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Review Article

High-dose S-adenosylmethionine combined with ursodeoxycholic acid is more suitable for the treatment of cholestatic liver disease

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Abstract: This study set out to compare the efficacy of different doses of S-adenosylmethionine combined with ursodeoxycholic acid on cholestatic liver disease and its effect on liver function. Altogether 177 patients with cholestatic liver disease who visited our hospital from June 2016 to April 2018 were collected as research participants. Among them, 64 cases treated with high-dose S-adenosylmethionine combined with ursodeoxycholic acid were placed into group A, 59 cases treated with low-dose S-adenosylmethionine combined with ursodeoxycholic acid were placed into group B, and 54 cases treated with ursodeoxycholic acid alone were placed into group C. The efficacy and adverse reactions of the three groups were compared. Liver function indexes AST, ALT and TBIL were detected via an automatic biochemical instrument before and after treatment, and inflammatory indexes IL-6 and TNF-α were detected via ELISA before and after treatment. The total effective rate of treatment in group A was dramatically higher than that in group C, and the incidence of adverse reactions in group A was dramatically lower than that in group B and group C. After treatment, AST, ALT, TBIL, IL-6 and TNF-α in three groups were lower than those before treatment, and group A was dramatically lower than those in group B and group C. Compared with a low-dose regimen, the high-dose SAMe combined with ursodeoxycholic acid has no remarkable improvement in efficacy, but can markedly improve liver function and adverse reactions.

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

Introduction

Cholestatic liver disease refers to liver disease with excessive bile accumulation [1]. This disease is mainly caused by bile acid uptake and binding of liver cells or bile duct blockage. Common causes include viral infection, poisoning, hormone secretion and genetic diseases. If not controlled, it might develop into life-threatening complications such as end-stage liver disease, portal hypertension and massive hemorrhage of esophageal varices [2]. At present, the most familiar adult cholestatic liver diseases are primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). As there are few drug treatments suitable for cholestatic liver diseases, the mortality of patients is relatively high and some of them need liver transplantation in the later stages [3].

Ursodeoxycholic acid is a naturally occurring hydrophilic bile acid, which is present in a small amounts in the human body and is used in clinical treatment of various cholestatic diseases. It is the main current pancreatic therapeutic drug, which can effectively reduce the morbidity, mortality and liver transplantation rate of some patients [4, 5]. It can up-regulate liver metabolic enzymes and bile acid transporters to increase bile acid excretion, has protective and anti-inflammatory effects on liver cells, can regulate the damage caused by cytokines, and may also reduce the total cholesterol of patients [6, 7]. However, Santiago et al. [8] mentioned that some patients did not respond well to ursodeoxycholic acid treatment, so these patients had a greater risk of disease development, and some new drugs were needed to ensure their efficacy. S-Adenosyl-L-Methionine (SAMe) is a

biological methyl donor required for a large number of intracellular reactions and is tied to the development of many liver diseases. Therefore, it has preventive and therapeutic effects on many liver diseases. Long-term SAME administration can inhibit the development of liver cancer cells [9, 10]. Yang et al. [11] found that injecting SAMe to cholestatic liver injury mice could effectively prevent liver injury in them. Hence, we suspected that SAMe combined with ursodeoxycholic acid might improve the efficacy of treatment in cholestatic liver diseases, but there was no study on the efficacy and dosage of the combined therapy.

This study hopes to compare the efficacy of different doses of S-adenosylmethionine combined with ursodeoxycholic acid in treating cholestatic liver diseases and provide basis and direction for clinical practice.

Materials and methods

Clinical data of patients

Altogether 177 patients with cholestatic liver diseases treated in Cangzhou Infectious Disease Hospital from June 2016 to April 2018 were collected as research participants. Among them, 64 cases treated by high-dose S-adenosylmethionine combined with ursodeoxycholic acid were divided into group A, including 39 males and 25 females, with an average age of 46.6±9.4 years; 59 cases treated by low-dose S-adenosylmethionine combined with ursodeoxycholic acid were divided into group B, including 31 males and 28 females, with an average age of 46.3±9.0 years; and 54 cases treated with ursodeoxycholic acid alone were divided into group C, including 24 males and 30 females, with an average age of 45.9±8.6 years. The study was approved by the Medical Ethics Committee of Cangzhou Infectious Disease Hospital, and is in line with the Declaration of Heisinki. All patients were informed of the study contents and they signed informed consent forms.

