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Curative effect of silybin combined with pituitrin−phentolamine for pulmonary tuberculosis complicated by acute hemoptysis

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ABSTRACT

Objective: To study the curative effect of silybin combined with pituitrin-phentolamine for pulmonary tuberculosis complicated by acute hemoptysis. **Methods:** A total of 78 patients with pulmonary tuberculosis complicated by acute hemoptysis who were treated in this hospital between December 2013 and April 2017 were divided into control group (n=39) and silybin group (n=39) by random number table. Control group received pituitrin-phentolamine hemostasis therapy, silybin group received pituitrin-phentolamine combined with silybin therapy, both were treated for 1 week. The differences in peripheral blood liver function and coagulation index levels as well as serum oxidative stress index contents were compared between the two groups of patients before treatment and after 1 week of treatment. **Results:** Before treatment, the differences in peripheral blood liver function and coagulation index levels as well as serum oxidative stress index contents were not statistically significant between the two groups. After 1 week of treatment, peripheral blood liver function indexes ALT, AST, ALP and STB contents of silybin group were lower than those of control group; peripheral blood coagulation indexes PT, APTT and TT levels were lower than those of control group whereas Fib level was higher than that of control group; serum oxidative stress indexes AOPPs and LHP contents were lower than those of control group whereas GSH-Px and T-AOC contents were higher than those of control group. **Conclusion:** pituitrin-phentolamine combined with silybin therapy can effectively protect the liver function, optimize the coagulation function and reduce the oxidative stress response in patients with pulmonary tuberculosis complicated by acute hemoptysis.

1. Introduction

Hemoptysis is one of the most typical clinical manifestations in patients with severe pulmonary tuberculosis, frequent episodes of massive hemoptysis can eventually cause patients′ shock and death, and it has been found at present that at the same time of active hemostasis, tuberculosis patients with severe hemoptysis can develop obvious liver dysfunction, which is speculated to be because that major blood loss influences liver cell function, anti-tb drugs produce side effects of liver function damage, etc[1,2]. Silybin is a kind of antioxidant that is extracted from plant milk thistle and can significantly stabilize liver cell membrane, it has been successfully applied in liver cirrhosis, cholangitis, liver cancer and other liver diseases, some scholars have currently recommended it for the pulmonary tuberculosis patients with liver dysfunction after hemoptysis, but the few studies are carried out at present[3−5]. In the study, at the same time of pituitrin-phentolamine hemostasis, combined silybin therapy was added in pulmonary tuberculosis patients with hemoptysis, and the effects of the drug on liver function, blood coagulation function, oxidative stress and other aspects were explored to provide reference for subsequent treatment of similar diseases.

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2. Information

2.1 Case information

A total of 78 patients with pulmonary tuberculosis complicated by acute hemoptysis who were treated in this hospital between December 2013 and April 2017 were divided into control group (n=39) and silybin group (n=39) by random number table. The two groups were included as follows: (1) with pulmonary tuberculosis-induced hemoptysis; (2) combined with liver dysfunction; (3) the families of the patients signed the informed consent; (4) cooperating with and successfully completing the treatment plan. The exclusion criteria were as follows: (1) combined with blood loss caused by other reasons; (2) combined with liver cirrhosis, liver cancer and other basic liver diseases; (3) combined with silybin, pituitrin and phenolamine allergy; (4) combined with pregnancy or breast feeding. Control group included 21 males and 18 females that were 27-56 years old; silybin group included 20 males and 19 females that were 25-55 years old. The difference in above basic data distribution was not significant between the two groups, and the follow-up clinical study was approved by the hospital ethics committee.

2.2 Therapy

Both groups were treated with conventional anti-tb drugs, including isoniazid, pyrazinamide, rifampicin, and so on, and also given anti-infection treatment. Control group received pituitrin-phenolamine hemostasis, which was as follows: pituitrin 24 U and phenolamine 10 mg, by intravenous drip, 12 h/time, lasting for 1 week. On the basis of pituitrin-phenolamine hemostasis, silybin group received silybin therapy, which was as follows: the silybin capsule, taken orally, 70 mg/time, 3 times/d, lasting for 1 week.

2.3 Observation indexes

Before treatment and after 1 week of treatment, fasting cubital venous blood specimens were extracted from two groups of patients and anti-coagulated, then automatic biochemical analyzer was used to detect the liver function indexes alanine aminotransferase (ALT), aspertate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin (STB) contents; coagulometer was used to detect the levels of coagulation indexes thrombin time (PT), partial thromboplastin time (APTT), thrombin time (TT) and fibrinogen (Fib). A number of peripheral blood specimens were collected and centrifuged at low speed to separate the upper serum, and ELISA was used to detect the levels of oxidative stress products advanced oxidation protein products (AOPPs), lipid hydroperoxide (LHP), glutathione peroxidase (GSH-Px) and total antioxidant capacity (T-AOC).

