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Original Article

Comparison of the efficacy and liver function with different doses of S-adenosylmethionine combined with ursodeoxycholic acid for cholestatic liver disease

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Abstract: Objective: To explore the clinical efficacy and liver function improvement of different doses of S-adenosylmethionine (SAM) combined with ursodeoxycholic acid (UDCA) for cholestatic liver disease. Methods: 115 patients with cholestatic liver disease in our hospital (February 2019 to January 2020) were selected and divided into two groups according to the random number table method. Same dose of UDCA treatment was given in two groups, the control group used 1000 mg SAM, and the observation group used 2000 mg SAM. The improvement of itching, serum inflammatory factors IL-12, IL-18 and liver function indexes alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), and total bile acid (TBA) content were observed to evaluate the efficacy and adverse reactions of the two groups of patients. Results: The itching score of the observation group was significantly lower than that of the control group (0.52±0.16 vs 1.29±0.34, t=15.580, P<0.05); the serum IL-12 and IL-18 levels of the observation group and liver function indexes ALT, AST, TBil, TBA contents were significantly lower than those of the control group (all P<0.05); compared with the control group, higher total effective rate was seen in the observation group (96.55% vs 78.95%, χ^2=6.768, P<0.05); no significant difference was detected in the occurrence of the reaction between the two groups (P>0.05). Conclusion: High-dose SAM combined with UDCA for the treatment of cholestasis liver disease can notably improve the clinical symptoms of patients and play a part in anti-inflammatory and recovery of liver function, thereby improving clinical efficacy and safety. It is therefore worthy of popularization and application.

Keywords: S-adenosylmethionine, ursodeoxycholic acid, cholestatic liver disease

Introduction

Cholestatic liver disease is a syndrome characterized by partial or complete cholestasis in the liver, and it is usually resulted from abnormal uptake and transport of liver and serum on bile fluids such as bilirubin and bile salts. Since the bile fails to pass through the bile duct to the intestinal lumen, it accumulates in the liver and back flows into the bloodstream, thereby affecting the hepatobiliary system and causing multiple organ dysfunction, metabolic dysfunction, and organic damage. Persistent cholestatic liver disease can progress into liver fibers, cirrhosis, and even liver failure, which endanger the life of the patient and increase the difficulty of clinical treatment. This disease shows such symptoms as skin itching, jaundice, fatigue, decreased appetite, dark yellow urine, and gastrointestinal discomfort [1]. At present, combination of Ursodeoxycholic acid (UDCA) and S-adenosyl-L-methionine (SAM) is the first choice for the treatment of cholestatic liver disease [2, 3], and has been proved as an effective method. The combination of UDCA and SAM has been widely used in various cholestatic liver diseases treatment. Researches showed that it mainly protects liver cells, detoxifies, promotes excretion, plays a role in preventing further damage to liver and gallbladder cells, and anti-fibrosis. The molecular biological mechanism in the treatment of cholestatic liver disease has not yet been fully understood so far. With the continuous development of molecular

biology, immunology, and genetics, the application fields and mechanism of UDCA and SAM will be gradually enriched and perfected [4-6]. Some scholars have proposed that the traditional recommended dose of SAM is 500-1000 mg/d, yet outcomes remained unsatisfactory. Therefore, this paper compared different doses of SAM combined with UDCA for patients with cholestasis liver disease, aiming to provide a reference for the clinic by observing the improvement of liver function and clinical efficacy after treatment.

Materials and methods

General information

115 patients with cholestatic liver disease in our hospital (February 2019 to January 2020) were selected. Inclusion criteria: ① patients who met the diagnostic criteria for cholestatic liver disease in the guidelines [7], including total bile acid (TBA) >10 μmol/L, had slightly and moderately elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in liver function, mild total bilirubin (TBil) stasis, cholestasis, combined with signs of fatigue, itching, etc.; ② patients without usage of related liver and gallbladder drugs two weeks before the consultation; ③ patients who voluntarily signed an informed consent. Exclusion criteria: ① patients with hepatobiliary stones, biliary and pancreatic tumors, and severe organs impairment; ② patients who were allergic to the drugs in this study, including contraindications; ③ patients with poor compliance. The ethics committee of our hospital approved this study. According to the random number table method, they were divided into a control group (n=57) and an observation group (n=58). There were 78 males and 37 females; the average age was 44.68±7.40 years; the average disease course was 8.56±1.78 years; the average weight was 62.25±8.67 kg. The general data was basically the same in the two groups.