Inclusion and exclusion criteria

Inclusion criteria: All patients were diagnosed with cholestatic liver disease by pathology. The diagnostic criteria were based on the diagnostic guidelines for cholestatic liver disease issued in 2015 in China [12]. Patients who were complicated with liver failure or end-stage liver disease. Their clinical data were complete and they could be followed up by telephone.

Exclusion criteria: Patients with advanced malignances and serious cardiovascular and cerebrovascular diseases were excluded, drug treatment for related liver diseases had been carried out within 3 months before treatment, and liver transplantation was expected to be required within 1 year in pregnant or lactating women.

Therapeutic regimens

Patients in group C were treated with ursodeoxycholic acid orally, 3 times a day, 5 mg each time, and those in group A received an additional intravenous drip of S-adenosylmethionine once a day at a dose of 1200 mg added to 100 ml of 5% glucose solution; and in addition to treatment in group C, those in the group B also received an additional intravenous drip of S-adenosylmethionine once a day at a dose of 800 mg added to 100 ml of 5% glucose solution. All groups' treatment time was one month.

Efficacy evaluation

Clinical effects of patients after treatment were divided into remarkable effectiveness, effectiveness and ineffectiveness: markedly effective: ALT, AST and TBIL levels of patients decreased by more than 50%, and clinical signs and symptoms basically disappeared; effective: ALT, AST and TBIL decreased by 50%-25%, and clinical signs and symptoms were improved; ineffective: FT3, FT4, and TSH dropped by < 25%, and clinical signs and symptoms did not improve or worsen. Total effective treatment = markedly effective+effective.

Instruments and reagents

Main instruments and reagents were as below: IL-6, TNF-α ELISA kit (Elabscience Biotechnology Co., Ltd., Wuhan, China, E-EL-H0102c, E-EL-H0109c), full automatic biochemistry (Beckman Coulter, Inc., AU5800), ursodeoxycholic Acid (Shanghai Zhongxi Sunve Pharmaceutical Co., Ltd., China).

Detection methods

After the patients were admitted to Cangzhou Infectious Disease Hospital and the next morn-

ing after the treatment was completed, 5 mL of sterile venous blood was collected and centrifuged to collect serum (3000 × g at 4°C for 10 min) and stored in a -80°C freezer. The IL-6 and TNF-α expression levels were detected by ELISA. Blank wells, standard sample wells and sample wells to be tested were set up. S0 standards with a concentration of 0 were added into the blank wells. Also, 50 μL of standards with different concentrations were added into the standard wells. Then, 10 μL of each sample to be tested was added to the sample wells, 40 μL of sample diluent was then added, and nothing was added into the blank wells. In addition to the blank wells, 100 μL of HRP labeled detection antibody was added into each of the standard wells and the sample wells. The reaction wells were sealed with a sealing plate membrane and incubated for 65 min in a water bath at 37°C. The liquid was discarded, and the absorbent paper was patted dry. Each well was filled with washing liquid, allowed to stand for 2 min, the washing liquid was removed, and the absorbent paper was patted dry. This was repeated 6 times. Substrates A and B were added to each well, 50 μL each, and incubated 10 min at 37°C in the dark. The OD value of each well was measured at 450 nm wavelength within 15 min after stop solution (50 μL) was added. Concentration was then calculated. After treatment, patients in both groups were tested for alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin (TBil) by automatic biochemical analyzer.

Outcome measures

Main outcome measures: Efficacy of patients in all groups after treatment were compared, so was the case on the AST, ALT and TBIL expression levels before and after treatment.

Secondary outcome measures were: Adverse reactions found after treatment of patients in all groups, expression of inflammatory indicators IL-6 and TNF-α before and after treatment.

Statistical methods

The collected data were statistically analyzed via SPSS 20.0 (Chicago SPSS Co., Ltd.) and pictures were drawn via GraphPad Prism 7 (San Diego GraphPad Software Co., Ltd.). The usage (%) of counting data was conducted by chi-square test and expressed by x^2. When the sample number was ≥40, theoretical frequency was less than 1, Fisher's test was employed. The measurement data were expressed by mean ± standard deviation (Mean ± SD), and all data conformed to a normal distribution. Comparison between the two groups was analyzed by independent-samples t test, comparison with the same group was analyzed by paired t test and expressed by t, and comparison among three groups was done with one-way analysis of variance. LSD-t test was used for back testing and expressed as F. $P<0.05$ was regarded as a significant difference.

