leaf is a specific remedy for stagnation of blood, which has the effect of promoting blood circulation. Modern medicine pharmacology studies confirmed that its active ingredients – terpene lactone compounds - can inhibit platelet aggregation and resist the activity of platelet activating factor. It can reduce blood viscosity, fibrinogen and hypercoagulable state by improving microcirculation and hemorrheology[3]. The paper is focused on researching of Ginkgo injection for treating hypercoagulable state by gastrointestinal tumor and intended to provide the basis for clinical use.

EXPERIMENTAL SECTION

Materials: in the experiment, there were 98 patients attended from 2010.6 to 2013.2 in oncology of the affiliated Hospital of Hebei University. They were 67 males and 33 females form 41~68 years old and 55.3 in average. All patients underwent physical examination, laboratory tests, medical imaging examination, endoscopy and biopsy, including 30 cases of esophageal cancer, 37 cases of gastric cancer, 31 cases of colorectal cancer. All patients have been confirmed by cytologic or histologic examination. Inclusion criteria: (1) in three month before treatment, they did not use anticoagulant drugs and blood-activating drugs; (2) Kamofsky ratings >60; (3) expected survival time > 6 months; (4) no contraindications to chemotherapy. Exclusion criteria: (1) patients' expected survival time < 6 months; (2) contraindications to chemotherapy; (3) contraindication for anticoagulant drags and blood-activating drugs; (4) complication with severe cardiovascular and cerebrovascular diseases; (5) active ulcer disease; (6) cannot be follow-up visited. All patients were received chemotherapy at the first time. They were divided into two groups by digital randomization method: control group is treated by low-molecular-weight heparin sodium injection (49 cases); treatment group is treated by Ginkgo injection (49 cases). At the same time, healthy group was also formed by 56 cases, including 35 males and 21 females at the age from 35~55, and the average age is 40.2. Treatment group and control group was comparable that their age, gender and site had no statistically difference (P>0.05). Patients group and healthy group was also comparable that their age and gender had no statistically difference (P>0.05).

Methods and determination of curative efficacy: Gastrointestinal cancer patients were used standard chemotherapy method by NCCN Guidelines. Drug was used two courses, and dose was computed by body surface area method. In treatment group, 20ml Ginkgo was mixed with 5%G.S. to form the intravenous infusion for 2 courses of treatment which was composed of 20 days. In control group, the 5000 IU low-molecular-weight heparin sodium was used for 2 courses of treatment which was composed of 20 days. Coagulation was detected timely when patients had bleeding tendency in both two groups.

Coagulation indexes and platelets were detected before and after 2 courses treatment in all the three groups. The treatment was effective when the level of Fibrinogen (Fib), D-dimer and Platelet (PLT) was decreased, but non-effective when the level was increased or changeless. Some coagulation indicators can be used as monitoring indicators for hypercoagulable state. Plasma Fib was proved to be a highest level of coagulation proteins in the blood that associated with the formation of blood clotting disorders and tumor growth or metastasis. The significantly increase of cancer patients' Fib levels and related degradation products in the plasma was enhanced adhesion role of PLT for tumor cells, but also conducive to cancer metastasis. D-dimer is a kind product of cross-linked proteins specific, and is also confirmed as a secondary fibrinolysis specific indicator. Rise of D-dimer level indicates that secondary fibrinolysis becomes strong in the host, and can be considered a molecular marker of hypercoagulable state and fibrinolysis [4]. Vardy J. et al. found that D-dimer level was closely related to tumor progression [5]. The cancer cells will stimulate the release of platelet procoagulant excepting their own impact. Its direct or indirect role can lead to platelet activation, aggregation and adhesion. Therefore, the level of PLT is closely associated with tumor. Related studies have shown that there were 60% cancer patients with elevated platelet levels [6].

Facilities and reagents: the level of Fib and D-dimer was tested by Stago Inc. STA-R Evolution Expert Series System 58177. Reagents were also from Stago corresponding to the system. PLT was tested by automated hematology analyzers Sysmex Kx-21 from Sysmex Inc.