2.4 Statistical methods

Liver function indexes, coagulation indexes and oxidative stress indexes were input in software SPSS 26.0 as measurement data, t test was used to calculate statistic P and $P<0.05$ was set as the standard of statistical significance in differences.

3. Results

3.1 Liver function indexes

Comparison of peripheral blood liver function indexes ALT (U/L), AST (U/L), ALP (U/L) and STB (μmol/L) contents between the two groups was as follows: before treatment, the differences in peripheral blood ALT, AST, ALP and STB contents were not significant between the two groups ($P>0.05$). After 1 week of treatment, peripheral blood ALT, AST, ALP and STB contents of both groups were lower than those before treatment; peripheral blood ALT, AST, ALP and STB contents of silybin group were lower than those of control group ($P<0.05$), shown in Table 1.

3.2 Coagulation indexes

Comparison of peripheral blood coagulation indexes PT (s), APTT (s), TT (s) and Fib (g/L) levels between the two groups was as follows: before treatment, the differences in peripheral blood

Table 1.

Comparison of liver function index contents.

Groups	n	ALT		AST		ALP		STB	
		Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment
Control group	39	65.28±7.19	40.72±4.95*	57.29±6.25	43.75±5.09*	139.47±15.88	102.94±13.61*	29.48±3.51	21.04±2.63*
Silybin group	39	66.03±7.85	29.55±3.71*	58.15±6.19	34.62±4.26*	138.95±16.43	74.81±8.39*	29.36±3.42	12.88±1.76*
t		0.291	12.415	0.174	19.023	0.158	9.261	0.238	14.394
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

Table 2.

Comparison of coagulation index levels.

Groups	*n*	PT		APTT		TT		Fib	
		Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment
Control group	39	17.35±2.06	14.26±1.75*	35.28±4.11	29.71±3.27*	17.49±1.63	15.11±1.79*	1.37±0.18	2.45±0.31*
Silybin group	39	17.41±2.13	12.35±1.68*	35.37±4.07	26.08±2.71*	17.53±1.84	13.42±1.63*	1.34±0.16	3.27±0.43*
t		0.291	7.192	0.117	8.364	0.169	9.023	0.235	6.348
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

Table 3.

Comparison of oxidative stress index contents.

Groups	*n*	AOPPs		LHP		GSH-Px		T-AOC	
		Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment	Before treatment	After 1 week of treatment
Control group	39	49.28±5.61	37.95±4.51*	69.72±7.84	51.59±6.43*	40.26±4.81	53.94±5.81*	15.38±2.11	24.71±3.52*
Silybin group	39	49.31±5.48	25.88±3.17*	69.61±7.35	37.05±4.27*	40.42±4.79	67.43±8.05*	15.41±2.09	40.95±5.81*
t		0.093	9.204	0.274	15.382	0.138	11.584	0.216	20.937
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

Note: compared with same group before treatment, *$P<0.05$.

PT, APTT, TT and Fib levels were not significant between the two groups ($P>0.05$). After 1 week of treatment, peripheral blood PT, APTT and TT levels of both groups were lower than those before treatment whereas Fib levels were higher than those before treatment; peripheral blood PT, APTT and TT levels of silybin group were lower than those of control group whereas Fib level was higher than that of control group ($P<0.05$), shown in Table 2.

3.3 Oxidative stress indexes

Comparison of serum oxidative stress indexes AOPPs (μmol/L), LHP (umol/L), GSH-Px (g/L) and T-AOC (U/mL) contents between the two groups was as follows: before treatment, the differences in serum AOPPs, LHP, GSH-Px and T-AOC contents were not significant between the two groups ($P>0.05$). After 1 week of treatment, serum AOPPs and LHP contents of both groups were lower than those before treatment whereas GSH-Px and T-AOC contents were higher than those before treatment; serum AOPPs and LHP contents of silybin group were lower than those of control group whereas GSH-Px and T-AOC contents were higher than those of control group ($P<0.05$), shown in Table 3.