Results

Clinical data

By comparing the clinical data of all groups, we found that there was no statistical difference in age, gender, place of residence, BMI, creatinine, cirrhosis, cholangiocarcinoma, drug-induced liver injury, autoimmune liver disease, TBA and GGT between both groups (**Table 1**).

Efficacy

By comparing the efficacy in all groups, we found that there was no marked difference between the three groups, but the total effective rate of group A was dramatically higher than that of group C ($P<0.05$) (**Table 2**).

Effect of treatment on liver function

We compared ALT, AST and TBIL of the three groups. Before treatment, there was no difference in ALT, AST, TBIL in group A (237.24±42.61, 223.75±36.55, 75.33±18.42), group B (227.18±40.92, 221.48±34.62, 79.36±17.36) and group C (224.54±31.71, 232.76±38.56, 76.3±16.21). After treatment, ALT, AST and TBIL in group C (77.09±14.75, 81.32±11.57, 44.21±14.67) were dramatically higher than those in group A and group B, and the levels in group A (46.37±15.21, 41.53±13.23, 25.57±12.54) were remarkably lower than those in group B (69.25±18.43, 60.35±15.36, 37.96±13.17) (**Figure 1**).

Adverse reactions

By comparing the adverse reactions of the three groups, we found that there was no sta-

Table 1. Clinical data table

	Group A (n=64)	Group B (n=59)	Group C (n=54)	X^2/t/F	P
Age (years)	46.6±9.4	46.3±9.0	45.9±8.6	0.086	0.917
Gender				3.210	0.201
Male	39 (60.94)	31 (52.54)	24 (44.44)		
Female	25 (39.06)	28 (47.46)	30 (55.56)		
Place of residence				0.576	0.750
Cities and towns	48 (75.00)	47 (79.66)	40 (74.07)		
Countryside	16 (25.00)	12 (20.34)	14 (25.93)		
BMI (kg/m^2)	21.26±2.46	21.30±2.69	21.05±2.25	0.164	0.849
Creatinine (mg/dl)	0.93±0.26	0.90±0.23	0.89±0.21	0.470	0.626
Cirrhosis	14 (21.88)	15 (25.42)	9 (16.67)	1.292	0.524
Cholangiocarcinoma	29 (45.31)	24 (40.68)	18 (33.33)	1.761	0.415
Drug-induced liver injury	21 (32.81)	20 (33.90)	14 (25.93)	0.978	0.613
Autoimmune liver disease	24 (37.50)	26 (44.07)	20 (37.04)	0.759	0.684
TBA (μmol/L)	73.22±32.43	70.43±31.65	71.92±29.38	0.122	0.885
GGT (U/L)	314.37±23.74	321.56±24.52	317.50±20.66	1.488	0.229

Table 2. Efficacy

	Group A (n=64)	Group B (n=59)	Group C (n=54)	X^2	P
Markedly effective	21 (32.81)	14 (23.73)	10 (16.67)	3.290	0.193
Effective	35 (53.13%)	35 (59.32)	29 (64.81)	0.424	0.809
Ineffective	8 (14.06)	10 (16.95)	15 (18.52)	0.445	0.801
Total effective	56 (85.94)	49 (83.05)	39 (81.48)^A		

Note: ^{A}represents P<0.05 compared with group A.

tistical difference between them in diarrhea, malaise, pruritus and jaundice. However, the incidence of adverse reactions in group A was remarkably lower than that in group B and C (**Table 3**).

Effect of treatment on inflammation

We compared the changes of inflammatory response factors IL-6 and TNF-α before and after treatment. Before treatment, there was no marked difference in IL-6, TNF-α (65.36± 9.54, 332.55±47.88), IL-6, TNF-α (67.68±6.32, 337.94±41.69) between groups A and C (67.22±5.54, 345.22±35.54). After treatment, the expression of each group was lower than that before treatment, the expression of IL-6 and TNF-α in group C was remarkably higher than that in groups A and B (45.15±4.36, 275.15±24.36), and that in group A (29.56± 9.26, 176.12±24.62) was markedly lower than that in group B (37.86±7.45, 221.56±27.37) (**Figure 2**).