Treatment schemes

The two groups of patients were given ursodeoxycholic acid capsules (producer: Losan Pharma GmbH, Germany; SDFA approval number: H20181059; specification: 250 mg*25 s), 0.25 g/time, 2 times/day after basic treatment such as vitamins and compound glycyrrhizin. 1000 mg SAM (French biovea; SDFA approval number: X20000442) was diluted with 250 ml 0.9% saline for intravenous injection in the control group, once a day. 2000 mg SAM was diluted with 250 ml 0.9% saline and administered through intravenous injection in the observation group, once a day. Both groups of patients were treated for 2 consecutive weeks.

Outcome measures

Itching score: The itching score was employed to evaluate the degree of itching before and after treatment [8]: 0 points indicates no itching; 1 point indicates occasional itching; 2 points indicates that itching is intermittent with no noticeable symptom fluctuations; 3 points indicates that itching is intermittent with obvious symptoms fluctuations; 4 points indicates persistent itching.

Liver function indexes and inflammation indexes: 5 ml of venous blood was extracted before and after treatment, and the liver function indexes including ALT, AST, TBil, and TBA were detected by an automatic biochemical analyzer. In the same period, the levels of interleukin-12 (IL-12) and IL-18 were detected by ELISA. The kit was provided by Shanghai Enzyme Biotechnology Co., Ltd, and the procedures were in strictly accordance with the instructions.

Assessment of efficacy: Cured: the symptoms completely disappeared, and liver function returned to normal. Markedly effective: the main clinical symptoms such as skin itching disappeared, inflammation and liver function index relief ≥80%, slight tenderness in the liver area. Effective: the clinical symptom relief, inflammation and liver function indexes improved by ≥50%. Ineffective: clinical symptoms, inflammation and liver function indexes did not change significantly or even worsened. Total effective = cured + markedly effective + effective.

Adverse reactions: The occurrence of adverse reactions in the two groups during medication was recorded.

Statistical methods

SPSS18.0 statistical software was employed. The count data were represented by n (%), and

Table 1. Comparison of general information between the two groups

	Control group	Observation group	X^2/t	*P*
Gender (n)				
Male	40	38	0.593	0.286
Female	17	20		
Age	44.51±7.32	45.72±7.10	0.900	0.370
Course of disease (years)	8.23±1.45	8.65±1.80	1.377	0.171
Weight (kg)	61.37±8.82	62.15±8.41	0.485	0.628
AST (U/L)	275.14±65.80	282.36±68.72	0.575	0.566
TBIL (μmol/L)	48.79±8.42	46.43±9.12	1.441	0.152
TBA (μmol/L)	59.46±9.27	61.23±10.25	0.971	0.334
ALT (U/L)	308.65±54.79	314.36±62.81	0.519	0.605
Types of liver disease			0.699	0.716
Drug-induced liver disease	22	25		
Alcoholic cirrhosis	9	11		
Cirrhosis after hepatitis	26	22		

Table 2. Comparison of itching scores between two groups of patients ($\bar{x}$ ± sd)

Group	Itching score (points)		X^2	*P*
	Before treatment	After treatment		
Control group	3.35±0.75	1.29±0.34	18.890	<0.001
Observation group	3.43±0.68	0.52±0.16	31.720	<0.001
t	0.600	15.580		
P	0.550	<0.001		

χ^2 test was performed; the measurement data were represented by x ± sd, and the t test was performed. P<0.05 represented that there was statistically significant difference.

Results

Comparisons of the general data

There was no statistically significant difference between the two groups of patients in terms of gender, age, course of disease, weight, AST, TBIL, TBA, ALT and etiology (P>0.05, **Table 1**).

Itching score

After treatment, the itching scores of the two groups of patients decreased, and the observation group saw much lower scores (P<0.05). See **Table 2**.

Liver function and inflammation index

After treatment, the liver function indexes of TBil, TBA, ALT and AST of the two groups decreased compared with those before treatment; the liver function indexes of the observation group were significantly lower than those of the control group (P<0.05). See **Table 3** and **Figure 1**. At the same time, the levels of IL-12 and IL-18 in both groups were also lower than those before treatment, and the levels of IL-12 and IL-18 in the observation group after treatment were also significantly lower than those in the control group (P<0.05) (**Figure 1**; **Tables 3** and **4**).