4. Discussion

The long-term use of rifampicin, isoniazid and other anti-tb drugs can cause certain damage to liver function of patients with pulmonary tuberculosis, and when pulmonary bronchial vascular rupture causes acute massive hemoptysis, the declined blood supply of liver will further increase the liver dysfunction, decrease blood coagulation factor synthesis and result in the continuous progression of haemoptysis. Pituitrin-phenolamine are the main drugs for pulmonary tuberculosis with hemoptysis, pituitrin is known as the "internal scalpel" and can shrink capillaries and reduce pulmonary circulating blood volume to achieve hemostatic effect, but large doses can cause the sympathetic nervous excitement and pulmonary circulation pressure elevation[6,7]; phentolamine is competitive 1 and 2 receptor blocker that can cause vasodilation and hypotension, and the combination of pituitrin-phenolamine can both shrink blood vessels to stop bleeding and maintain the stability of blood pressure[8,9]. But at the same time of above hemostatic therapy, the continuous progress of liver function damage is not conducive to the eventual realization of hemostatic effect and the optimization of the overall condition, so some scholars recommend adding targeted drugs to protect the liver function. Silybin is extracted from plant milk thistle, which has the functions such as maintaining the integrity of liver cells and accelerating liver cell DNA synthesis, can prevent liver cirrhosis and suppress liver cancer cell proliferation, and is one of the reliable drugs for prevention and treatment of liver-related diseases. In this study, silybin was added in the therapy for patients with pulmonary tuberculosis complicated by acute hemoptysis, and the effects of its adjuvant therapy on liver function, coagulation function and systemic oxidative stress were discussed.

Anti-tb drugs have a certain hepatotoxicity, massive hemorrhage directly results in decreased blood supply to liver, and the function of damaged liver cells further declines, and serious cases can cause hepatic dysfunction[10,11]. ALT, AST, ALP and STB are typical four indexes for liver function. When apparent liver dysfunction occurs, the levels of above indexes rise, and the specific rising degree is consistent with the abnormal degree of liver function[12-14]. The study showed that the serum liver function indexes ALT, AST, ALP and STB levels of both groups after treatment were lower than those before treatment, and the decrease in above index levels was more significant in silybin group after treatment, it indicates that adjuvant silybin therapy can significantly optimize the liver function of pulmonary tuberculosis patients with acute hemoptysis, and this is consistent with the pharmacological action of silybin and confirms that the adjuvant silybin therapy can effectively protect liver cell function.

Without timely hemostasis, acute hemoptysis can cause continuous consumption of clotting factors, the synthesis of clotting factors

decreases after liver function damage, and they lead to difficult hemostasis, shock and increased risk of DIC in tuberculosis patients[15,16]. Blood coagulation function in patients with pulmonary tuberculosis complicating acute hemoptysis is directly related to the hemostatic effect and liver function state. The study showed that peripheral blood PT, APTT and TT levels of both groups after treatment were lower than those before treatment whereas Fib levels were higher than those before treatment, and the change in above coagulation index levels in peripheral blood of silybin group was bigger after treatment, it shows that adjuvant silybin therapy can effectively optimize the blood coagulation function in patients with pulmonary tuberculosis complicating acute hemoptysis, and this is related to its effects on optimizing liver function, increasing the liver blood coagulation factor synthesis, etc, and further confirms the feasibility and effectiveness of the auxiliary silybin treatment.

The occurrence of acute hemoptysis and the severe blood loss of the body can both lead to the occurrence of systemic oxidative stress. Severe oxidative stress response is one of the important mechanisms of liver cell injury[17,18]. Silybin is an antioxidant that promotes fat transfer, prevents excessive oxidation of fat and reduces oxygen free radicals and lipid peroxidation processes so as to equalize the balance of oxidation/anti-oxidation[19,20]. AOPPs and LHP are typical oxidative metabolites, which have strong oxidization and can injure the cells of multiple tissue viscera; GSH-Px and T-AOC have antioxidant effects, which are combined with oxidative products to stabilize the overall oxidative stress of the body[21]. The study showed that serum AOPPs and LHP contents of both groups decreased whereas GSH-Px and T-AOC contents increased after treatment, and the change in serum contents of above indexes of silybin group was bigger after treatment, it explains that adjuvant silybin therapy can more effectively inhibit synthesis of oxidative metabolites and enhance the body's antioxidant capacity, and this is also the intuitive manifestation of the antioxidant effect of silybin, and is one of the core mechanisms of its to protect liver cell function and maintain the blood coagulation function stability.

Adjuvant silybin therapy on the basis of pituitrin-phentolamine hemostasis can effectively protect the liver function and enhance the coagulation function in patients with pulmonary tuberculosis complicating acute hemoptysis, and specific mechanism is directly related to its effect on reducing the oxidative stress reaction.

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