Discussion

SAMe participates in many biochemical reactions in the human body. It supplements and restores glutathione storage in the liver and attenuates liver injury by establishing methyl reactions. Hence, it is a key metabolite that regulates hepatocyte growth, death and differentiation [13]. Nowadays, it is used as a therapeutic drug for chronic hepatitis B to relieve jaundice symptoms of patients and has good liver protection effects [14]. Antoniv et al. [15] found that SAMe had good membrane stability on hepatocytes, and could stably eliminate cytolysis, cholestasis, interstitial inflammatory syndrome and other conditions in patients with nonalcoholic steatohepatitis.

ALT, AST and TBIL are crucial markers of cholestasis [16, 17]. Thus, we first detected and compared those in all groups. Through detection, we found that those of patients in both groups before treatment were obviously higher than the normal level range, which also indicated that our patients had liver injury to different degrees. With the completion of our treatment plan, ALT, AST and TBIL of patients in both groups all decreased remarkably, which indicated that their liver injury was relieved and reversed. In comparing ALT, AST and TBIL of all

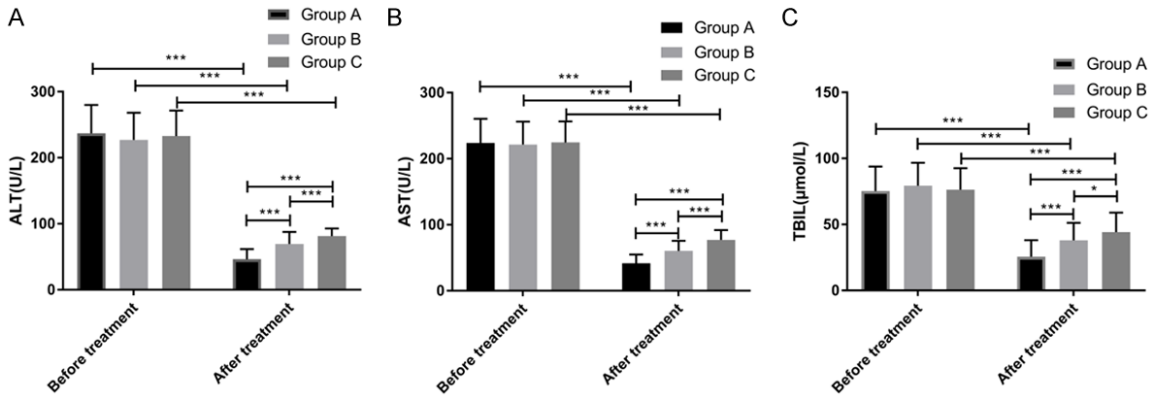

Figure 1. Changes of liver function before and after treatment. A. There was no difference in ALT among the three groups before treatment (F=0.932, P=0.396). After treatment, the ALT of the three groups decreased significantly; the ALT of group C was dramatically higher than that of group A and group B (P<0.001), and that of group A was dramatically lower than that of group B (P<0.001). B. There was no difference in AST between the three groups before treatment (F=0.122, P=0.885). After treatment, the AST of the three groups decreased dramatically; the AST of group C was dramatically higher than that of group A and group B (P<0.001), and that of group A was dramatically lower than that of group B (P<0.001). C. There was no difference in TBIL among the three groups before treatment (F=0.879, P=0.417). After treatment, TBIL in the three groups decreased dramatically; TBIL in group C was dramatically higher than that in group A (P<0.001) and group B (P=0.019), while TBIL in group A was dramatically lower than that in group B (P<0.001). * means P<0.05; *** means P<0.001.

Table 3. Adverse reactions

	Group A (n=64)	Group B (n=59)	Group C (n=54)	X^2	P
Diarrhea	2 (3.13)	4 (6.78)	4 (7.41)	1.220	0.544
Malaise	1 (1.56)	3 (5.08)	4 (7.41)	2.384	0.304
Pruritus	4 (6.25)	6 (10.17)	5 (9.26)	0.670	0.715
Jaundice	3 (4.69)	7 (11.86)	6 (14.81)	2.329	0.312
Total adverse reactions	10 (15.63)	20 (33.90)[A]	19 (38.89)[A]	7.305	0.026

Note: [A]represents P<0.05 compared with group A.