Clinical efficacy

After treatment, the total number of effective cases in the control group was 45 (78.95%), while that was 56 (96.55%) in the observation group. Significant difference was noted (χ^2=6.768, P=0.009), see **Table 5**.

Adverse reactions

During treatment, there was one case of nausea in the control group; one case of nausea and one case of dizziness in the observation group, and no significant difference was detected (P>0.05).

Discussion

The accumulation of bilirubin can easily induce a large amount sediment of bile salts in liver cells and bile duct cells and result in damage of liver cells or bile duct cells (apoptosis and necrosis) [9]. If not treated in timely manner, it will further damage liver tissue and liver microcirculation, cause liver into ischemic and hypoxic, destroy the membrane structure, physicochemical properties and enzyme activity of the liver cells, and eventually intrahepatic cholestasis [10]. UDCA is currently the preferred choice for the treatment of cholestatic liver disease. It is a hydrophilic dihydroxycholic acid, which plays a role in protecting cells, suppressing the cytotoxicity of hydrophobic bile acids,

Table 3. Changes of TBIL, TBA, ALT and AST levels before and after treatment in the two groups ($\bar{x}$ ± sd)

Liver function index	Before treatment		After treatment	
	Control group	Observation group	Control group	Observation group
TBil (μmol/L)	48.79±8.42	46.43±9.12	32.57±6.05*	19.46±5.61*,#
TBA (μmol/L)	59.46±9.27	61.23±10.25	28.34±7.16*	15.70±6.69*,#
ALT (U/L)	308.65±54.79	314.36±62.81	125.64±31.85*	68.29±20.17*,#
AST (U/L)	275.14±65.80	282.36±68.72	127.28±23.79*	61.57±11.25*,#

Note: *means $P<0.05$ compared with before treatment; #means $P<0.05$ compared with control group.

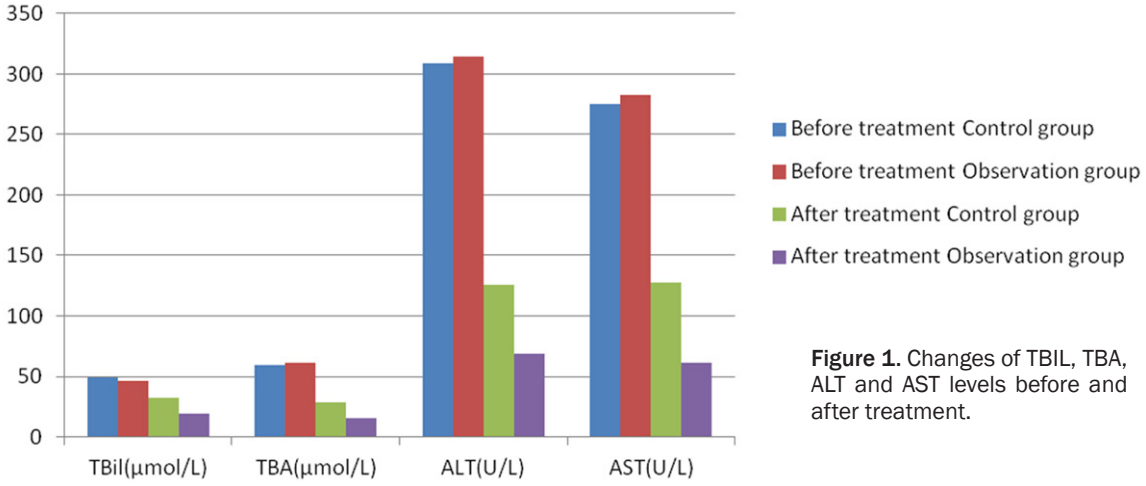

Figure 1. Changes of TBIL, TBA, ALT and AST levels before and after treatment.

Table 4. Comparison of the levels of IL-12 and IL-18 between the two groups before and after treatment ($\bar{x}$ ± sd)

Group	IL-12/(pg·mL^{-1})		IL-18/(pg·mL^{-1})	
	Before treatment	After treatment	Before treatment	After treatment
Control group	68.16±16.43	35.47±6.75*	105.46±30.21	76.58±10.38*
Observation group	65.72±14.79	19.63±5.82*,#	101.76±29.63	50.61±8.95*,#
t	0.837	13.480	0.663	14.380
P	0.404	<0.001	0.509	<0.001

Note: * means $P<0.05$ compared with before treatment; # means $P<0.05$ compared with control group.