Statistical analysis methods: data were analyzed by software system SPSS 17.0. Measurement data were expressed as the form of mean ± standard deviation. Different groups were compared using independent sample t test. Count data expressed as percentage by χ^2 test. The difference was statistically significant when P<0.05.

RESULTS AND DISCUSSION

Comparison of coagulation between gastrointestinal cancer group and healthy group: In gastrointestinal cancer group, the level of Fib, D-dimer and PLT was significantly higher than healthy group, and the difference had statistically significant (P<0.05). The testing results are shown in table 1.

Changes of hypercoagulable states before and after treatment in gastrointestinal cancer group: In control and treatment group, there is no statistical significance before and after treatment by comparing the level of Fib, D-dimer and PLT between the two groups (P>0.05). The levels were all lower than before that after treatment in two groups, and there is statistical significance (P<0.05) as shown in table 2.

Table 1. Comparison of coagulation between gastrointestinal cancer group and healthy group

Group	Fib（g/L）	D-D（μg/L）	PLT（$\times10^{11}$个/L）
gastrointestinal cancer group (n=100)	5.02±0.53 *	523.26±48.24 *	398.52±30.13 *
healthy group (n=50)	2.83±0.24	169.24±19.26	312.10±19.31
T	36.34	40.021	8.153
P	0.000	0.000	0.000

*In table 1, * means P<0.05 that compared with healthy group.*

Table 2. Changes of hypercoagulable states before and after treatment in gastrointestinal cancer group

Groups	Treatment group(n=49)		Control group(n=49)	
	Before treatment	After treatment	Before treatment	After treatment
Fib （g/L）	4.89±0.53 #◇	3.63±0.25 *	4.90±0.53 ◇	3.21±0.49
D-D（μg/L）	558.67±30.28 #◇	257.70±50.12*	561.24±46.72◇	230.56±30.21
PLT （$\times10^{12}$个/L）	394.15±35.62 #◇	321.15±34.14*	385.24±30.86◇	319.26±30.42

In table 2, # means comparison result P>0.05 between control and treatment group before treatment; * means comparison result P>0.05 after treatment; ◇ means comparison result P<0.05 by each group itself before and after treatment.

Comparison of adverse reactions: the adverse reactions were compared during the treatment in gastrointestinal cancer group. There were 3 cases of adverse reactions in treatment group at incidence rate of 6.12%; and there were 21 cases in control group at the rate of 42.85%. There were significant differences (P <0.05). In these cases, allergic reactions and bleeding gums showed no significant difference in the two groups (P> 0.05). Incidence rate of skin bruising and melena was 0 in treatment group, but was 26.53% and 8.16% in control group. Treatment group was significantly lower than the control group, and the difference was statistically significant (P <0.05). The results are shown in table 3.

Table 3. Comparison of adverse reactions in gastrointestinal cancer group

Groups	Treatment group/ Ginkgo injection (n=49)		Control group/ Low molecular weight heparin (n=49)	
	Cases (n)	Incidence rate (%)	Cases (n)	Incidence rate (%)
Allergic reactions	2	4.08	2	4.08
Bleeding gums	1	2.04	2	4.08
Skin bruising	0 *	0.0	13	26.53
Melena	0 *	0.0	4	8.16
Total	3 *	6.12	21	42.85

*In table 3, * means P<0.05 that compared with control group.*

Factors affecting the treatment of Ginkgo injection on hypercoagulable state: The treatment group was divided into groups by gender, site and metastasis situation for comparing the effect of Ginkgo injection treating on hypercoagulable state. In gender groups, 24 male patients were effective at efficiency rate of 80.0%, and 15 females were effective at the rate of 78.9%. There was no significant difference (P>0.05). In site groups, the effect for treating hypercoagulable state of esophageal cancer, gastric cancer and colorectal cancer was 83.3%, 81.0% and 80%. There was no significant difference (P>0.05). The effective rate was 55.9% for patients with metastasis, and was 66.7% for patients without metastasis. And there was significant difference (P<0.05). They were shown in table 4.