groups after treatment, we found that those of the group A were dramatically lower than those of the group B, so we suspected that high dose SAMe had better liver protection and liver repair functions. At the same time, we also compared the efficacy of patients in all groups. The efficacy was relatively good, but there was no remarkable difference in those with remarkable effectiveness and effectiveness rate after treatment, and the total effective rate of group A was dramatically higher than that of group C. We suspected that the reason was that SAMe's main function in combined therapy was to protect the liver, while ursodeoxycholic acid was effective in improving the cholestasis environment. There was no difference in ursodeoxycholic acid between all groups, so the difference in efficacy was not remarkable. We also compared the adverse reactions and found that the incidence of adverse reactions in group A was markedly lower than that in group B. Finally, we also observed the IL-6 and TNF-α levels before and after treatment. Cholestatic liver diseases are often accompanied by some inflammatory reactions in many studies, and these inflammatory reactions will also damage normal liver cells [18, 19], so improving inflammation in patients and observing inflammatory reactions can help to treat them better [20]. We found that the inflammatory reaction in all groups decreased in the later stage of treatment, and the levels of IL-6 and TNF-α in groups A and B were remarkably lower than those in group C, and group A was markedly lower than that in group B. Ursodeoxycholic acid and SAMe have anti-inflammatory effects [21-23], so the group with higher dosing has stronger anti-inflammatory effects. Avezov et al. [24] confirmed that ursodeoxycholic acid combined with SAMe was more effective in primary biliary cirrhosis. However, Zhang et al. [25] compared the efficacy of ursodeoxycholic acid combined with SAMe and the two drugs alone in treating intrahepatic cholestasis dur-

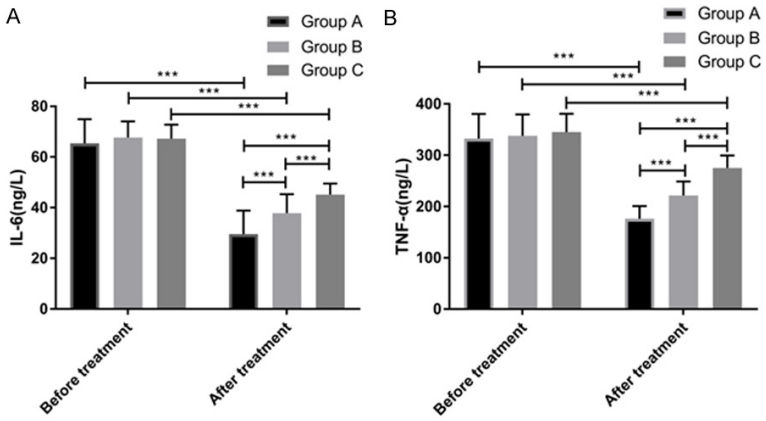

Figure 2. Changes in inflammatory response during treatment. A. There was no marked difference in IL-6 between group A and group B (F=1.674, P=0.191). After treatment, the IL-6 level in group C was remarkably higher than that in group A and group B (P<0.001), and that in group A was remarkably lower than that in group B (P<0.001). B. There was no difference in TNF-α between groups before and after treatment (F=1.312, P=0.272). After treatment, TNF-α in group C was remarkably higher than that in group A and group B (P<0.001), and that in group A was remarkably lower than that in group B (P<0.001). *** means P<0.001.

ing pregnancy, and found that the combination of drugs was dramatically better than SAMe alone in improving liver function, but there was no marked difference compared with ursodeoxycholic acid alone. We suspect that one reason for this difference may also be related to the dose difference of SAMe concentration.

However, our research also has some limitations. First of all, we have not carried out basic experiments. We still do not fully understand the specific mechanism of SAMe and ursodeoxycholic acid affecting cholestatic liver disease and liver function, and hope to increase corresponding basic experiments in a later period. Secondly, our study only included patients with cholestatic liver disease and did not include normal healthy people for comparison. Hence, we still do not know the difference between patients and normal healthy people before and after treatment. Finally, some studies have also found that some new drugs are employed in treating cholestatic liver diseases; for instance, Bolier et al. [26] discovered that bezafibrate could improve pruritus symptoms of moderate to severe cholestatic liver diseases with poor response to ursodeoxycholic acid, reduce cholestasis, improve liver function and quality of life, and it has high safety. Some researchers pointed out that fibrates might have certain potential, but there is still a lack of high-quality evidence to support their use in routine clinical treatment [27]. At the moment, it is not clear how the efficacy of fibrates are compared with our therapeutic schemes, so we hope that corresponding research can be added to improve our argument.

Overall, high-dose SAMe combined with ursodeoxycholic acid has no remarkable improvement in efficacy compared with low-dose regimen, but can improve liver function and adverse reactions.

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Disclosure of conflict of interest

None.

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