Table 5. Comparison of clinical efficacy of two groups of patients after treatment [n (%)]

	Cured	Markedly effective	Effective	Ineffective	Total effective
Control group	3 (5.26)	11 (19.30)	31 (54.39)	12 (21.05)	45 (78.95)
Observation group	8 (13.79)	33 (56.90)	15 (25.86)	2 (3.45)	56 (96.55)
X^2					6.768
P					0.009

regulating immunity, anti-oxidation, anti-apoptosis and cholagogue. It has multiple protective effects on the liver, but the outcome was not ideal in clinical symptoms and biochemical indicators after using UDCA in some patients [11].

It was reported by some studies that UDCA combined with SAM treatment can improve the liver function of patients with cholestatic liver disease. SAM is a physiologically active substance that exists in the body. It can regulate

the fluidity of the membrane by stimulating the phospholipid methylation of hepatocyte membranes, and promote the synthesis of sulfide products to improve the detoxification ability of liver [12]. If the SAM in the body is reduced, the plasma membrane phospholipid methylation will be reduced, the membrane fluidity will be weakened, Na+/K+-ATPase activity will be inhibited, and eventually a large amount of bile will be deposited in the liver cells, and the liver detoxification ability will be impaired. Meanwhile, hepatocellular damage will be aggravated. Thus, supplementing exogenous SAM can promote liver function recovery, increase hepatocyte uptake and secretion of bilirubin, promote bile acid conversion and excretion, and metabolize glutathione and taurine [13]. Previous studies pointed out that the combination of the above two drugs for cholestatic liver disease can effectively decrease the blood AST and TBil levels and improve the symptoms of itching [14-16], which was consistent with the results of this study. The itching score and liver function indexes TBil, TBA, ALT, and AST of the two groups of patients were significantly improved after treatment, confirming the effectiveness of the combination.

In addition, studies suggested that immune molecules are involved in the process of cholestasis liver disease. Once the immune microenvironment is destroyed, liver function will be affected [17, 18]. Therefore, the occurrence of cholestasis liver disease is speculated to be closely related to the imbalance of patients' immune function. IL-18 can stimulate and activate NK cells and T lymphocytes in hepatocellular apoptosis or necrosis pathway and cause liver parenchymal cell immune damage. While IL-12, a pro-inflammatory cytokine, is involved in specific or non-specific immune processes. It not only can independently mediate the inflammatory response of hepatocytes, but also promote the inflammatory effect of IL-18, further aggravating the damage of hepatocytes [19-21]. Therefore, inhibition of inflammatory response of IL-12 and IL-18 helps improve liver function of patients with cholestatic liver disease. It has been confirmed that UDCA has the functions of regulating cellular immunity and anti-oxidation, which can improve the anti-apoptotic effect of liver cells [22]. SAM can inhibit oxidative stress response, remove excessive oxygen free radicals, and in turn protect liver cells [23]. A meta-analysis showed that SAM can significantly promote chronic cholestasis liver disease by regulating the growth of hepatocytes and has a significant anti-apoptotic effect [24]. It is found in present study that IL-12 and IL-18 levels in the two groups of patients before treatment were higher, but the levels significantly decreased after treatment, indicating that the combination of two drugs in the treatment of patients with cholestatic liver disease can play a certain role in the regulation of cellular immunity, level reduction of inflammatory factors IL-12 and IL-18, and anti-inflammatory and liver protection.

Under normal circumstances, the conventional recommended dose of SAM is 1000 mg/d, and some scholars have reported that the clinical efficacy of SAM with 2000 mg/d in the treatment of cholestatic liver disease is better than the conventional dose [24]. The results of this study also confirmed that the high-dose SAM in the observation group had better outcome in terms of itching scores, inflammatory factors IL-12, IL-18 levels, and liver function TBil, TBA, ALT, and AST levels. The clinical efficacy was significantly higher in the observation group than the control group (96.55% vs 78.95%), with no obvious adverse reactions. However, though we tried to make sure that these two groups are similar in demographics, such as having a similar mix of ages, genders and health statuses, small differences, such as lifestyle and genetic factors can skew the effects of the drugs on the subjects. Therefore, a more refined and comprehensive study still needs to be conducted to verify the results.

In summary, the high-dose SAM combined with UDCA is more effective in the treatment of cholestatic liver disease. It can significantly improve the clinical symptoms of patients, play a part in anti-inflammation and recovery of liver function, thereby improving clinical efficacy and safety.

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Disclosure of conflict of interest

None.

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