Table 4. Factors affecting the treatment of Ginkgo injection on hypercoagulable state [n,(%)]

Results	Gender		Site			Metastasis situation*	
	Male (n=30)	Female (n=19)	Esophageal cancer (n=18)	Gastric cancer (n=21)	Colorectal cancer (n=10)	Metastasis (n=34)	No metastasis (n=15)
Effective	24, (80.0)	15, (78.9)	15, (83.3)	17, (81.0)	8, (80.0)	19, (55.9)	10, (66.7)
Ineffective	6, (20.0)	4, (21.1)	3, (16. 7)	4, (19.0)	2, (20.0)	15, (51.1)	6, (33.3)
χ^2	0.021		2.213			4.186	
P	0.863		0.634			0.031	

*In table 4, * means P<0.05 comparing between groups.*

Hypercoagulable state is very common complication in patients with gastrointestinal cancer. It is concerned with tumorigenesis, metastasis and recurrence, and seriously affected the prognosis and survival of patients. It is an important risk factor of poor prognosis [7-9]. Hypercoagulable state is also called prothrombotic state. It is a pathological state for vascular endothelial cell injury by variety of pathological factors causing coagulation, fibrinolysis and anticoagulant system dysfunction, which increased blood coagulation and conducive to thrombosis

[10]. In the experiment results of the paper, the level of Fib, D-dimer and PLT was high in all the 98 gastrointestinal cancer patients, which rich to (5.02±0.53)g/L, (523.26±48.24)μg/L and (398.52±30.13)×10^{12} /L. It is significantly higher than healthy people. That is verified that the blood of gastrointestinal cancer patients were in hypercoagulable states.

Studies have shown that the anticoagulant treatment can prolong the median survival time of cancer paptients [11, 12], and reduce the risk of thrombosis. However, the anticoagulant process easily increases the risk of bleeding, recurrent thrombosis, osteoporosis and heparin-induced thrombosis. And coagulation index must be tested repeatedly. That is not conducive to clinical application and promotion. Hypercoagulable state is very similar to stagnation of blood in Chinese medicine. Blood circulation is main method of treating blood stagnation in Chinese medicine. It is popular in integrative medicine clinical applications and gets good results in treatment. The active ingredients in Ginkgo injection is flavonol glycosides and Ginkgolides, which has effect on blood circulation and treating hypercoagulable state.

In this paper, we used Ginkgo injection in treatment group and low-molecular-weight heparin sodium injection in control group to compare treatment efficacy. The comparison of Fib, D-dimer and PLT before and after treatment showed that there was no statistical significance (P>0.05), but these indicators were all reduced after treatment in both two groups that had statistical significance (P<0.05). That indicated that both Ginkgo injection and low-molecular-weight heparin sodium injection had the same treatment efficacy. Moreover, we divided treatment group into groups by gander, site and metastasis situation to analyze. The results showed that the different gander and site had no influence on efficacy (P>0.05), and there were some influence for metastasis patients that the efficacy was better for patients without metastasis. By comparing adverse reactions, there were only 3 cases in treatment group in contrast to 21 cases in control group (P<0.05). And there was significant difference in rate of skin bruising and melena (P<0.05). That indicates that Ginkgo injection was better than low-molecular-weight heparin sodium injection in security.

CONCLUSION

Most of patients with cancer, especially patients with advanced were in hypercoagulable state, which have been confirmed in many clinical studies, so preventive anticoagulant therapy has been recognized by clinicians. In this paper, the treatment efficacy for gastrointestinal tumor patients with hypercoagulable states was researched by comparing Fib, D-dimer and PLT before and after treatment using Ginkgo injection and low-molecular-weight heparin sodium injection in different groups. The experimental results showed that Ginkgo injection and low-molecular-weight heparin sodium injection had the same treatment efficacy, and Ginkgo injection was better than low-molecular-weight heparin sodium injection in security. Ginkgo injection can improve blood hypercoagulable state in patients with gastrointestinal cancer, and unrelated with the disease site and gender. It is a safe and effective medicine that is worthy of clinical application.

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